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The effect of green tea on C-reactive protein and biomarkers of oxidative stress in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Introduction: The beneficial effects of green tea on regulating insulin sensitivity and preventing the development of type 2 diabetes mellitus (T2DM) have been identified.

Objectives: We aimed to investigate the effect of green tea on serum levels of C-reactive protein (CRP) and biomarkers of oxidative stress in patients with T2DM.

Methods: A systematic search was performed in the ISI Web of science, PubMed and Scopus to find articles related to the effect of the green tea on CRP, malondealdehyde (MDA) and total antioxidant capacity (TAC) in T2DM patients, up to June 2019. There was no language and time limitation. Meta-analyses were performed using both the random and fixed effects model where appropriate, and I2 index was used to evaluate the heterogeneity.

Results: Initial search yielded 780 publications. Eight articles with 614 T2DM patients were eligible. Following green tea consumption, CRP levels significantly decreased (weighted mean difference (WMD): −5.51 mg/dl, 95% CI: −9.18 to −1.83, $p = 0.003$) compared with the controlled group. Green tea consumption had no significant effect on plasma levels of TAC and MDA (0.02 mg/dl, CI: −0.06 to 0.10; −0.14 mg/dl, CI: −0.40 to 0.12; respectively).

Conclusion: This systematic review and meta-analysis indicated that green tea significantly reduced the circulating levels of CRP, whereas, it had no significant effect on MDA and TAC. Overall, green tea can be considered as a healthy drink to reduce CRP levels in T2DM patients.

1. Introduction

Type 2 diabetes mellitus (T2DM), which accounts for 95% of all cases of diabetes, is a major global health challenge that is characterized by the abnormalities in the metabolism of carbohydrate, lipid and protein, resulting from an insufficient secretion of insulin and insulin resistance.[1] T2DM is associated with major comorbidities such as cardiovascular disease (CVD), retinopathy, nephropathy, and peripheral nerve damages.[2] It is well known that hyperglycemia increases the production of free radicals and consequently oxidative stress.[3] While increased oxidative stress has been shown to be associated with the progression of diabetes-related complications, the mechanisms by which this occurs are still not fully understood.[4,5] Diabetes is not considered an immune disease; however, increasing evidence suggests an effective role of inflammation in type 1 and type 2 diabetes.[6] One of the most known inflammatory mediators is the C-reactive protein (CRP).[7] CRP is a part of the innate immunity which can activate the classical complement pathway.[8] It is well known that the CRP has pro-atherogenic properties.[9] Epidemiological studies indicated that CRP is an important biomarker to predict the incident of CVD.[10] It also can increase the expression of pro-inflammatory cytokines such as IL-6 in human endothelial cells.[11]

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The management of T2DM commonly depends on lifestyle intervention, medication, and complementary and alternative treatment (CMT).[12] According to the literature green tea is suggested as a modulator of insulin sensitivity and inhibitor of the T2DM development.[13] Green tea is provided from fresh leaves of Camellia sinensis.[14] The main biological components of the green tea extracts is polyphenolic compound called epicatechins.[14] Increased oxidative stress and inflammation induced by hyperglycemia in T2DM, can be modulated by antioxidant propertied of green tea.[13] Therefore, green tea could have a significant therapeutic effect in the management of T2DM.[13] Experimental studies have shown the antidiabetic effects of green tea extract, which is assumed to be due to its antioxidant activity.[15] However, epidemiologic studies which have investigated the relationship between green tea consumption and both the insulin resistance and the glycemic control have always shown inconsistent findings.[16–18] Moreover, results of the randomized, controlled trials (RCTs) assessed the effects of green tea supplementation on inflammation and oxidative stress in T2DM are controversial. A study by Mousavi et al [19] reported that green tea consumption had no significant effect on the oxidative stress parameters of diabetic patients. Whereas, another study indicated that green tea is capable of reducing oxidative damage in diabetic patients with complications.[20] Due to the inconsistent results found in the literature, we performed a systematic review and meta-analysis of RCTs to assess the effect of green tea on CRP and biomarkers of oxidative stress in patients with T2DM.

2. Method

The present systematic review and meta-analysis adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline.[21]

2.1. Search strategy

We systematically searched electronic databases including the ISI Web of science, PubMed and Scopus to detect RCTs that evaluated the effect of green tea on CRP and biomarkers of oxidative stress in patients with T2DM, until June 2019; without any language and date restriction. The merge of MESH and non-MESH terms were used as follows: ("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). Also, we manually checked all reference lists of included articles and related reviews to avoid missing any relevant studies.

2.2. Including and excluding criteria

The following criteria were considered as including criteria: 1) RCTs that were conducted on T2DM patients, 2) RCTs included adult subjects (≥18 years old), 3) RCTs that provided sufficient data on baseline and final measures of CRP and biomarkers of oxidative stress in both green tea and control groups. Studies were excluded if they; 1) were done on children, animal and subjects without T2DM, 2) were not RCT, 3) did not provide sufficient information for the outcomes in green tea or control groups.

2.3. Data extraction

Two investigators (OA and FF) individually screened the records. Two authors (VA and RC) extracted the data, any disagreements were resolved under a chief investigator (AA). The following data were extracted from each study; first author's name, publication year, study design, region of the study, study duration, mean age and sex of the participants, sample size in each group, mean and SD of outcome measures at the baseline and the final stage of the study.

2.4. Quality assessment

We evaluated the quality of eligible studies by using the Cochrane scoring system.[22] This scoring system includes 7 criteria to evaluate the risk of bias: 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 source of biases. After evaluating the studies based on these items, each item takes one of the following points: (1) high risk, (2) low risk, and (3) unknown risk. All the selected articles were scored by 2 authors (VA and RC). Disagreement between the authors was resolved by a third assessor (AA).

2.5. Data synthesis and statistical analysis

Effect sizes of all intended outcomes were expressed as weighted mean differences (WMDs) and 95% CI. The effect sizes were pooled exerting a random effects model with DerSimonian and Laird method.[23] The mean net changes (mean values ± standard deviation) of the CRP, malondealdehyde (MDA) and total antioxidant capacity (TAC) for each study were calculated. Mean changes for the outcomes listed above were calculated by the difference between the final and initial values for each data, in both groups. Standard deviations (SDs) of the mean were calculated using the following formula: SD = square root [(SD pre-treatment) 2 + (SD post-treatment) 2 – (2 × 0.8 × SD pre-treatment × SD post- treatment)].[22] When standard error of the mean (SEM) was reported, standard deviation (SD) was estimated by using the following formula: SD = SEM × sqrt (n) (n is the number of subjects).[24] Heterogeneity between studies was evaluated by Cochrane's Q test (significance point at $p < 0.05$) and I^2 index. Publication bias assessment was conducted by using Egger's regression test. All statistical analyses were done using STATA software version 14 (STATA Corp, College Station, Texas). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Literature search

In the initial search in electronic databases, 780 relevant studies were detected. After removing duplicates (n = 35), 554 articles remained for evaluating based on title and abstract. Then, 529 articles were excluded due to animal (n = 87), review (n = 261) and unrelated study (n = 191. In the next step, 15 articles were eligible for full-text evaluation. Finally, 7 articles were removed for failing to report the required data and 8 articles[19,20,25–30] were included in the present meta-analysis. The flow diagram of the selected studies is presented in Fig. 1.

3.2. Characteristics of included studies

Table 1 outlines the main characteristics of the eligible studies. These 8 articles were done between 2005 and 2016. The studies were conducted in the Japan,[25,26] Iran,[19,27] Lithuania,[20,28] Taiwan[29] and Brazil.[30] The trial sample size ranged from 31[28] to 120 [26] patients, and conducted on both gender. Participant's age ranged from 52[19] to 62.18[20] years old, and BMI ranged from 25.5 to 35.23 kg/m^2. Intervention duration were between 2 [19,25–27] and 9 [20,28] months and green tea dosage were between 400[20,28] and 5000[19] mg. The design of all the studies were parallel.

3.3. Quality assessment

The assessors agreed on 42 of the 56 items, resulting in 75%

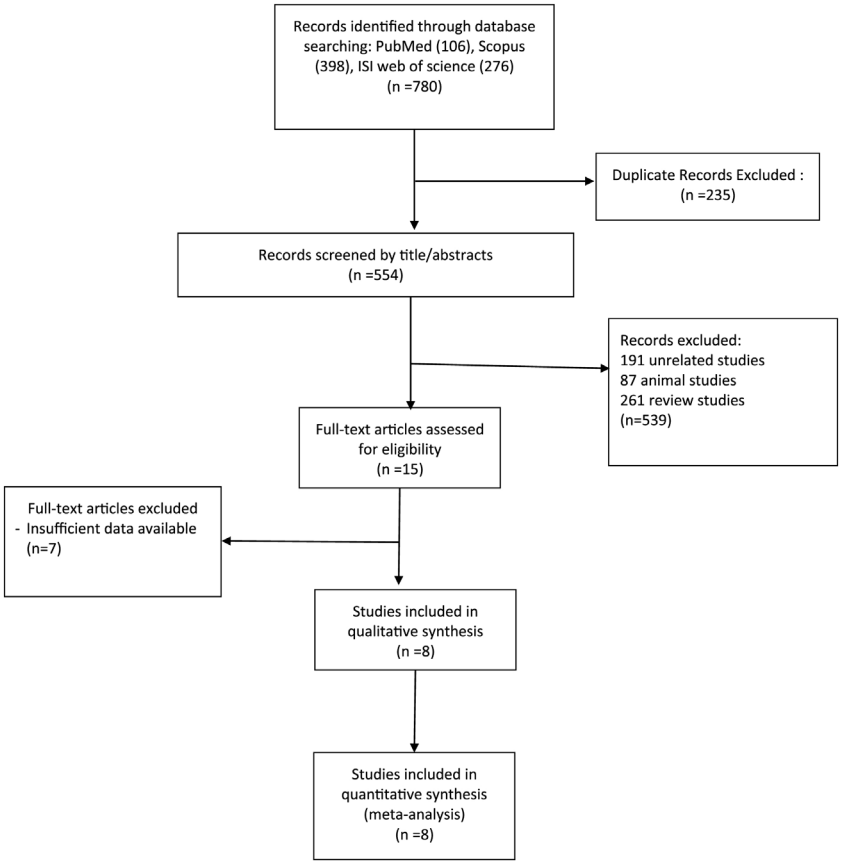

Fig. 1. Flow chart of selection of studies for inclusion in meta-analysis.

agreement rate. After discussion and consulting with a third assessor (AA), 100% agreement was reached. All the studies did provide a sufficient information about random sequence generation. However, all the studies did not provide an enough available information about allocation concealment. Four trials[19,25–27] showed high risk of bias in relation to blinding of participants and personnel. All the trials had a low risk of bias in the incomplete outcome data item. Details of the quality of bias assessment are illustrated in Table 2.

3.4. The effect of green tea on serum levels of CRP

Fig. 2 shows the forest plot of the pooled effect of green tea consumption on plasma CRP levels. There were 5 trials with 383 patients (intervention group = 191 and controlled group = 192) that compared CRP levels between green tea and controlled group. Following green tea consumption, CRP levels significantly decreased (weighted mean difference (WMD): −5.51 mg/dl, CI%: −9.18 to −1.83, $p = 0.003$) compared with controlled group. The between-study heterogeneity was significant ($I^2 = 96.1\%$, $p < 0.001$). There was no evidence of publication bias, based on egger's regression test ($p = 0.113$).

3.5. The effect of green tea on serum levels of TAC

Fig. 3 shows the forest plot of the pooled effect of green tea intake on plasma TAC levels. We combined 6 effect sizes from 3 studies included 178 patients (intervention group = 125 and controlled group = 53). Result of analysis showed that green tea consumption had no significant effect on plasma TAC levels (WMD: 0.02 mg/dl, CI%:

Table 1
Characteristic of the included studies.

Author	Year	Country	Study design	sex	Mean age (intervention / control)	Trial duration	Daily dose of GT (mg)	Sample size (intervention / control)	BMI (intervention / control)
Y, Fukino	2005	Japan	Parallel	F/M	53.5/53.5	2 M	554	33/33	25.5/25.9
Y, Fukino	2008	Japan	Parallel	F/M	53.9/53.4	2 M	544	60/60	25.4/26
S, Mohammadi	2010	Iran	Parallel	F/M	55.14/55.14	8 W	1500	29/29	28.64/29.37
A, Mousavi	2013	Iran	Parallel	F/M	54.6/52	8 W	10000	26/14	27.4/28.1
					56.2/52		5000	25/14	28.1/28.1
L, Lasaite	2014	Lithuania	Parallel	F/M	57.2/56.8	9 M	400	17/14	NR
					57.2/56.8		600	17/14	
C.Y, Liu	2014	Taiwan	Parallel	F/M	55.06/53.56	16 W	500	46/46	NR
A, Spadiene	2014	Lithuania	Parallel	F/M	62.18/62.18	9 M	400	20/25	35.23/34.98
					62.18/62.18		600	20/25	35.23/34.98
C.M, Borges	2016	Brazil	Parallel	F/M	63/59	12 W	800	23/24	30.6/32.7

F, female; M, male; M, months, W, weeks; NR, not reported.

Table 2
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	L	U	H	H	L	U	L
Y, Fukino	L	U	H	H	L	U	L
S, Mohammadi	L	H	H	H	L	U	L
A, Mousavi	L	U	H	H	L	L	L
L, Lasaite	L	U	L	L	L	L	H
C.Y, Liu	L	U	L	U	L	U	L
A, Spadiene	L	H	L	H	L	U	H
C.M, Borges	L	U	L	L	L	L	L

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

−0.06 to 0.10, $p = 0.576$). A significant between-study heterogeneity was exist ($I^2 = 80.8\%$, $p < 0.001$). There was no evidence of publication bias based on egger's regression test ($p = 0.474$).

3.6. The effect of green tea on serum levels of MDA

We combined 4 effect sizes from 2 studies with 169 participants (intervention group = 91 and controlled group = 78). Results indicated that green tea consumption had no significant effect on plasma MDA levels (WMD: −0.14 mg/dl, CI%: −0.40 to 0.12, $p = 0.306$). There was no significant between-study heterogeneity ($I^2 = 8.9\%$, $p = 0.349$). Moreover, there was no evidence of publication bias based on egger's regression test ($p = 0.880$) (Fig. 4).

4. Discussion

In this meta-analysis of eight trials including 614 T2DM patients, we assessed the effect of green tea on CRP and oxidative stress biomarkers. Results of our meta-analysis demonstrated that green tea consumption significantly reduced the serum levels of CRP, whereas, it had no effect on both MDA and TAC.

The beneficial effects of green tea in many diseases such as CVD are related to its anti-inflammatory effects.[31,32] Green tea components can increase production of the anti-inflammatory cytokines such as IL-10, regulate synthesis and signaling of IL-6, decrease the pro-inflammatory cytokines such as IL-1β and TNF-α and decrease production of destructive matrix metalloproteinases through TNF-α induced phosphorylation of mitogen-activated protein kinases (MAPKs). Evidence suggest that the green tea catechins can downregulate several inflammatory cytokines and chemokines like IL-1α, IL-6, IL-8, CRP and interferon gamma (INF-γ).[33,34] A systematic review and meta-analysis revealed that the tea drinking appears to play a significant role in reducing inflammation.[32] One of the most important inflammatory factors that have a great clinical importance is CRP. Several epidemiological studies indicated that CRP is an important biomarker to predict the incident of CVD such as myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death.[10] These clinical data along with experimental and laboratory evidence suggest that the CRP is a stronger biomarker to predict CVD than the low-density lipoprotein cholesterol.[10] Results of our meta-analysis indicated that green tea reduced serum levels of CRP in T2DM patients. Therefore, green tea may reduce the risk of CVD in T2DM patients by lowering CRP levels in these patients. However, a meta-analysis of 11 RCTs indicated that the green tea catechins had no significant effect on plasma CRP concentrations.[35] In addition, a recent meta-analysis found that green tea leaves and extract decreased TNF-α, increased IL-6, and had no effect on CRP levels.[36] The authors concluded that green tea might not be able to modify inflammatory markers particularly in diseases with low inflammation.[36] The reasons for the discrepancy between the results of the meta-analyses regarding the effects of green tea on CRP could partly be due to

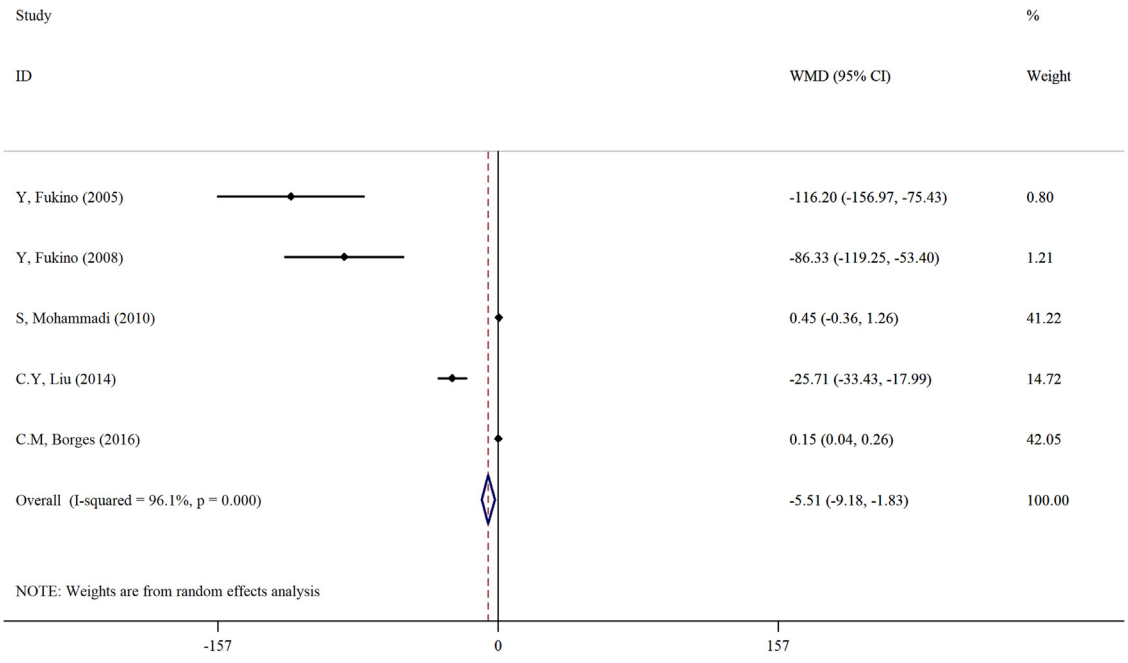

Fig. 2. Forest plot of the random-effects meta-analysis of the effect of the green tea on serum levels of C-reactive protein.

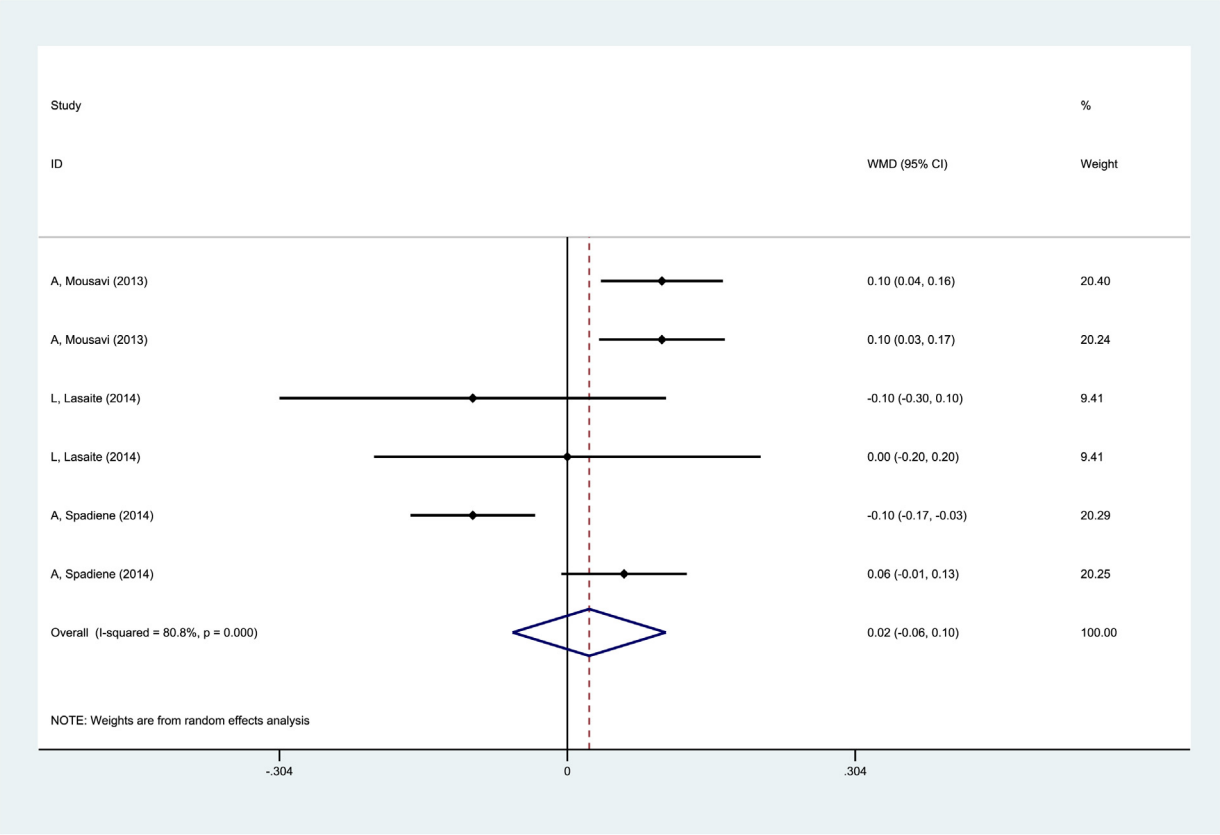

Fig. 3. Forest plot of the random-effects meta-analysis of the effect of the green tea on total antioxidant capacity.

the difference in participants included in these meta-analyses. Most of the previous meta-analyses had no restriction on the similarity of studies based on the types of participants and included both healthy subjects and patients with different types of diseases. It is well known that the existence of human interindividual polymorphism affects the bioavailability and metabolic fate of tea flavonoids.[35]

Several investigations have shown that green tea catechins can reduce reactive oxygen species (ROS) levels and increase TAC levels.[33,37,38] In addition, according to the results of experimental studies, the antidiabetic effects of green tea have been postulated to be due to its antioxidant activity.[13,39] However, in vitro studies indicated that the epigallocatechin-3-gallate (EGCG) at concentrations higher than 10 μM can induce ROS generation.[40] A study by Yin et al showed that EGCG induced primary cultures of rat hippocampal neurons death through

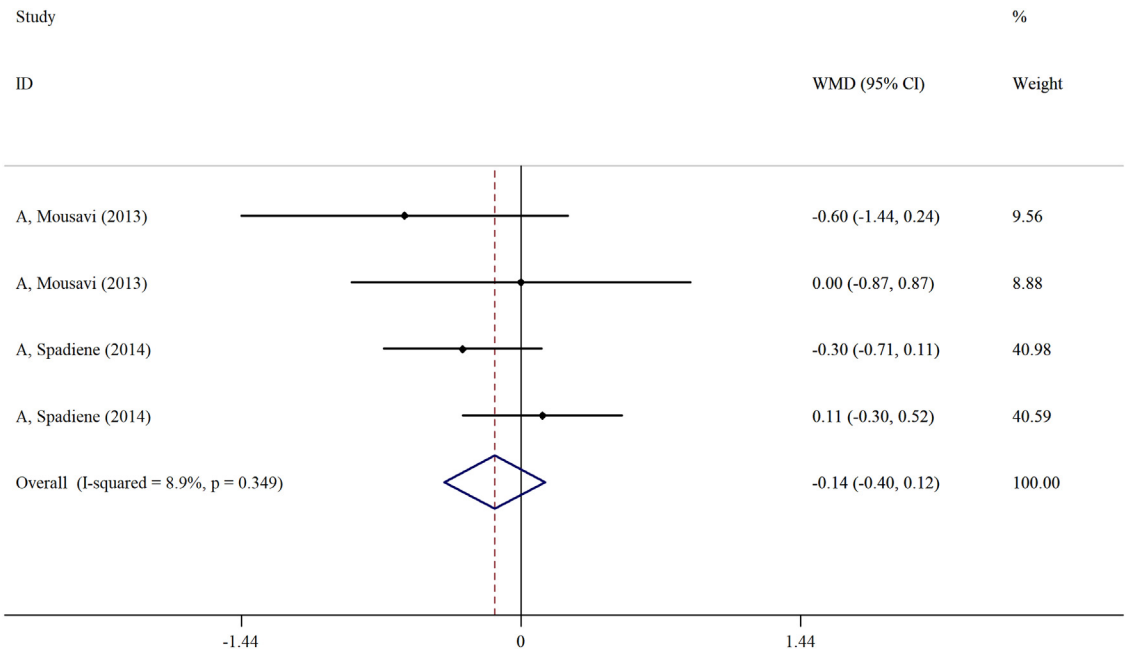

Fig. 4. Forest plot of the fixed-effects meta-analysis of the effect of the green tea on serum levels of malondealdehyde.

oxidative stress.[41] Another study reported that a four-day intraperitoneal treatment with EGCG (5 mg/kg/day) reduced the beta-cell response to the high glucose in the diabetic rats.[42] They indicated that EGCG increased the loss of islet cell mass and insulin-immunoreactivity in beta cells. They also suggested that EGCG had a pro-oxidant properties even at the nanomolar plasma concentrations in the beta cells.[42] Moreover, Mirzae et al reported that green tea consumption had no effect on the oxidative status of diabetic patients.[43] Results of our meta-analysis also indicated that green tea had no significant effect on TAC and MDA levels in T2DM patients.

Our systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of green tea on CRP and oxidative stress biomarkers in T2DM. 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 our meta-analysis is the low number of trials that were available for the meta-analysis which limits the strength of the conclusion of the present meta-analysis; however, we hope this study will be helpful for future studies.

In conclusion, this systematic review and meta-analysis indicated that green tea significantly reduced the circulating levels of CRP, whereas, it had no significant effect on MDA and TAC. Overall, green tea can be considered as a healthy drink to reduce CRP levels, an important CVD risk assessment tool, in T2DM patients. However, further well-designed studies are needed to confirm the results of the present study.

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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 OA reviewed and selected the articles. RC and VA extracted needed data from articles. AA and OA performed data analysis and interpretation. MJG revised the article for important intellectual content. AA drafted the manuscript.

Declaration of Competing Interest

The authors declare that no conflict of interest exists.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.08.019.

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