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Review

Effect of Green Tea Supplementation on Inflammatory Markers among Patients with Metabolic Syndrome and Related Disorders: A Systematic Review and Meta-Analysis

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ABSTRACT: Several randomized controlled trials (RCTs) have investigated the potential benefits of green tea on the inflammatory process in metabolic syndrome (MetS). However, the results are inconclusive and inconsistent. In the present study, we performed a literature review and meta-analysis to evaluate the effect of green tea supplementation on inflammatory markers [e.g., tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6)] among patients with MetS and related disorders. We systematically searched for relevant publications up to March 2022 in the PubMed, Scopus, Web of Science, and SciELO databases. The review was registered with PROSPERO (CRD42022320345). Mean differences with 95% confidence intervals were pooled on the basis of the random effects model to compare the effects of green tea with placebo. We used meta-regression and subgroup analyses to determine the cause of heterogeneity and performed study quality assessment using the Grading of Recommendations Assessment, Development, and Evaluation method. We assessed publication bias using funnel plots and Egger's tests. Out of the total 15 RCTs that were included in this systematic review, 12 were chosen for the meta-analysis. The results revealed that green tea significantly decreased TNF-α levels but did not affect CRP and IL-6 levels. Subgroup analysis showed that green tea supplementation in studies lasting ≤8 weeks significantly increased CRP levels. Furthermore, meta-regression analysis demonstrated a significant association between increasing IL-6 concentration and treatment duration. According to our meta-analysis, green tea was shown to considerably lower circulating TNF-α levels. To confirm these findings, carefully planned trials are required.

Keywords: green tea, inflammation, meta-analysis, metabolic syndrome, randomized controlled trial

INTRODUCTION

In recent years, metabolic syndrome (MetS) has become a significant health concern. Thus, it is important to understand its manifestations and consequences and to develop treatment methods. Because of the increasing rates of obesity and sedentary lifestyles, the global prevalence of MetS is increasing, affecting up to 20%～25% of the adult population (Saklayen, 2018; Strauss et al., 2022). MetS is also characterized by a number of pathophysiological changes that increase the risk of cardiovascular diseases (CVDs), including insulin resistance, obesity, dyslipidemia, and hypertension (Angelico et al., 2023).

Chronic low-grade inflammation and immune system activation can be observed in abdominal obesity, and these factors may be components of MetS (Semmler et al., 2023). Insulin resistance and obesity involve downstream inflammatory cascades, which can lead to tissue fibrosis, atherogenesis, and CVDs (Kawai et al., 2021). Thus, substances that can decrease these inflammatory conditions may be beneficial for patients with MetS.

Recently, there has been increasing interest in using medicinal herbs for the management of MetS (Payab et al., 2020). For example, green tea (*Camellia sinensis*), which is a popular beverage in China, may delay the development or progression of metabolic diseases such as hypertension and cardiovascular disorders (James et al., 2023; Surma et al., 2023). The presence of flavonoids, specifically catechins, in green tea may contribute to its potential health benefits. Additionally, green tea contains quercetin, chlorogenic acid, gallic acid, thearubigins, theaflavins, theanine, and caffeine (Cercato et al., 2015; Alipour et al., 2018).

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These compounds exhibit anti-inflammatory, antioxidant, anticarcinogenic, and anti-obesity properties (Ohishi et al., 2016; Kumazoe et al., 2021).

Several clinical trials have investigated how green tea affects inflammatory biomarkers in individuals with MetS-related conditions. However, the findings are inconsistent. In randomized controlled studies, green tea intervention showed no effects on inflammatory markers in healthy smokers (de Maat et al., 2000), healthy individuals (Alexopoulos et al., 2008), and subjects with diabetes (Ryu et al., 2006). However, green tea supplementation significantly reduced interleukin-6 (IL-6) and C-reactive protein (CRP) levels in overweight middle-aged men (Bagheri et al., 2020). These conflicting findings may be because of the different health conditions present in the populations studied, which may reflect different levels of inflammation. To the best of our knowledge, no systematic review and meta-analysis have investigated the effects of green tea on inflammatory mediators in patients with MetS-related disorders. Thus, in the present meta-analysis, we aimed to investigate the effects of green tea on CPR, IL-6, and tumor necrosis factor-α (TNF-α) concentrations in these patients.

MATERIALS AND METHODS

Search strategy and selection criteria

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria (Liberati et al., 2009) and PRISMA 2020 checklist (Page et al., 2021). Moreover, it was registered in PROSPERO (www.crd.york.ac.uk/prospero/), with registration number CRD42022320345.

We systematically searched for relevant studies published before March 2022 in the PubMed, Scopus, Web of Science, and SciELO databases by using the following search terms: "green tea" OR "catechin" OR "camellia sinensis" OR "tea polyphenols" OR "catechinic acid" AND "metabolic syndrome" "OR "diabetes" OR "obese" OR "hypertension" OR "coronary heart disease" OR "chronic kidney disease" OR "non-alcoholic fatty liver disease" OR "hypercholesterolemia" OR "polycystic ovary syndrome" AND "inflammation" AND "randomized controlled trial." In addition, we manually reviewed the references of identified studies and meta-analyses with similar studies. We also contacted the investigators of previous studies to obtain further unpublished data or clarifications. There were no limitations on language or publishing date.

The search was independently carried out by three authors (DJPL, GLV, and FSOA). Any disagreements were settled by discussion with a fourth investigator (MS).

Inclusion/exclusion criteria

Studies that satisfied the following inclusion criteria were included in the meta-analysis: (1) crossover or parallel design human trials; (2) studies including a control group and employing green tea preparations, green tea extract, purified green tea polyphenols, or pure green tea catechins as the intervention; (3) studies measuring CRP, TNF-α, and IL-6 levels in patients with MetS and related metabolic diseases; (4) studies involving adult subjects; and (5) studies stabilizing the drug dosage at the beginning of the experiment and using the same drug in the placebo and intervention groups. Letters, brief correspondence, reviews, animal experiments, and *in vitro* research were not included in this meta-analysis. Studies that were excluded included trials with insufficient data, duplicate studies, and interventions that combined green tea with other substances. This evaluation did not include studies that combined physical exercise and green-tea-containing supplements. Extensive treatment arm trials (e.g., different doses of green tea) were incorporated into the meta-analysis as independent studies.

Data extraction and quality assessment

Four researchers independently performed data extraction. The following data were extracted: study design, demographic data (number and sex of participants), type and quantity of green tea supplementation, study duration, health conditions of participants, and information on inflammatory markers between the intervention and control groups (main outcomes).

The Cochrane risk-of-bias tool for randomized controlled trials (RCTs) was used to evaluate the quality of included studies (Higgins et al., 2011). Sequence allocation concealment from participants, participant and outcome assessor blinding, insufficient outcome data, selective reporting of outcomes, and other possible risk factors were used to evaluate quality. On the basis of the study's data, each domain was rated as having a low, high, or uncertain risk of bias. Uncertainty regarding bias was used when there was insufficient experimental detail to make a determination. Disputes were settled by agreement.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to evaluate the quality of evidence for every domain (Ryan and Hill, 2016). The quality of evidence is divided into four categories by GRADE: high, moderate, low, and very low quality. The GRADE method was used to rate all outcomes, accounting for the uncertainty of pooled effects resulting from small numbers of participants and the possibility of bias in factors influencing the level of evidence. The risk of bias may arise from sequence generation inconsistencies, lack of blinding, loss to follow-up, and incomplete results. If these factors were found in more than 70% of analyzed data, we reduced this cri-

terion by one point.

Statistical analysis

We took averages from the intervention and control groups at baseline and after the intervention for every measure being investigated. Assuming that the correlation coefficient (R) was equal to 0.5, the standard deviations (SDs) of mean differences were computed using the following formula:

SD=square root [(SDpre-treatment)2
+(SDpost-treatment)2
−(2R×SDpre-treatment×SDpost-treatment)]
(Hozo et al., 2005; Higgins and Green, 2008)

In studies that supplied standard errors, we computed the SDs using the following formula:

SD=SEM×square root (n)

where "n" is the number of subjects. The meta-analysis was carried out using R software (R Foundation for Statistical Computing, https://www.R-project.org, 2020).

The Cochran test was used to confirm the statistical heterogeneity of treatment effects across studies (Borenstein et al., 2010). We employed the I^2 statistic to determine heterogeneity. An I^2 value of more than 50% or more was regarded as significant heterogeneity between trials. Mean differences with 95% confidence intervals (95% CIs) were used to indicate effect sizes. Statistical significance was considered at $P<0.05$. Funnel plots were used to visually show publication bias that was measured using Egger's test.

We performed subgroup analysis to evaluate the source of heterogeneity in the results. This analysis was developed by intervention types, dose, study design, mean age, sex, and study duration. Moreover, we used meta-regression analysis to examine the association between the treatment duration and the dose of green tea with pooled effect size.

RESULTS

Search results

Fig. 1 presents a flowchart of the identified studies. A total of 279 studies were identified in the first literature search. After excluding studies that did not meet the inclusion criteria, a total of 23 studies remained. We performed full-text evaluation of these studies. Subsequently, eleven studies were excluded (one study involved supplementation with other drugs, one study was short communications, three trials involved green tea supplementation and physical exercise, and three studies did not quantify outcomes, three studies with data presentation inappropriate for quantitative synthesis. Out of the remaining studies, 12 studies (13 arms) were included in the quantitative analysis, and 15 studies were included in the systematic review.

The main characteristics of the 15 studies are listed in Table 1. The selected studies included individuals with different health conditions: six studies including adults with diabetes mellitus (DM) (Fukino et al., 2005; Mohammadi et al., 2010; Liu et al., 2014; Borges et al., 2016; Bazyar et al., 2020; Hadi et al., 2020), one study including hypertensive patients (Bogdanski et al., 2012), one study including glucose abnormalities (Fukino et al., 2008), one study including polycystic ovary syndrome

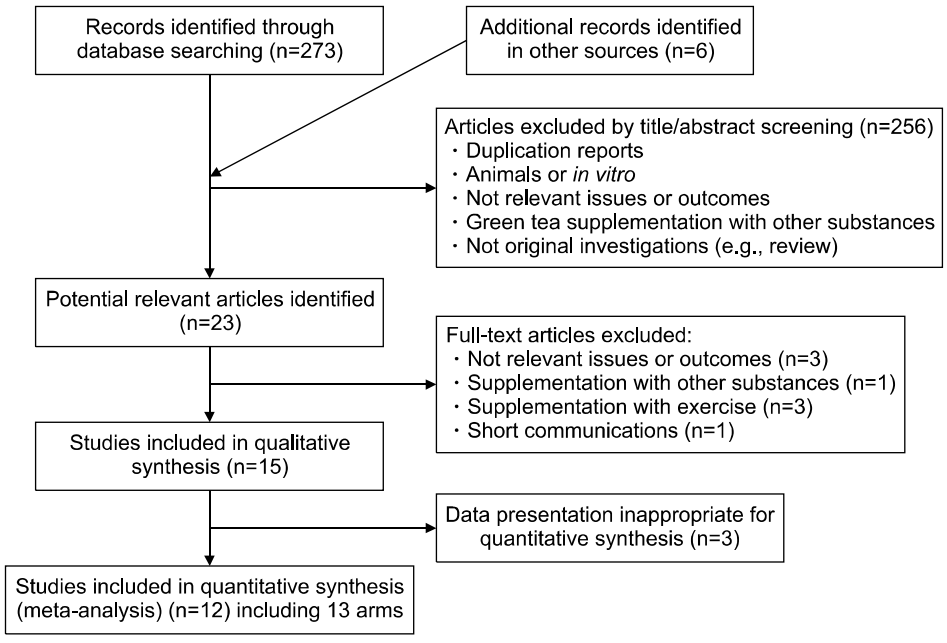

Fig. 1. Flow chart of the literature search and review for study selection.

Table 1. Characteristics of included studies

Reference	Design	No. of participants (sex)	Mean age (year)	Type and amount of green tea	Duration	Notes about participants	Main outcome
Bazyar et al., 2020	Double-blind/parallel	Placebo = 22 (10 male) Green tea = 22 (11 male)	Placebo = 52.61±7.22 Green tea = 51.75±6.79	300 mg/d epigallocatechin-3-gallate	2 months	T2DM with duration of more than 2 years, were recruited from outpatient, without insulin injection	IL-6
Hadi et al., 2020	Double-blind/parallel	Placebo = 22 (10 male) Green tea = 22 (9 male)	Placebo = 54.84±5.96 Green tea = 51.47±8.42	300 mg/d epigallocatechin-3-gallate	8 weeks	T2DM without insulin therapy or diabetic treatment history that lasted for three months	CRP
Mombaini et al., 2017	Double-blind/parallel	Placebo = 23 (female) Green tea = 22 (female)	Placebo = 24.17±6.83 Green tea = 23.22±5.24	500 mg/d green tea leaf powder	45 days	Polycystic ovary syndrome screened from a gynecology clinic, without combined diseases	CRP, IL-6, TNF-α
Hussain et al., 2017	Double-blind/parallel	Placebo = 40 (26 male) Green tea = 40 (28 male)	Placebo = 28±15 Green tea = 25±18	500 mg/d green tea extract	12 weeks	NAFLD patients were recruited from outpatient, with elevated aminotransferases (mild to moderate) and ultrasound with fatty liver grading 1, 2, 3	CRP
Gutiérrez-Salmeán et al., 2016	Double-blind/parallel	Placebo = 10 (NR) Green tea = 20 (NR)	18~55	100 mg/d epicatechin	4 weeks	Hypertriglyceridemia (200~499 mg/dL) without medication other than statins at a stable dose of ≥6 weeks	CRP
Borges et al., 2016	Double-blind/parallel	Placebo = 21 (16 male) Green tea = 21 (11 male)	Placebo = 59 (49~63) Green tea = 63 (60~65)	800 mg/d epigallocatechin gallate	12 weeks	Diabetic type 1 or 2 with nephropathy during routine visits in hospital, treatment with maximum doses of ACE inhibitors and/or ARBs for at least 8 weeks prior to the screening	CRP, TNF-α
Nogueira et al., 2017	Double-blind/crossover	20 (female)	41.1±8.4	500 mg/d green tea extract	4 weeks	Obese prehypertensive women, recruited at the Department of Plastic Surgery among the candidates for lipoplasty, without any medication known to interfere with body weight, blood pressure, and metabolic profile	CRP, IL-6, TNF-α
Dower et al., 2015	Double-blind/crossover	37 (25 male)	66.4±7.9	100 mg/d epicatechin	4 weeks	(Pre)hypertensive without chronic diseases or users of medication	CRP, IL-6, TNF-α
Liu et al., 2014	Double-blind/parallel	Placebo = 38 (18 male) Green tea = 39 (14 male)	Placebo = 53.5±7.0 Green tea = 55.0±6.6	500 mg/d green tea extract	16 weeks	T2DM (glycemic hemoglobin higher than 6.5% within 3 months) and lipid abnormalities (fasting triglyceride≥150 mg/dL or fasting low-density lipoprotein (LDL) cholesterol≥100 mg/dL)	CRP

Table 1. Continued

Reference	Design	No. of participants/sex	Mean age (year)	Type and amount of green tea	Duration	Notes about participants	Main outcome
Mielgo-Ayuso et al., 2014	Double-blind/parallel	Placebo = 39 (female) Green tea = 39 (female)	19~49	300 mg/d epigallocatechin-3-gallate	12 weeks	Obese women with total cholesterol levels≤7 758 mmol/L, TAG levels≤3 387 mmol/L and blood pressure levels≤140/90 mmHg. Women free of medication for hypertension, hyperlipidemia, hyperuricemia or other illness	CRP
Bogdanski et al., 2012	Double-blind/parallel	Placebo = 28 (15 male) Green tea = 28 (13 male)	Placebo = 51.5±7.4 Green tea = 49.2±8.8	379 mg/d green tea extract	3 months	Obese and hypertensive screened at our outpatient clinic with BMI≥30 kg/m^2 and blood pressure levels ≤160/100 mmHg. Stable treatment for at least 6 months	CRP, TNF-α
Basu et al., 2011	Single-blind/parallel	Placebo = 12 (2 male) Green tea = 13 (3 male)	Placebo = 44.6±3.2 Green tea = 42.8±2.6	110 mg/d green tea extract	8 weeks	Obese subjects with metabolic syndrome with stable medications (except hypoglycemic and hypolipidemic agents)	CRP, IL-6
Basu et al., 2011	Single-blind/parallel	Placebo = 12 (2 male) Green tea = 10 (3 male)	Placebo = 44.6±3.2 Green tea = 39.5±3.0	500 mg/d green tea extract	8 weeks	Obese subjects with metabolic syndrome with stable medications (except hypoglycemic and hypolipidemic agents)	CRP, IL-6
Mohammadi et al., 2010	Double-blind/parallel	58 (8 male)	36.5±14.55	4.5 g/d of green tea extract	8 weeks	T2DM with duration of more than 2 years, were recruited from outpatient. Taking oral medications to control blood sugar and not having a history suffering from other diseases	CRP
Fukino et al., 2008	Without blinding/crossover	60 (49 male)	Placebo = 53.97±8.6 Green tea = 53.47±7.7	500 mg/d green tea extract	2 months	Glucose abnormalities (fasting blood glucose level of ≥6.1 mmol/L or a nonfasting blood glucose level of ≥7.8 mmol/L)	CRP
Fukino et al., 2005	Parallel	Placebo = 33 (26 male) Green tea = 33 (27 male)	Placebo = 53.5±7.5 Green tea = 53.5±8.5	500 mg/d green tea extract	2 months	Borderline diabetes or diabetes (fasting blood glucose level of ≥110 mg/dL or a nonfasting blood glucose level of ≥140 mg/dL)	CRP

Values are presented as mean±SD.
T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; TAG, triacylglycerols; BMI, body mas index; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; NR, not reported.

(Mombaini et al., 2017), one study including obesity and MetS (Basu et al., 2011), one study including nonalcoholic fatty liver disease (Hussain et al., 2017), and one study including hypertriglyceridemia (Gutiérrez-Salmeán et al., 2016). The study size ranged from 20 to 78 participants, and the treatment period ranged from 4 to 16 weeks. The average age of participants ranged from 18 to 66 years. Three studies (Mielgo-Ayuso et al., 2014; Mombaini et al., 2017; Nogueira et al., 2017) exclusively enrolled female participants, whereas one study (Gutiérrez-Salmeán et al., 2016) did not disclose the sex of participants.

With regard to the intervention method, one study (Mombaini et al., 2017) used green tea leaf powder, eight studies (Fukino et al., 2005, 2008; Mohammadi et al., 2010; Basu et al., 2011; Bogdanski et al., 2012; Liu et al., 2014; Hussain et al., 2017; Nogueira et al., 2017) employed green tea extract, and six studies (Mielgo-Ayuso et al., 2014; Dower et al., 2015; Borges et al., 2016; Gutiérrez-Salmeán et al., 2016; Bazyar et al., 2020; Hadi et al., 2020) used epigallocatechin-3-gallate (EGCG). The dose of green tea ranged from 100 to 9,000 mg/d. Fifteen RCTs measured CRP, six RCTs measured IL-6, and five studies measured TNF-α.

Assessment of risk of bias

The results of Cochrane risk-of-bias evaluation, which was used to assess the quality of studies, are shown in Table 2. Seven studies provided comprehensive descriptions of random sequence creation (Dower et al., 2015; Borges et al., 2016; Gutiérrez-Salmeán et al., 2016; Hussain et al., 2017; Mombaini et al., 2017; Bazyar et al., 2020; Hadi et al., 2020). Six studies had unclear or high risk of bias with regard to allocation concealment (Fukino et al., 2005, 2008; Mohammadi et al., 2010; Basu et al., 2011; Bogdanski et al., 2012; Bazyar et al., 2020). Meanwhile, four studies exhibited a high or unclear risk of bias with regard to participant or personnel blinding (Fukino et al., 2005, 2008; Basu et al., 2011; Hussain et al., 2017). However, when it came to the blinding of outcome assessors, most studies showed an unclear risk of bias. Two high-risk studies (Basu et al., 2011; Gutiérrez-Salmeán et al., 2016) and one study with unclear risk (Fukino et al., 2005) examined incomplete outcome data. With the exception of the study by Fukino et al. (2005), all studies showed minimal risk of selective outcome reporting. Seven studies had possible threats to validity (Fukino et al., 2005, 2008; Basu et al., 2011; Liu et al., 2014; Borges et al., 2016; Gutiérrez-Salmeán et al., 2016; Nogueira et al., 2017).

Systematic review

The study by Borges et al. (2016) did not show major changes in CRP (P=0.29) after using 800 mg/d of EGCG for over 12 weeks among type 1 or 2 diabetic patients with nephropathy aged between 49 and 65 years. However, the groups that used ECGC showed a reduction in TNF-α levels (P=0.003).

Dower et al. (2015) aimed to determine how green tea affected endothelial dysfunction and inflammatory biomarkers. In their study, 100 mg of epicatechin was administered daily for a period of 4 weeks. The participants were apparently healthy and prehypertensive, nonsmokers (aged between 40 years and 80 years) with a body mass index (BMI) between 20 and 40 kg/m^2. The results showed that treatment with 100 mg of epicatechin

Table 2. Overview of review authors' assessments of risk-of-bias categories for the included research

Reference	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Bazyar et al., 2020	L	U	L	U	L	L	L
Hadi et al., 2020	L	L	L	U	L	L	L
Mombaini et al., 2017	L	L	L	U	L	L	L
Hussain et al., 2017	L	L	U	U	L	L	L
Gutiérrez-Salmeán et al., 2016	L	L	L	U	H	L	H
Borges et al., 2016	L	L	L	U	L	L	H
Nogueira et al., 2017	U	L	L	U	L	L	H
Dower et al., 2015	L	L	L	U	L	L	L
Liu et al., 2014	U	L	L	U	L	L	H
Mielgo-Ayuso et al., 2014	H	L	L	U	L	L	L
Bogdanski et al., 2012	H	U	L	U	L	L	L
Basu et al., 2011	H	H	H	H	H	L	H
Mohammadi et al., 2010	U	U	L	U	L	L	L
Fukino et al., 2008	U	H	H	H	L	L	H
Ryu et al., 2006	U	U	U	U	U	U	U
Fukino et al., 2005	U	H	H	H	U	U	H

L, low risk of bias; U, unclear risk of bias; H, high risk of bias.

for 4 weeks did not significantly affect CRP (P=0.57), TNF-α (P=0.81), and IL-6 levels (P=0.81).

Quantitative analysis

***Effect of green tea on CRP*:** After analyzing the results of 13 studies, the meta-analysis failed to confirm whether green tea supplementation had an important effect on CRP levels (0.2613 mg/dL; 95% CI, −0.1401 to 0.6626; P=0.2021), with between-study heterogeneity ($P \leq 0.0001$, I^2=88.69%) (Fig. 2). Subgroup analysis revealed that the trial duration had an impact on the outcomes. However, the types of interventions, doses, study designs, mean age, and sex did not influence green tea supplementation. On the basis of the pooled estimate from nine trials conducted for less than or equivalent to eight weeks, Table 3 shows a significant increase in CRP levels after drinking green tea (0.50 mg/dL; 95% CI, 0.08∼0.92; P=0.0188).

***Effect of green tea on TNF-α*:** A meta-analysis utilizing three RCTs was conducted to examine TNF-α levels. The results showed that green tea supplementation had a significant effect (−0.4293 pg/mL; 95% CI, −0.7821 to −0.0764; P=0.0171), with no between-study heterogeneity (P=0.4106, I^2=0%) (Fig. 3).

***Effect of green tea on IL-6*:** A meta-analysis using five studies found no significant change in serum IL-6 levels after green tea supplementation (−0.6409 pg/mL; 95% CI, −1.6139 to 0.3321; P=0.0722), with between-study heterogeneity (P=0.0002, I^2=81.70%) (Fig. 4). Subgroup analysis showed that mean age, study design, treatment duration, dose, sex, and type of intervention were not significant causes of heterogeneity (Table 3).

Publication bias

Funnel plots and Egger's linear regression test were used to assess publication bias. Upon visual inspection, the funnel plots did not appear to reflect publication bias in any of the included studies (Supplementary Fig. 1∼3). The absence of publication bias was also verified by Egger's linear regression test (P=0.6694 for CRP, P=0.9292 for IL-6, and P=0.6680 for TNF-α).

GRADE's quality of evidence for the outcome

The results were categorized as having moderate or low quality of evidence using the GRADE method. Because of the risk of bias and small numbers of participants, some studies received lower rankings due to the imprecision of pooled effects (inconsistencies that may impair the quality of evidence) (Table 4).

Meta-regression analysis

Meta-regression analysis was used to evaluate the association between treatment duration and green tea dose with inflammatory status. The results showed no significant association between changes in CRP, TNF-α, and IL-6 levels with the dose of green tea. On the basis of the treatment duration, the analysis did not show that green tea supplementation significantly altered CRP and TNF-α levels. Nevertheless, a substantial correlation was observed between treatment duration and increasing IL-6 levels (slope: 0.83; 95% CI, 0.27∼1.40; P=0.0039) (Fig. 5).

DISCUSSION

To the best of our knowledge, this meta-analysis is the first to assess how green tea supplementation affects inflammatory markers among patients with MetS and related disorders. The analysis of 12 RCTs, including 13 arms, showed that green tea consumption substantially decreased serum TNF-α levels while having no effect on IL-6 or CRP levels. However, subgroup analysis revealed an increase in CRP levels in studies with a duration of less than or equal to 8 weeks, and meta-regression analysis revealed a significant association between increased IL-6 concentration and treatment duration with green tea.

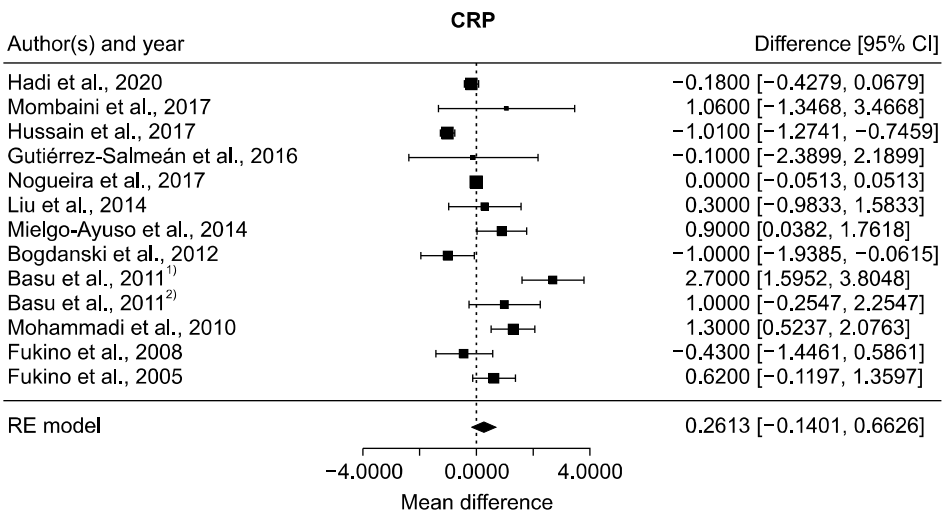

Fig. 2. Forest plot of the effect of green tea supplementation on C-reactive protein (CRP) levels. 95% CI, 95% confidence interval. 1)Basu et al., 2011 Experiment with 110 mg/d green tea. 2)Basu et al., 2011 Experiment with 500 mg/d green tea.

Table 3. Outcomes of the subgroup analyses of parameters

Subgroup	No. of trials (no. of participants)	Effect size (95% CI)	*P*-value	I^2 (%)	*P* heterogeneity	*P* for between subgroup heterogeneity
CRP						
Mean age (year)						<0.0001
≤50	8 (384)	0.47 (−0.18, 1.11)	0.1550	93.06	<0.0001	
>50	4 (247)	0.01 (−0.43, 0.45)	0.9534	37.72	0.1857	
Study design						<0.0001
Parallel	11 (581)	0.44 (−0.19, 1.1)	0.1677	89.47	<0.0001	
Crossover	2 (80)	−0.001 (−0.05, 0.05)	0.9667	0	0.4075	
Dose (mg/d)						<0.0001
≤300	4 (177)	0.86 (−0.50, 2.24)	0.2147	89.70	<0.0001	
>300	9 (471)	0.07 (−0.46, 0.60)	0.7864	89.58	<0.0001	
Duration (week)						<0.0001
≤8	9 (370)	0.50 (0.08, 0.92)	0.0188	81.06	<0.0001	
>8	4 (291)	−0.26 (−1.25, 0.73)	0.6068	85.26	0.0001	
Sex						<0.0001
Female	3 (143)	0.39 (−0.36, 1.13)	0.3132	59.31	0.0856	
Both	10 (505)	0.28 (−0.35, 0.90)	0.3896	89.57	<0.0001	
Type of supplementation						<0.0001
Epigallocatechin	3 (152)	0.21 (−0.63, 1.05)	0.6230	64.11	0.0617	
Tea	4 (196)	0.95 (−0.41, 2.32)	0.1691	82.61	0.0006	
Extract	6 (313)	0.01 (−0.64, 0.66)	0.9797	93.10	<0.0001	
IL-6						
Mean age (year)						<0.0001
≤50	4 (125)	−0.76 (−2.12, 0.59)	0.2724	86.27	<0.0001	
>50	1 (44)	−0.44 (−1.16, 0.28)	0.2343	0	1	
Study design						0.2374
Parallel	4 (136)	−0.19 (−0.68, 0.30)	0.4533	29.13	0.2374	
Crossover	1 (20)	−4.0 (−5.71, −2.28)	<0.0001	0	1	
Dose (mg/d)						<0.0001
≤300	2 (69)	−0.27 (−0.80, 0.27)	0.3223	0	0.4947	
>300	3 (87)	−1.10 (−3.29, 1.08)	0.3218	90.34	<0.0001	
Sex						0.0008
Female	2 (65)	−2.16 (−5.58, 1.25)	0.2143	92.61	0.0002	
Both	3 (91)	−0.02 (−0.67, 0.63)	0.9469	39.63	0.1908	
Type of supplementation						<0.0001
Epigallocatechin	1 (44)	−0.44 (−1.16, 0.28)	0.2343	0	1	
Tea	2 (70)	−0.31 (−0.83, 0.22)	0.2487	0	0.4129	
Extract	2 (42)	−1.52 (−6.30, 3.27)	0.5349	95.13	<0.0001	

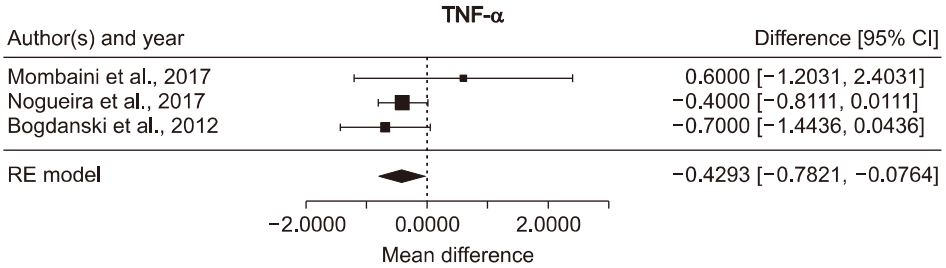

Fig. 3. Forest plot of the effect of green tea supplementation on tumor necrosis factor-α (TNF-α) levels. 95% CI, 95% confidence interval.

Elevated levels of circulating inflammatory markers are a reliable indicator of type 2 DM (T2DM), hypertension, CVD, and MetS (Son et al., 2022; Yihui and Yanfeng, 2023). Among them, CRP is one of the most relevant inflammatory indicators in clinical medicine. Several studies have indicated that CRP is an important biomarker for predicting the incidence of metabolic diseases, including CVD, diabetes, hypertension, and dyslipidemia (Hage, 2014; Raeven et al., 2020; Stinson et al., 2021). According to our meta-analysis, green tea did not change CRP levels in patients with MetS. Two meta-analyses corroborated our findings. In their meta-analysis including 11 RCTs, Serban et al. (2015) found that green tea had no effect on plasma CRP concentrations in the general population.

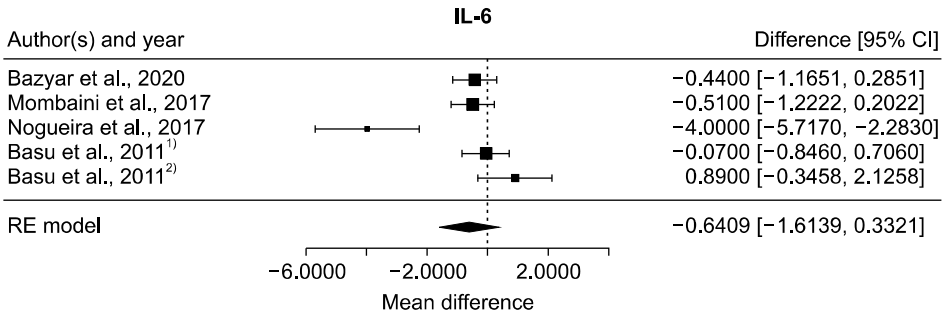

Fig. 4. Forest plot of the effect of green tea supplementation on interleukin-6 (IL-6) levels. 95% CI, 95% confidence interval. [1)]Basu et al., 2011 Experiment with 110 mg/d green tea. [2)]Basu et al., 2011 Experiment with 500 mg/d green tea.

Table 4. Summary of key findings on the basis of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) analysis

Outcome	Study	Participant	Effect estimate	*P*-value	Quality of evidence (GRADE)
CPR	13	661	0.2613 (−0.1401, 0.6626)	0.2021	⊕⊕⊕⊖ Moderate[1)]
IL-6	5	156	−0.6409 (−1.6139, 0.3321)	0.0722	⊕⊕⊖⊖ Low[1),2)]
TNF-α	3	121	−0.4293 (−0.7821, −0.0764)	0.0171	⊕⊕⊖⊖ Low[1),2)]

[1)]Downgraded because of risk of bias (inconsistencies that may affect the quality of evidence).
[2)]Reduced in value because of imprecision and insufficient precision (less than 400 individuals).
CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

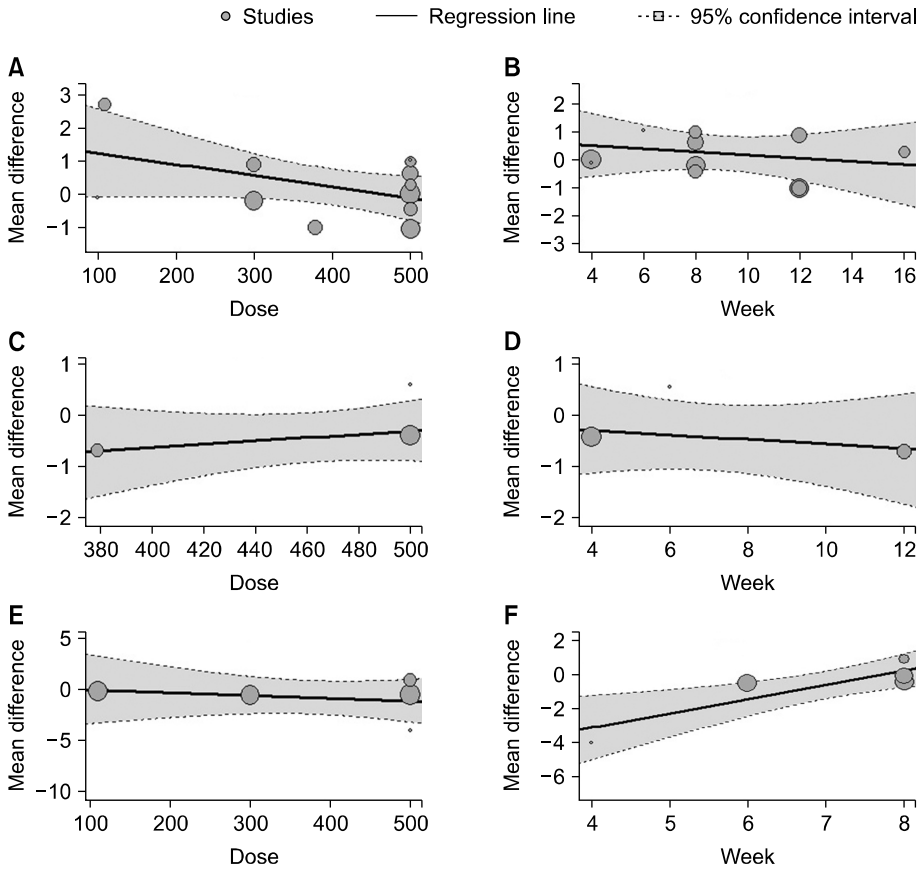

Fig. 5. Meta-regression plots of the association of mean changes in plasma C-reactive protein concentrations with the dose of green tea (A) and treatment duration (B). Meta-regression plots of the association of mean changes in plasma tumor necrosis factor-α concentrations with the dose of green tea (C) and treatment duration (D). Meta-regression plots of the association of mean changes in plasma interleukin-6 concentrations with the dose of green tea (E) and treatment duration (F).

Moreover, Haghighatdoost and Hariri (2019) found no change in CRP levels. They attributed the findings to the low-inflammatory diseases of the population included in their study. However, Asbaghi et al. (2019) found that green tea supplementation decreased CRP levels in patients with T2DM. This finding may be because they included patients with only one type of disease and possibly a greater degree of inflammation than individuals in other studies.

TNF-α is a cytokine that is implicated in numerous pathogenic processes. It affects lipid metabolism, inhibits insulin signal transmission, and modifies numerous other variables implicated in the pathophysiology of insulin resistance (Gwozdziewiczová et al., 2005; Park et al., 2022).

Moreover, research has shown that lipocytes and macrophages that have infiltrated adipose tissue release TNF-α, which is crucial for the development of atherogenesis, insulin resistance, MetS, and non-alcoholic fatty liver disease (Anfossi et al., 2010; Kawai et al., 2021). Moreover, there is a significant association between TNF-α concentration and BMI, which is associated with obesity and overweight in T2DM (Recinella et al., 2020). Our findings showed that green tea significantly reduced TNF-α concentrations in patients with MetS and related disorders. In their meta-analysis, Haghighatdoost and Hariri (2019) also found a decrease in TNF-α concentration among obese and overweight participants who received green tea supplementation, suggesting that green tea can reduce fat mass (Baladia et al., 2014), thereby affecting TNF-α concentrations.

The pleiotropic cytokine IL-6 is essential for immunological responses and other critical functions, including inflammation, hematopoiesis, bone metabolism, and embryonic development (Rose-John, 2020; Aliyu et al., 2022). Studies have shown a correlation between IL-6 and systemic inflammation, which may be related to MetS (Mohammadi et al., 2017). Moreover, significant correlations between blood IL-6 levels and MetS constituents have been observed. Research has also demonstrated a positive correlation between IL-6 and T2DM, hypertension, fasting insulin levels, and BMI (Noronha et al., 2019; Koshino et al., 2022). However, because of the limited number of studies, they do not provide conclusive evidence. According to some research, green tea can reduce the levels of several inflammatory cytokines in humans, including IL-6 (Reygaert, 2017; Bagheri et al., 2020). However, other studies involving adults with various types of comorbidities found that green tea supplementation did not affect IL-6 levels (Ryu et al., 2006; Basu et al., 2011), corroborating our findings. In our meta-analysis, almost all participants were consistently taking medication for MetS, which might be attributed to the lack of effect of green tea.

The differences in CRP and IL-6 levels found in this meta-analysis in relation to treatment duration may be because the included patients had different types of metabolic diseases. Interactions with other nutrients during absorption, metabolism, and membrane transport may alter the bioavailability of catechins (Ishii et al., 2019). The existence of interindividual polymorphism in humans influences the bioavailability and metabolic destiny of tea flavonoids, which is another explanation for this finding (Bathgate et al., 2023). Moreover, drinking green tea has been linked to hepatotoxicity (Zhao et al., 2022), which could account for the increase in these inflammatory markers during various treatment phases.

This meta-analysis had several significant strengths. First, we conducted this systematic review and meta-analysis in accordance with PRISMA guidelines, thereby reducing the risk of bias. The results of Egger's test and funnel plots did not suggest asymmetry regarding the estimate of the overall effect. Subgroup and meta-regression analyses were performed to detect the sources of heterogeneity in the outcomes. Furthermore, our review was registered in PROSPERO and conducted using the GRADE method.

Despite the strengths, this meta-analysis has a few limitations. The most important finding is that there were only a small number of trials available for the meta-analysis, which was reflected in the subgroup analysis. Moreover, we identified large variations in study designs, dosage and type of green tea, age, and trial quality. In the studies included in this meta-analysis, some individuals might not have high enough inflammation levels, making it difficult to determine the effects of green tea. These factors may have contributed to our inability to identify variations as statistically significant sources of heterogeneity.

In conclusion, this meta-analysis exhibited the positive effects of green tea supplementation on inflammatory markers in patients with MetS and related disorders. Green tea supplementation significantly decreased the circulating levels of TNF-α; however, it did not significantly affect plasma CRP and IL-6 concentrations. Thus, green tea can be considered as an adjuvant food in the inflammatory processes of patients with MetS and related disorders. To further understand the effects of green tea on inflammatory markers, larger and more carefully designed trials are required to rule out confounding variables, including sex, treatment duration, and dose.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: FSOA, MS. Analysis and interpretation: FSOA, LRM, MS. Data collection: FSOA, GLV, DJPL, MS. Writing the article: FSOA, GLV, DJPL, LRM, MS. Critical revision of the article: FSOA, LRM, MS. Final approval of the article: all authors. Statistical analysis: FSOA, MS. Obtained funding: FSOA, LRM, MS. Overall responsibility: FSOA, GLV, DJPL, LRM, MS.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3746/pnf.2024.29.2.106

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