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Effect of green tea extract on lipid profile in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

Omid Asbaghi^a, Faezeh Fouladvand^a, Sajjad Moradi^{b,c}, Damoon Ashtary-Larky^d, Razieh Choghakhori^e, Amir Abbasnezhad^{f,*}

^a Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran

^b Halal Research Centre of IRI, FDA, Tehran, Iran

^c Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

^d Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

^e Razi Herbal Medicines Research Center, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

^f Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

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ABSTRACT

Background: Previous studies have indicated controversial results regarding the efficacy of green tea extract (GTE) in improving the lipid profile of type 2 diabetes mellitus (T2DM) patients. We aimed to conduct a systematic review and meta-analysis to pool data from randomized controlled trials (RCTs).

Methods: A systematic search was performed in Web of Science, PubMed, and Scopus databases, without any language and time restriction until August 2019, to retrieve the RCTs which examined the effects of GTE on serum concentrations of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) or total cholesterol (TC) in T2DM patients. Meta-analyses were carried out using a random effects model. I² index was used to evaluate the heterogeneity.

Results: Initial search yielded 780 publications. Of these, seven studies were eligible. The supplementary intake of GTE improved lipid profile by reducing serum TG concentrations in patients with T2DM. Meanwhile, subgroup analyses based on duration of interventions (≤ 8 and > 8 weeks) and intervention dosage (≤ 800 and > 800 mg/day) showed that the GTE supplementation longer than 8 weeks and in doses > 800 mg/day resulted in a significant decrease in serum TG concentrations. Furthermore, intervention longer than 8 weeks with doses lower than 800 mg/day resulted in a significant reduction in serum TC concentrations.

Conclusion: In conclusion, present systematic review and meta-analysis revealed that the supplementary intake of GTE may improve lipid profile by reducing serum concentrations of TG in patients with T2DM. Furthermore, the results of our stratified analyses suggested that long-term GTE intervention may reduce serum concentrations of TG and TC.

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1. Introduction

Diabetes mellitus (DM) describes a cluster of metabolic disorders determined by high blood glucose concentration [1]. The global prevalence of DM has continued to increase. Based on the last reports from the International Diabetes Federation (IDF) the

prevalence of DM was estimated to be 8.4% in 2017 and anticipated to rise to 9.9% in 2045 [1]. DM increases the risk of several chronic diseases such as depression [2], renal disease [3], cancer [4], cardiovascular diseases [5] and dyslipidemia [6]. The high prevalence of DM and its complications have a great impact on public health and lead to a large health, social and financial burden around the world [1,7]. Thus, the effective prevention, management, and treatment of DM can help to decrease risk of DM complications and improve public health.

Dyslipidemia is common in DM patients and contributes to increased risk of cardiovascular disease (CVD) and mortality [8]. It is characterized by abnormalities in concentrations of high-density

* Corresponding author. Nutritional Health Research Center, Department of Nutrition, Lorestan University of Medical Sciences, GoleDasht Blvd, Khorramabad, PO Box: 6813833946, Iran.

E-mail addresses: abbasnezhad.amir@lums.ac.ir, Abbasnezhad.a@ajums.ac.ir (A. Abbasnezhad).

Table 1
Quality assessment (method: Cochrane Collaboration's tool for assessing risk of bias).

Study	Random Sequence Generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Y, Fukino, et al. [28], 2008	U	U	H	L	L	L	U
T, Nagao, et al. [29], 2009	U	U	L	L	L	L	U
S, Mohammadi, et al. [30], 2010	L	U	L	L	H	L	U
C.H, Hsu, et al. [31], 2011	L	L	L	L	L	L	U
A, Mousavi, et al. [32], 2013	U	U	U	L	L	L	U
C.Y, Liu, et al. [33], 2014	L	L	L	L	L	L	U
P, Quezada-Fernández et al. [34], 2019	L	L	L	L	L	L	L

L, low; H, High; U, Unclear.

lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) or total cholesterol (TC) [9]. Statins as main treatment of the abnormality of lipid profiles have some side effects including cataract, polyneuropathy, myositis, myopathy, myalgias, tendinopathy, rhabdomyolysis, weakness, memory loss and hepatotoxicity [10,11]. Using substitute treatments without the possible side-effects of pharmacological therapies, to treat dyslipidemia, has focused over the recent decades in majority of countries worldwide [12,13]. Especially, herbal medicine and their healing complements can potentially improve the serum lipid profile with the different pathways [14,15]. Herbs as functional

foods that are rich in bioactive component such as fiber, antioxidants, plant sterols, stanols, glycosides, saponins, flavonoids, triterpenoids and catechins, may be able to optimize lipids profile [12,16,17].

In recent years, the beneficial health effects of green tea extract (GTE) as an ancient medicinal plant have been further investigated [18]. GTE is an excellent source of phenolic antioxidants including epicatechin, epigallocatechin, epicatechin-3-gallate, and -epigallocatechin-3-gallate (EGCG) [18,19]. Several investigations suggested that GTE catechins attenuate dyslipidemia and improve glucose homeostasis in type 2 DM (T2DM) patients by inhibiting

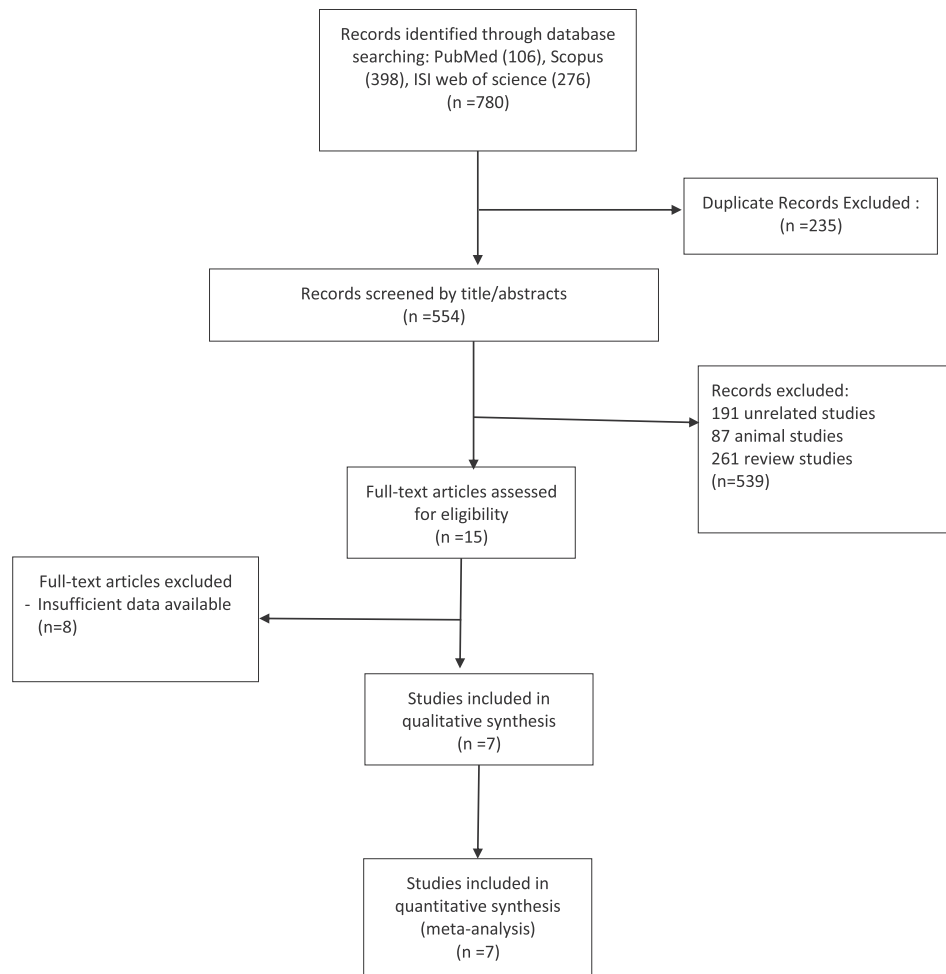


Fig. 1. Flow diagram of the literature search.

Table 2
Characteristic of the included studies in meta-analysis.

Author	Year	Country	Study design	sex	Mean age (intervention/control)	Trial duration	Daily dose of GT	Sample size (intervention/control)	BMI (intervention/control)
Y, Fukino, et al. [28]	2008	Japan	Cross-over	F/ M	53.9/53.4	2 months	544 mg GT polyphenols	60/60	25.4/26
T, Nagao, et al. [29]	2009	Japan	Parallel	F/ M	64.9/62.8 64.9/62.8	4 weeks 8 weeks 12 weeks	582.8 mg of GT catechins	23/20 23/20 23/20	25.6/24 25.6/24 25.6/24
S, Mohammadi, et al. [30]	2010	Iran	Parallel	F/ M	55.14/55.14	8 weeks	1500 mg GT extract	29/29	28.64/29.37
C.H, Hsu, et al. [31]	2011	Taiwan	Parallel	F/ M	50.5/52.2	16 weeks	1500 mg GT extract	35/33	NR
A, Mousavi, et al. [32]	2013	Iran	Parallel	F/ M	54.6/52 56.2/52	8 weeks	10000 and 5000 mg of GT	26/14 25/14	27.4/28.1 28.1/28.1
C.Y, Liu, et al. [33]	2014	Taiwan	Parallel	F/ M	55.06/53.56	16 weeks	500 mg GT extract	46/46	NR
P, Quezada-Fernández et al. [34]	2019	Mexico	Parallel	F/ M	50.2/56.1	12 weeks	400 mg of GT extract	10/10	29.8/30.4

F, female; M, male; NR, not reported; GT, green tea; BMI, body mass index.

intestinal glucose uptake, increasing tyrosine phosphorylation, and decreasing gene expression of both the gluconeogenic enzymes, and cholesterol 7 α -hydroxylase [20,21]. However, clinical trials have indicated controversial results regarding the efficacy of GTE or its components in improving the lipid profile in T2DM patients. Nagao et al., demonstrated that a catechin-rich beverage

significantly decreased triglyceride or total cholesterol compared with the control group [22]. However, several studies reported that supplemental intake of GTE had no significant effect on HDL-C, LDL-C, triglyceride or total cholesterol concentrations in T2DM patients [23–25]. Thus, we aimed to conduct a systematic review and meta-analysis to pool data from randomized controlled trials (RCTs) that

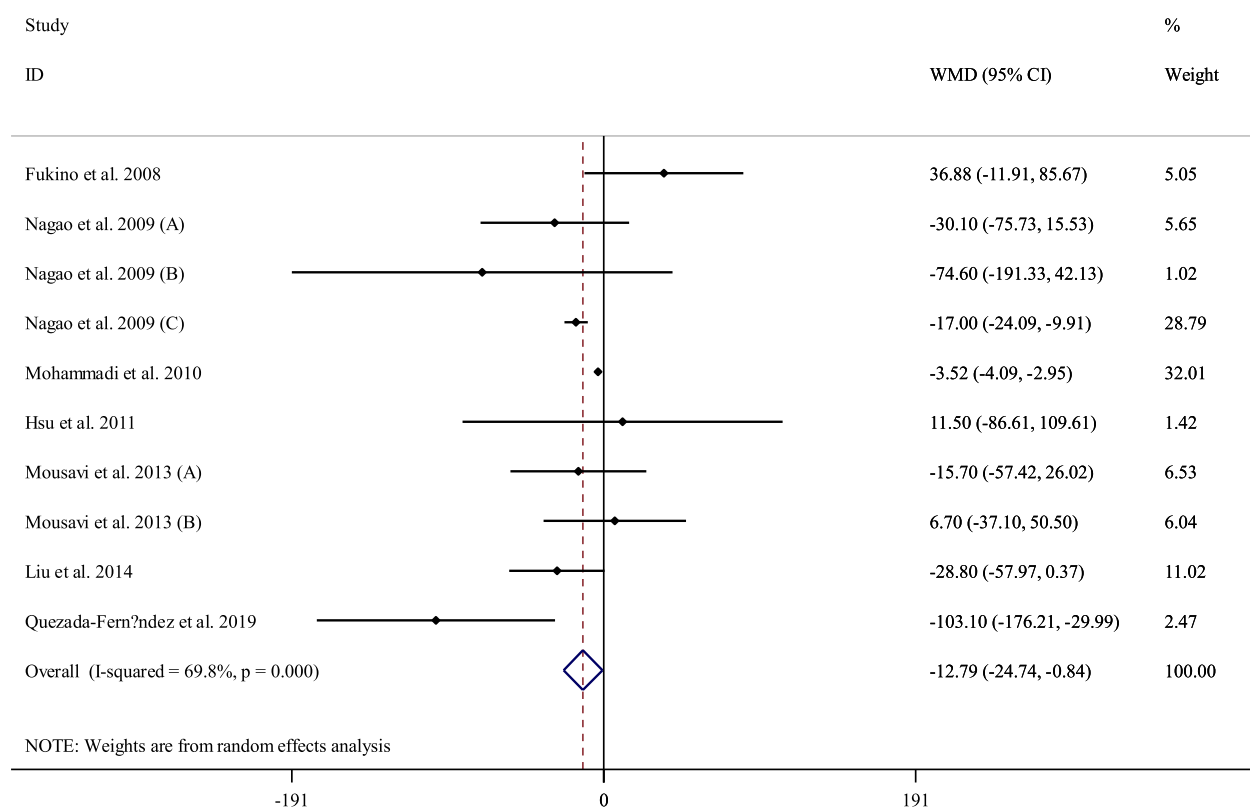


Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of green tea supplementation on serum triglyceride concentrations.

Table 3
Subgroup analyses.

	NO	WMD (95%CI)	P within group	P heterogeneity	I ² (%)
Subgroup analyses of green tea supplementation on serum TG concentrations.					
Trial duration (week)					
≤8	4	-2.74 (-9.95, 4.46)	0.456	0.366	5.4%
>8	6	-26.82 (-45.33, -8.32)	0.004	0.200	31.4%
Green tea dosage (mg/d)					
<800	6	-23.26 (-47.06, 0.53)	0.055	0.037	57.8%
≥800	4	-3.52 (-4.09, -2.94)	<0.001	0.890	0.0%
Subgroup analyses of green tea supplementation on serum TC concentrations.					
Trial duration (week)					
≤8	3	3.11 (-5.25, 11.49)	0.466	0.550	0.0%
>8	6	-11.14 (-20.93, -1.34)	0.026	<0.001	84.5%
Green tea dosage (mg/d)					
<800	5	-14.25 (-23.70, -4.80)	0.003	0.001	0.699
≥800	4	4.36 (-2.34, 11.06)	0.202	0.699	0.0%
Subgroup analyses of green tea supplementation on serum LDL concentrations.					
Trial duration (week)					
≤8	4	0.49 (-4.21, 5.19)	0.838	0.382	2.0%
>8	3	-1.89 (-8.18, 4.38)	0.554	0.020	74.3%
Green tea dosage (mg/d)					
<800	3	-0.04 (-5.38, 5.29)	0.987	0.032	71.0%
≥800	4	-0.68 (-5.99, 4.63)	0.801	0.231	30.2%
Subgroup analyses of green tea supplementation on serum HDL concentrations.					
Trial duration (week)					
≤8	2	-9.80 (-26.57, 6.96)	0.252	<0.001	98.2%
>8	3	1.12 (-1.16, 3.42)	0.336	0.294	18.4%
Green tea dosage (mg/d)					
<800	3	0.89 (-1.87, 3.67)	0.526	0.146	48.1%
≥800	2	-9.56 (-26.84, 7.72)	0.278	<0.001	98.1%

TG, triglycerides; TC, total cholesterol; LDL, low-density lipoproteins; HDL, high-density lipoproteins; WMD, weighted mean difference; CI, confidence interval.

assessed the effect of GTE on lipid profile in patients with T2DM. To the best of our knowledge, this is the first systematic review and meta-analysis in this field.

2. Methods

2.1. Literature search and selection

Present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [26]. A comprehensive and systematic literature search was carried out through the Web of Science, PubMed, and Scopus databases until August 2019. There were no language and time restrictions. Systematic search was conducted using the following search terms: ("green tea" OR "green tea extract" OR "green tea extract AR25" OR "catechin" OR "catechins" OR "EGCG" OR "Camellia sinensis" OR "tea polyphenols" OR "catechinic acid" OR "acid catechinic" OR "sinensis Camellia" OR "Thea sinensis" OR "sinensis Thea" OR "tea polyphenols") AND ("Type 2 diabetes" OR T2DM OR diabetes) AND (Intervention OR "Intervention Study" OR "Intervention Studies" OR "controlled trial" OR randomized OR randomized OR random OR randomly OR placebo OR assignment OR "clinical trial" OR Trial OR assignment OR "randomized controlled trial" OR "randomized clinical trial" OR RCT OR blinded OR "double blind" OR "double blinded" OR trial OR "clinical trial" OR trials OR "Pragmatic Clinical Trial" OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR parallel OR "parallel study" OR "parallel trial"). Electronic database searches were completed with reference list and citation check.

2.2. Eligibility criteria

Two investigators (FF and SM) selected eligible articles separately by reading titles, abstracts and whenever required the full-text of the publications. Any disagreements in this regard were resolved through discussion with the third researcher (AA). All human RCTs (either parallel or cross-over designs) which reported the effect of GTE on lipid profile (HDL-C, LDL-C, triglyceride or total cholesterol) in patients with T2DM were included. Following studies were excluded: (1) RCTs with treatment duration less than 2 weeks, (2) studies without any comparing control group.

2.3. Data extraction

The following data were extracted from the full-text of the included studies using a pre-designed abstraction form: first author's name, publication year, location of the study, study design and blinding, total sample size, study duration, patient characteristics (age, gender, and diseases), type and dose of intervention and placebo, and the ultimately result of lipid profile comparisons. In cases of lack of relevant data, we contacted the corresponding authors via e-mail to get their help. The whole process of data extraction was undertaken independently by two investigators (RC and DA) to minimize potential errors. If there was a disagreement, it was resolved by consensus.

2.4. Quality assessment of studies

We used Cochrane Collaboration's tools for quality assessment of the included studies [27]. The tool separates a judgment about the risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias. Two researchers (OA and FF) independently evaluated the methods and the quality of the eligible studies through Cochrane Collaboration's tools, which includes seven domains: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other sources of bias. For each item in the tool, the assessment of risk of bias is in two parts. The support for judgment provides a succinct free text description or summary of the relevant trial characteristic on which judgments of risk of bias are based and aims to ensure transparency in how judgments are reached [27]. Moreover, each scope was further classified into three classes: low risk, high risk, and unclear risk of bias. According to the guidelines, the general quality of each study was considered as good (low risk for more than two cases), fair (low risk for two cases) or weak (low risk for less than two cases) [27] (Table 1).

2.5. Meta-analysis of data

To analyze the effect size for lipid profile, the mean change and its standard deviation for intervention and control groups (as comparison group) were extracted. A random effects model was used to calculate weighted mean differences (WMDs) with 95% confidence intervals (CIs). Between-study heterogeneity was tested by Cochran's Q test and quantified by I² statistic. A subgroup analysis based on the dose and duration of intervention was conducted to detect potential sources of heterogeneity. Between-subgroup heterogeneity was assessed using a fixed effect model. Sensitivity analysis was conducted by removing each study one by one and recalculating the pooled evaluations. Begg's rank correlation test and Egger's regression asymmetry test were performed for detecting potential publication bias. Statistical analysis was conducted using STATA, version 11.2 (Stata Corp, College Station, TX).

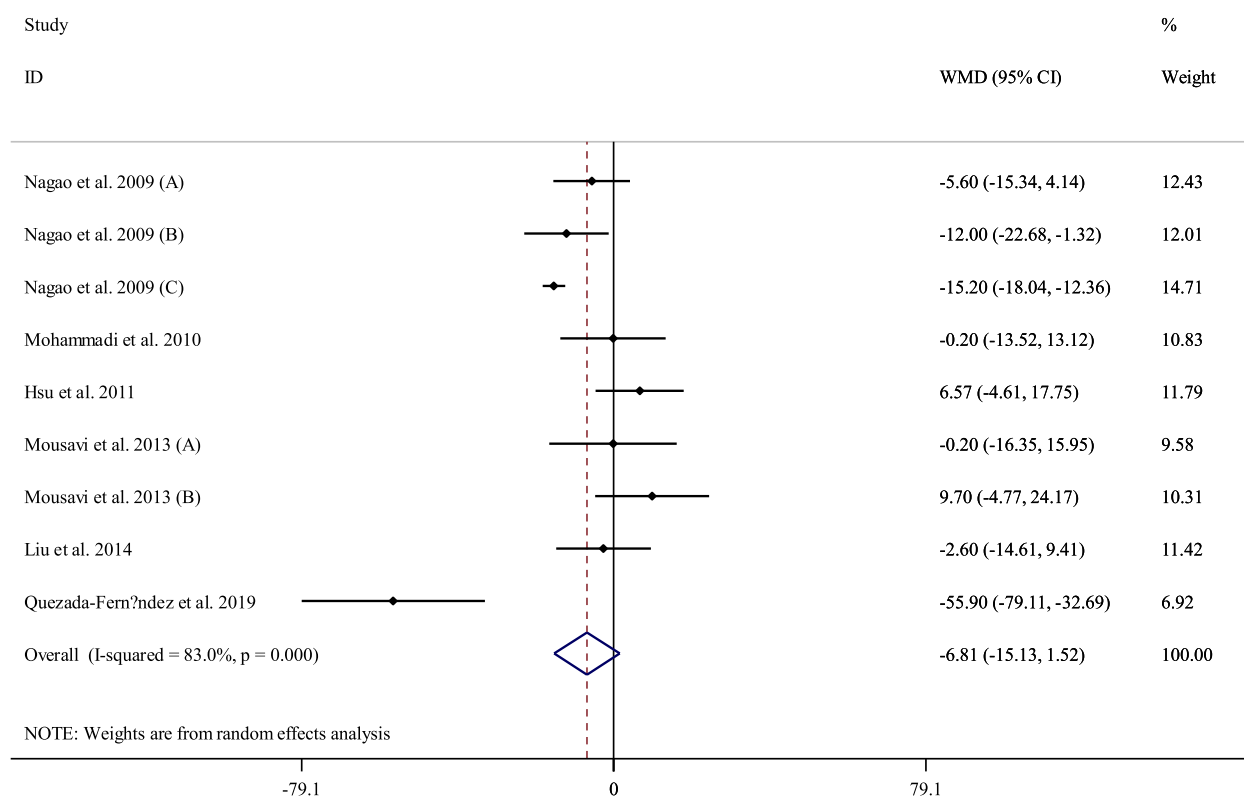


Fig. 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of green tea supplementation on serum total cholesterol concentrations.

The statistical significant value was defined as P values < 0.05 .

3. Results

3.1. Search result and systematic review

Flow diagram of the search process is illustrated in Fig. 1. In total 780 publications were found from databases search. Of these 235 publications were duplicates. Then, we screened 554 records based on title/abstract. 539 articles were excluded because of following reasons: 1) unrelated issue ($n = 191$), animal studies ($n = 87$) and review studies ($n = 261$). In the next step, 15 articles were remained for full-text assessment. Of 15 articles, 8 articles were excluded due to insufficient data available. Finally, 7 articles [28–34] were eligible to include to this meta-analysis.

3.2. Findings from systematic review

Main characteristics of the eligible studies are illustrated in Table 2. The mean age of patients ranged from 50.2 to 64.9 years. Included studies were conducted between 2008 and 2019 in Japan [28,29], Iran [30,32], Taiwan [31,33] and Mexico [34]. The number of subjects in the intervention group was 300 and in the control group was 212. The mean BMI of participants ranged from 24 to 30.4 kg/m². All the studies were performed on both sexes [28–34]. Trial duration ranged from 4 to 16 weeks and daily dose of GTE varied between 400 and 10000 mg/d.

3.3. Meta-analysis results

3.3.1. Effect of green tea extract supplementation on serum concentrations of TG

The effect of GTE supplementation on serum concentration of TG has been investigated in 7 studies (10 effect sizes) including 512 subjects (300 intervention and 212 controls). Pooled effect size from the random-effects model demonstrated that GTE supplementation significantly decreased TG serum concentrations (WMD: -12.79 mg/dl, 95% CI: $-24.74, -0.84$, $p = 0.036$; $I^2 = 69.8\%$, $p = 0.000$) (Fig. 2). Due to the considerable heterogeneity, we stratified studies regarding the dose (<800 vs. ≥ 800 mg/d) and the duration of intervention (≤ 8 vs. >8 weeks). Subgroup analysis showed that GTE supplementation reduced serum TG concentrations in doses ≥ 800 mg/d (WMD: -3.52 mg/dl, 95% CI: $-4.09, -2.94$, $p < 0.001$) and longer than 8 weeks (WMD: -26.82 mg/dl, 95% CI: $-45.33, -8.32$, $p = 0.004$). Results of subgroup analysis are presented in Table 3.

3.3.2. Effect of green tea supplementation on serum concentrations of TC

Seven trials (9 effect sizes) including a total of 512 subjects (300 intervention and 212 controls) reported serum concentrations of TC as an outcome measure. Pooled results by the random-effects model indicated that the GTE supplementation had no significant effect on serum TC concentrations (WMD: -6.81 mg/dl, 95% CI: $-15.13, 1.52$, $p = 0.109$; $I^2 = 83.0\%$, $p = 0.000$) (Fig. 3). The subgroup analysis demonstrated that doses of GTE lower than

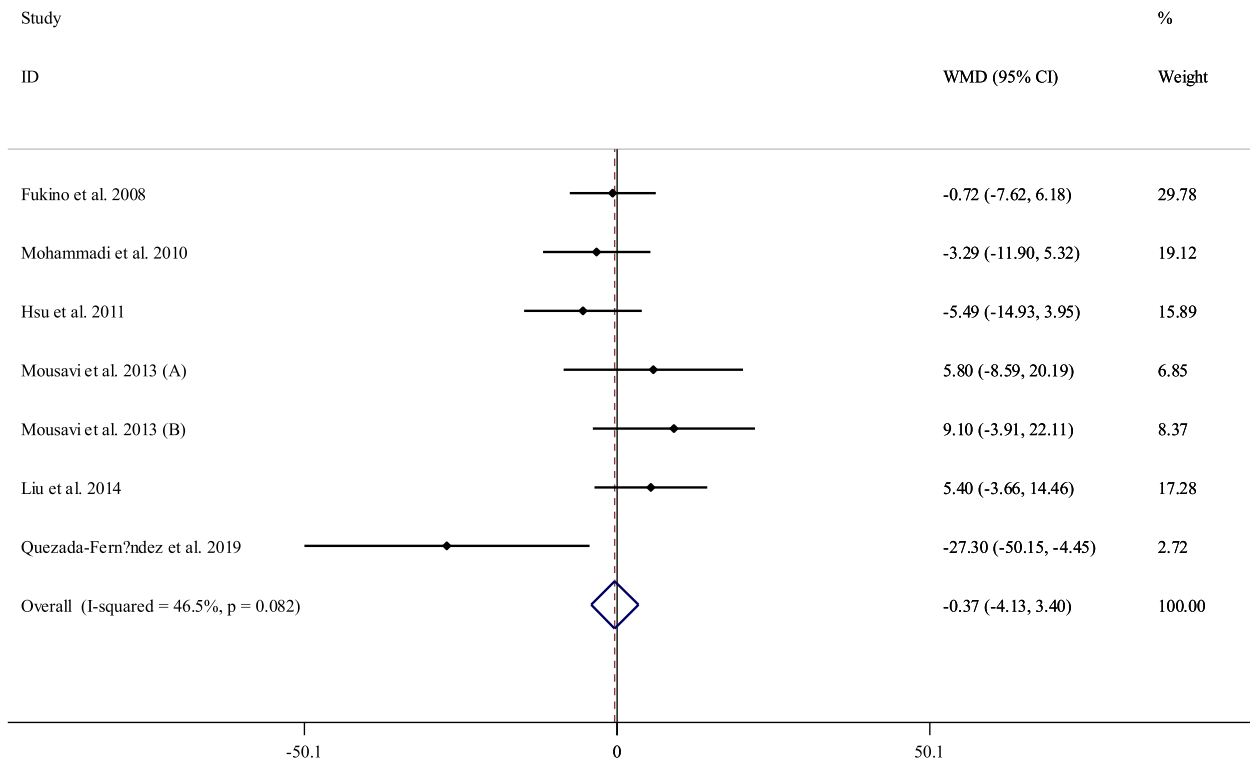


Fig. 4. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of green tea supplementation on serum low-density lipoprotein concentrations.

800 mg/d (WMD: -14.25 mg/dl, 95% CI: -23.70 , -4.80 , $p = 0.003$) and trial duration longer than 8 weeks (WMD: -11.14 mg/dl, 95% CI: -20.93 , -1.34 , $p = 0.026$) resulted in a significant reduction in serum TC concentrations.

3.3.3. Effect of green tea supplementation on serum concentrations of LDL

Pooled results of six studies (7 effect sizes) including 469 participants (277 intervention and 192 controls) showed that GTE supplementation had no significant effect on LDL concentrations (WMD: -0.37 mg/dl, 95% CI: -4.13 , 3.40 , $p = 0.849$; $I^2 = 46.5\%$, $p = 0.082$) (Fig. 4). The results of subgroup analysis based on duration and dose of intervention also did not show a significant effect on LDL concentrations.

3.3.4. Effect of green tea supplementation on serum concentrations of HDL

Six trials (5 effect sizes) including a total of 469 participants (277 intervention and 192 controls) provided data on HDL concentrations as an outcome measure. Pooled results showed that GTE supplementation had no significant effect on HDL serum concentrations (WMD: -3.10 mg/dl, 95% CI: -10.16 , 3.95 , $p = 0.389$; $I^2 = 95.4\%$, $p = 0.000$) (Fig. 5). In the subgroup analysis we also did not observe any significant effect.

3.3.5. Publication bias

Publication bias assessment by Egger's linear regression test showed no publication bias in the included studies for LDL

($p = 0.670$) and HDL concentrations ($p = 0.943$). However, there was a significant publication bias for serum TG ($p < 0.001$) and TC concentrations ($p = 0.007$). Visual inspection of funnel plot also showed the same (Supplemental Figs. 1A–D).

4. Discussion

The results of our meta-analysis showed that the supplementary intake of GTE may improve lipid profile by reducing serum TG concentrations in patients with T2DM. Meanwhile, subgroup analyses based on duration of interventions (≤ 8 and > 8 weeks) and intervention dosage (≤ 800 and > 800 mg/day) showed that the GTE supplementation longer than 8 weeks and in doses > 800 mg/day, resulted in a significant decrease in serum TG concentrations. Furthermore, intervention longer than 8 weeks with doses lower than 800 mg/day resulted in a significant reduction in serum TC concentrations. However, our analysis failed to find any significant effects of GTE supplementation on serum LDL and HDL concentrations.

Several epidemiological studies [35–40] have shown that the high serum concentrations of TC, TG, LDL, and low circulating levels of HDL, are major risk factors for CVD among diabetic patients. Dyslipidemia is the underlying cause of atherosclerosis and CVD in diabetic patients [41]. Therefore, treatment of dyslipidemia in diabetic patients can prevent cardiovascular complications of the disease [42]. Nowadays, different treatments, such as pharmacotherapy and diet therapy, are available to improve lipid profile in patients with diabetes. Statins are effective in reducing

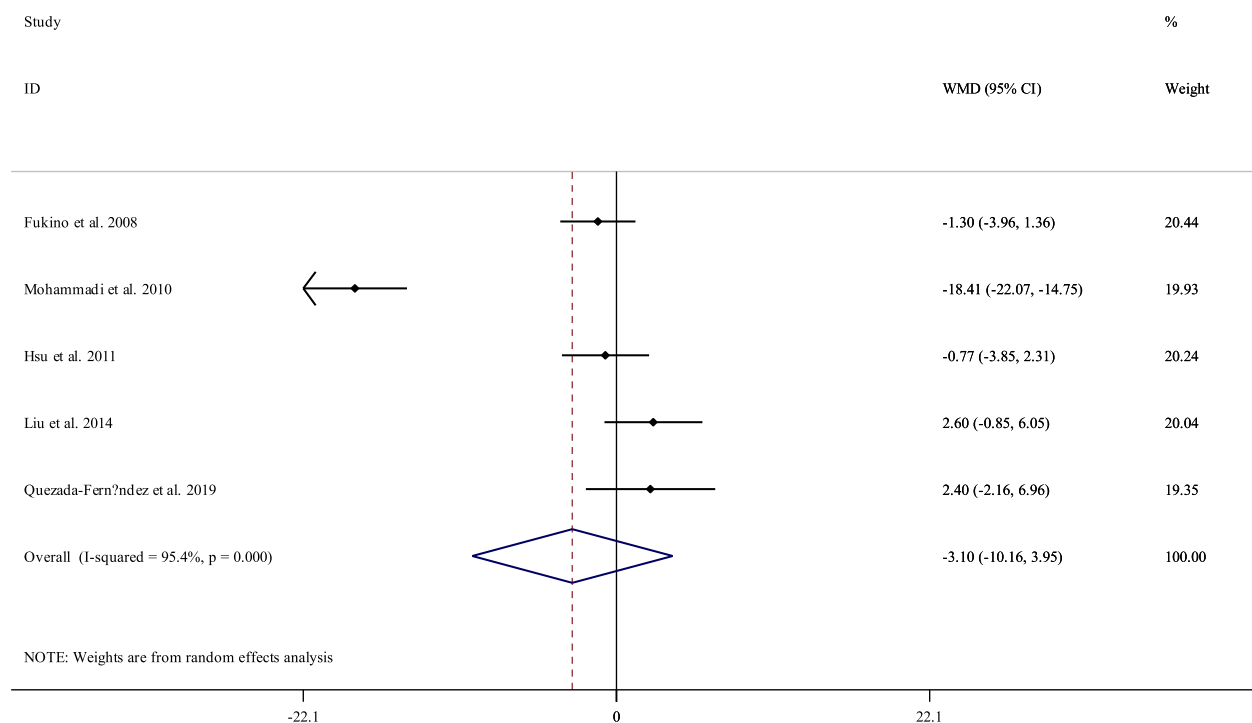


Fig. 5. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of green tea supplementation on serum high-density lipoprotein concentrations.

cardiovascular events and are safe for almost all patients. However, some patients unable to tolerate daily statin therapy [43,44]. Today, many treatments that involve the use of medicinal plants are recommended [45]. Among them GTE has gained significant popularity as a plant-based natural therapy which contains catechins (such as epigallocatechin-3-gallate [EGCG]), polyphenols, theanine, caffeine, chlorogenic acid and gallic acid [17]. Previous studies demonstrated that the GTE supplementation may improve lipid profile in healthy subjects [46] and patients with T2DM [47]. The protective effects of GTE for preventing CVD have been attributed to the high content of flavonoids, especially catechins, which are potent antioxidants [17,48]. One of these catechins high in GTE is epigallocatechin [49]. Numerous in vitro studies showed that epigallocatechin exerts have a protective effect against lipoprotein oxidation, namely, against LDL oxidation [46]. The GTE can improve lipid profile by reducing micellar solubility and intestinal absorption of cholesterol, and reducing hepatic cholesterol concentration [50,51]. GTE has been reported to decrease blood lipids, especially cholesterol, in streptozotocin-diabetic rats, and this effect was dose-dependent [52]. In addition, a possible mechanism involved in the decreasing effects of GTE on lipid profile is its anti-obesity property. Previous studies indicated that weight reduction can improve lipid profiles [53]. Previous meta-analysis showed that weight reduction can be a viable approach to help normalize plasma lipids by decreasing serum concentrations of TG, TC and LDL and enhancing HDL [54,55]. Most studies have reported that GTE supplementation can reduce body weight [56,57]. However, in most cases, the weight reduction effect of GTE was small [58]. It should be noted that the anti-obesity effect of GTE is influenced by

the amount of caffeine and ethnicity [58].

Although the majority of evidences in animal studies showed that GTE supplementation have hypolipidemic effects in diabetic rats [52,59], these effects have not showed in most human trials. In human studies, daily supplementation of GTE with a low-fat diet in mild-to-moderate hypercholesterolemic adults, decreased their total cholesterol, LDL-C, HDL-C, and triglyceride concentrations [60]. However, other studies with even one year supplementation of GTE capsules without a low-fat diet, showed no significant change in the lipid profile of diabetic patients [25]. The controversial results regarding the effects of GTE on lipid profile may be due to differences in the doses of GTE prescribed and the duration of supplementation in the studies. Some previous studies have shown that the decreasing effect of GTE on serum TC concentrations was observed in long-term interventions [22]. Nagao et al. [22], assessed the effect of catechins supplementation in patients with T2DM at weeks 4, 8 and 12. They reported that the reducing effect of the catechins on serum TC concentrations was significantly greater at week 12, and no significant changes were observed in short-term supplementations (4 and 8 weeks). In contrast, in another study by Quezada-Fernandez et al., GTE had no significant effect on serum TG and TC concentrations after 12-week [23]. Results of our subgroup analysis indicated that the long-term supplementation of GTE may improve serum TG and TC concentrations in patients with T2DM. Some of the previous meta-analyses confirmed that GTE supplementation may improve lipid profile. Onakpoya et al. [61] showed that GT intake resulted in significant reductions in serum concentrations of total cholesterol, and LDL cholesterol. Their meta-analysis was performed on both healthy

population and people with metabolic disorders. The limitation of previous meta-analyses was that their results were based on pooled data from non-specific populations [62,63]. Obviously, if a meta-analysis is not performed exclusively on specific patients, it is not often conclusive [64]. Since the results of the previous meta-analyses were not specific to patients with diabetes, the results cannot be generalized to these patients. Contrary to previous meta-analyses, our results are based on RCTs performed only in patients with diabetes. Our meta-analysis showed that the supplementary intake of GTE longer than 8 weeks and in doses >800 mg/day, resulted in a significant decrease in serum TG concentrations in patients with T2DM. In contrast, for TC, intervention longer than 8 weeks with doses lower than 800 mg/day was statistically effective. Furthermore, based on our results, GTE improves TC but not LDL levels in patients with T2DM. These controversial results maybe because of the difference in the dose and duration of these studies [51], caffeine content of GTE, ethnicity [65] and baseline blood lipid levels of participants. Moreover, the low number of studies in each subgroup may affect these results. However, these findings may suggest that daily consumption of GTE longer than 8 weeks is most beneficial for lowering TG and TC. Further research are needed to determine whether GTE supplements are able to improve lipid profile in patients with T2DM or not.

Our systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of GTE on lipid profile in T2DM patients. Second, we included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. Third, this review is based on an up to date literature search from a large number of databases. An important limitation of this meta-analysis is the low number of trials which were included in our analysis that limits the strength of the conclusion of the present meta-analysis; however, we hope this study will be helpful for future studies.

In conclusion, present systematic review and meta-analysis revealed that the supplementary intake of GTE may improve lipid profile by reducing serum TG concentrations in patients with T2DM. Furthermore, the results of our stratified analyses suggested that long-term GTE intervention may reduce serum TG and TC concentrations. However, additional long-term and well-designed RCTs are needed to confirm these findings.

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There are no financial or other competing interests for principal investigators, patients included or any member of the trial.

Author contributions

AA and OA designed the study. FF and SM reviewed and selected the articles. RC and DA extracted needed data from articles. AA and OA performed data analysis and interpretation. AA drafted the manuscript.

Declaration of competing interest

The authors declare that no conflict of interest exists.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dsx.2020.03.018>.

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