



Green Tea Supplement in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

Azadeh Lesani; MSc¹, Fatemeh Sharafi; MSc², Mahsa Hatami; MSc³ & Sakineh Shab-Bidar; PhD^{*1}

¹ Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.

² Department of Human Nutrition, School of Health, Qazvin University of Medical Services, Qazvin, Iran.

³ Department of Clinical Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.

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*Corresponding author:

s_shabbidar@tums.ac.ir

Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.

Postal code: 14155/6117

Tel: +98 21 88955975

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common metabolic disorder among age reproductive women. It could result in anovulation, infertility insulin resistance, and obesity. Dietary intake especially antioxidant components may improve some disorders. The current study is the first meta-analysis to assess the effect of green tea, a source of antioxidants, on anthropometric and insulin among women with PCOS. **Methods:** In this meta-analysis, the databases of PubMed/Medline, Scopus, Cochran, and Web of Science were searched up to March 2019. The I-square (I_2), a statistical measure of heterogeneity, was used to assess the heterogeneity. Egger's test was used for the assessment of publication bias. **Results:** Green tea reduced weight -3.07 kg (-6.53 to -0.44, $P = 0.03$), fasting insulin -0.50 mIU/l -3.72 (-5.16 -2.28, $P = 0.001$), waist to hip ratio (WHR) -0.04 (-0.06 to -0.017, $P = 0.001$), body mass index -0.32 to kg/cm² (-1.63 to 1, $P = 0.09$), and body fat percentage -1.13(-5.30 to 3.04, $P = 0.51$). **Conclusion:** The green tea supplement has some mild decreasing effect on weight, WHR, and fasting insulin significantly. It seems green tea could improve weight and glycemic control in women with PCOS.

Keywords: Green tea; Herbal tea; Catechin; PCOS; Polycystic ovary Syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder in reproductive age women by the prevalence of 3-10% in the world (Wolf *et al.*, 2018). The etiology of PCOS is not certainly cleared, but genetics, obesity, dyslipidemia, hyperinsulinemia, hyper androgenic, and increased oxidative stress have been studied in previous studies as contributing factors (Barbieri

and Ryan, 1983, Glintborg and Andersen, 2010). PCOS is characterized by symptoms of anovulation (irregular menstrual cycle, amenorrhea or oligomenorrhea), infertility, hyperandrogenism (hirsutism, acne or alopecia), insulin resistance, and obesity (Speroff and Fritz, 2005). The anovulatory infertility could have resulted in some common outcomes like female reproductive,

metabolic, cardiovascular, and psychological disorders. According to the Rotterdam 2003 consensus, two out of three following criteria are required for the diagnosis of this syndrome: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound (ESHRE and Group, 2004).

Insulin resistance prevalence are 50-75% among obese and lean PCOS (Dunaif *et al.*, 1989) due to defect in insulin signaling (serine kinase insulin receptor subunit). Insulin play an important role in increased and frequency of Gonadotropin Releasing Hormone (GnRH) and Luteinizing Hormone (LH) pulse secretion on hypothalamus-hypophis- ovary and adrenal signaling (Sekar *et al.*, 2000). In addition, hyperinsulinemia affects the Steroidogenic Acute Regulatory Protein (StAR), carrying cholesterol into mitochondria, leading more androgen production (Sekar *et al.*, 2000). Androgens increases beta-hydroxy steroid dehydrogenase and hormone-sensitive lipase in visceral adipose tissue (VAT), which leads to an increase in free fatty acids and the secretion of inflammatory cytokines from VAT (De Pergola, 2000).

Green tea includes catechins components belonging to a family of flavonols. Epigallocatechin gallate (EGCG), epigallocatechin, are epicatechin are flavonols found in green tea extract (Khan and Mukhtar, 2007). Green tea had some beneficial effect on preventing coronary heart disease, diabetes (Sikand *et al.*, 2015), promoting insulin resistance, metabolic disease, enhancing metabolic rate and fat-burning ability (Diepvens *et al.*, 2007, Dinh *et al.*, 2019), increasing energy expenditure (Dulloo *et al.*, 1999), and anti-oxidants and anti- hypertensive effects (Garcia *et al.*, 2017). Vivo and in vitro studies showed significant reduction in fasting plasma glucose, insulin, dyslipidemia, and glycated hemoglobin (HbA1c) in diabetic rats (Babu *et al.*, 2006, Quine and Raghu, 2005). In spite of this experimental fact, there were controversial results in randomized clinical trials. A meta- analysis on randomized clinical trials (RCTs) showed significant reduction on plasma glucose

concentration and promoting insulin sensitivity (Liu *et al.*, 2013). Another meta-analysis displayed no significant mean change in weight loss, waist circumference, fat mass percentage, and body mass index (BMI) with green tea extract consumption (Baladia *et al.*, 2014). However, a recent meta-analysis demonstrated a significant mean change in weight, BMI, and waist circumference, but not in body fat percentage after the intervention by green tea among adult population (Golzarand *et al.*, 2018). Also another recent meta-analysis did not show significant change in body weight, BMI, waist circumference, waist hip ratio, and body fat percentage among overweight and obese nondiabetic females after green tea products intervention (Lee *et al.*, 2019). So far, no systematic review and meta-analysis have investigated the effect of green tea on metabolic profile among women with PCOS. Therefore, this study aims to investigate the effect of green tea supplementation on anthropometric measures and fasting insulin among women with PCOS.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to guide the systematic review of the literature (**Supplementary Figure 1**)(Moher *et al.*, 2009).

Search strategy and study selection: A comprehensive search was conducted in PubMed/Medline, Scopus, Cochran, and Web of Science until 13 March 2019. The combination of following key words, including text words and Medical Subject Headings (Mesh) were searched for green tea extract, ECGC, catechine and PCOS, Stein Leventhal Syndrome, polycystic ovarian syndrome. Randomized controlled trials, clinical trials, and random allocation were used (**Supplementary Table 1**). The reference list of all related articles and reviews were also checked. The search was limited to published studies in English.

Eligibility and study selection: Two independent authors (Lesani A and Sharafi F) reviewed titles and abstracts of all randomized clinical trial studies. Studies were included in this review if they (1) were in RCT design, 2) with diagnosis of

PCOS by the presence 2 of 3 features: oligo- or anovulation, clinical or biochemical evidence of hyperandrogenism, and transvaginal ultrasound features showing more than 12 immature follicles less than 10 mm on either ovary among young women aged more than 18 years, (3) had interventions, such as green tea/green tea extract, (4) compared oral intervention supplement vs. placebo, (5) measured and reported at least one of the anthropometric measures, including weight, BMI, waist circumference and waist to hip ratio (WHR), percentage of body fat (PBF), and insulin fasting as outcomes. Some studies were excluded, including (1) animal studies or observational studies, (2) studies without placebo groups, (3) studies compared low-dose vs. high dose of supplement, (4) studies conducted in children, adolescents (aged < 18 y, and >55 y), pregnant or lactating women, (5) studies on chronic illness, and (6) research studies which were conducted on decaffeinated green tea vs. caffeinated green or placebo.

Data extraction and assessment for study quality: Two independent authors (Lesani A and Sharafi F) reviewed full text of selected eligible studies and extracted the following information: first author's name, publication year, study name, country, mean age and/or age range, number of participants/cases, mean and standard deviation (SD) of body weight, BMI, WC and PBF at baseline, end of the intervention and their changes from baseline, dosage, and length of intervention. Risk of bias was assessed in the included study (n=3). Two studies had low risk in all categories and one study had unclear bias in blindness of participants, and outcomes (**figure 1**). Additional information was requested by correspondence. Any discrepancies were resolved through discussion under the supervision of the third author (Shab-Bidar S).

Data synthesis and analysis: Meta-analysis index was mean and standard deviations (SD) of body weight, BMI, PBF, WHR ratio, and insulin fasting changes from baseline. The following formula was used to estimate the SD based on

studies in which the standard error of the mean (SEM) was reported: $(SD=SEM \times \sqrt{n})$ (n= number of participants). In studies that reported the upper and lower limit using 95% confidence intervals (CI), the SD was determined using the following formula: $(SD=\sqrt{n} \times \frac{(\text{upper limit}-\text{lower limit})}{3.92})$. If there was heterogeneity among the included studies, the random-effect model would be performed to calculate the pooled effect size; or the fixed effect model would be used. Heterogeneity was investigated by using I-squared (I^2) and Tau-squared (τ^2). The most commonly used heterogeneity measure was I^2 . Egger's regression symmetry test was used to determine publication bias. To investigate the effect of studies on the pooled effect size, sensitivity analysis was run. Meta-regression analyses were conducted to assess the source of heterogeneity. Age, dose, and length of intervention were determined as a source of heterogeneity. All statistical analysis was performed using STATA software version 12 (STATA Corp, College station, Texas).

Results

The flow diagram of literature search is shown in **Figure 2**. Systematic search identified 56 articles (21 articles in PubMed, 35 articles in Scopus) and 9 articles were identified through bibliography search with 17 duplicates. Thirty three other articles were considered as irrelevant, which were excluded at initial screening of title and abstract. Of the 15 remaining articles, 11 articles were excluded by full-text assessment. Detailed reasons for exclusions are presented in **Figure 2**. One study conducted combined intervention of lifestyle and 2 studies herbal medicine (Arentz *et al.*, 2017). Three randomized clinical trials studies (Allahdadian *et al.*, 2015, Chan *et al.*, 2006, Mombaini *et al.*, 2017) (data of one study reported in two different articles) (Allahdadian *et al.*, 2015, Tehrani *et al.*, 2017) and 1 crossover study were identified (Tomatis *et al.*, 2015). Finally, 3 studies (including 139 participants, 70 in the intervention group and 69 in the placebo group) were included for the meta-analysis. Characteristics of included studies are

presented in **Table 1**.

Meta-analysis: Three studies investigated the effect of green tea supplement on body weight (Allahdadian *et al.*, 2015, Chan *et al.*, 2006, Mombaini *et al.*, 2017) , two studies on WHR ratio, BMI, body fat percentage (Chan *et al.*, 2006, Mombaini *et al.*, 2017) , and fasting insulin (Allahdadian *et al.*, 2015, Chan *et al.*, 2006) . **Table 2** showed the effect of green tea on anthropometric measurement and fasting insulin.

Forest plot of studies that assessed the effect of green tea/green tea extract on weight, BMI, WC, PBF, and fasting insulin are displayed in **Figures 3–6**, respectively. Green tea/green tea extract

significantly reduced body weight by -3.07 kg (-6.53 to -0.44, $P = 0.03$), fasting insulin -3.724 mIU/l (-5.16 to -2.28, $P = 0.001$), WHR (-0.04 (-0.06 to -0.017, $P = 0.001$). However, no significant changes were found in BMI -0.32 to kg/cm² (-1.63 to 1, $P = 0.09$) and PBF -1.13 (-5.30 to 3.04, $P = 0.51$). There was no heterogeneity among studies on body weight ($I^2=1.13%$, $P = 0.56$), BMI ($I^2=0.1%$, $P = 0.94$), WHR ($I^2=0.0%$, $P = 1$), PBF ($I^2=0.8$, $P = 0.77$), and fasting insulin ($I^2=0.0%$, $P = 0.75$).

Publication bias: There was an evidence of publication bias for Egger’s asymmetry test ($P = 0.04$) or Begg’s test ($P = 0.35$).

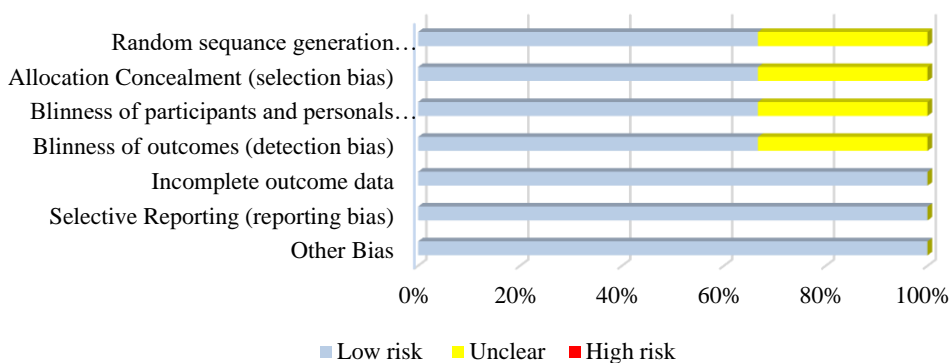


Figure 1. Risk of bias overall diagram

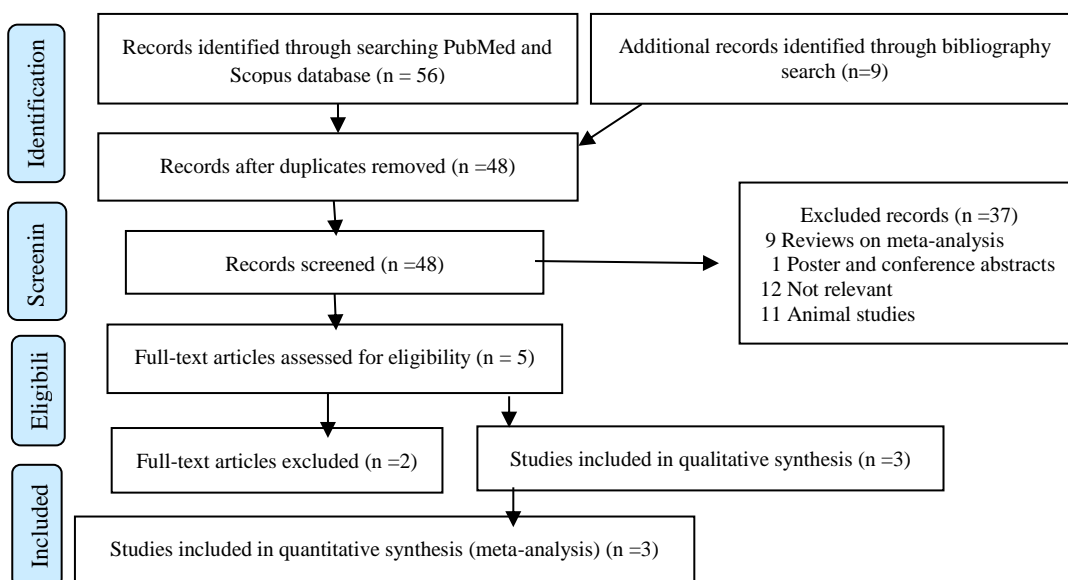


Figure 2. Flow chart of article processing

Table 1. Characteristics of the included studies.

Author	Year	Country	Type of study	Number Intervention/Placebo	Mean (SD) age	Daily dosage	Follow-up	Outcomes
Chan, et al.	2006	Hong Kong	Randomized placebo controlled Study	34 18/16	34.8 (4.2)	540 mg/d Green tea extract capsule	12 Week	No significant reduction in BMI in green tea group Significant rise in BMI, weight, and body fat in the control group No difference in hormonal level No significant reduction in amenorrhoeic
Mombaini, et al.	2017	Iran	Randomized double-blind controlled Study	45 22/23	23.2 (5.2)	500 mg/d Green tea capsule	6 Week	Significant reduction in BMI, weight, and body fat in green tea group No significant change in inflammation marker level (IL6,TNF-a, h-CRP)
Allahdadian, et al.	2015	Iran	Randomized controlled study	60 30/30	30.0(5.0)	500 mg/d Green tea tablet	12 Week	Significant reduction in weight, fasting insulin, and free testosterone in green tea group

Mean age of participants was 34 ± 3.35 y. Dose range of green tea extract capsule were 500-540 mg/day, mean duration of intervention was 10 ± 2 week (6-12 week).

Table 2. The effect of green tea on body weight, body mass index, body fat, waist hip ratio, and fasting insulin.

Variables	Effect size (95%CI)	P Significant	P Heterogeneity	I ² (%)
Body weight	-3.07 (-5.70 - -0.44)	0.022	0.568	1.13
Body mass index	-0.17 (-1.50 - 1.14)	0.792	0.940	0.01
Body fat	-0.55 (-4.24 - 3.12)	0.766	0.778	0.08
Waist hip ratio	-0.04 (-0.06 - -0.01)	0.001	1	0.0
Fasting insulin	-3.72 (-5.16 - -2.28)	0.001	0.756	0.0

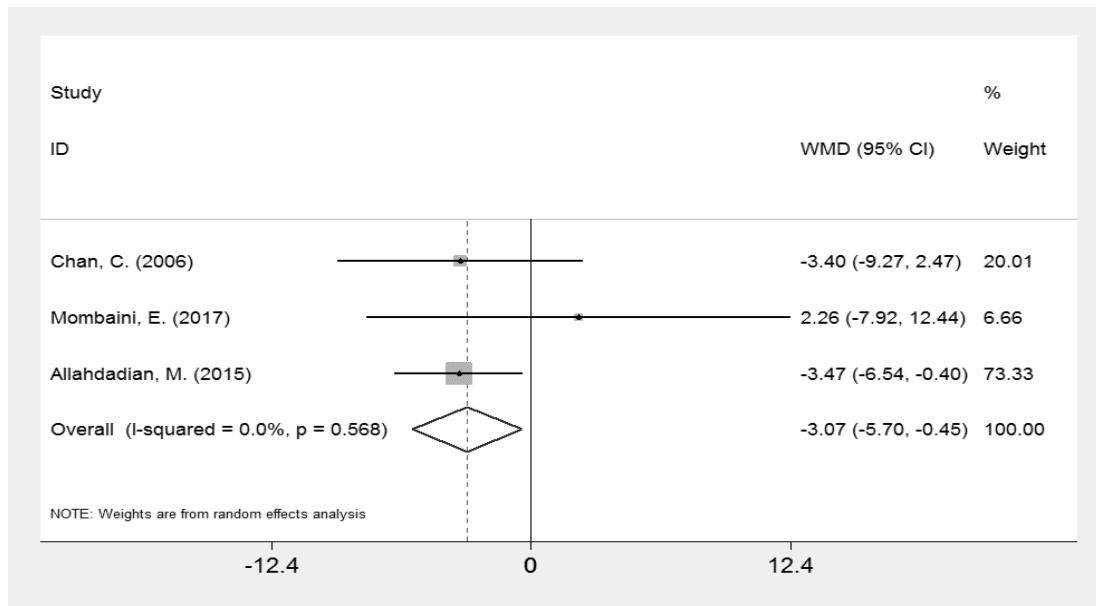


Figure 3. Forest plot for the effect of green tea supplement on body weight

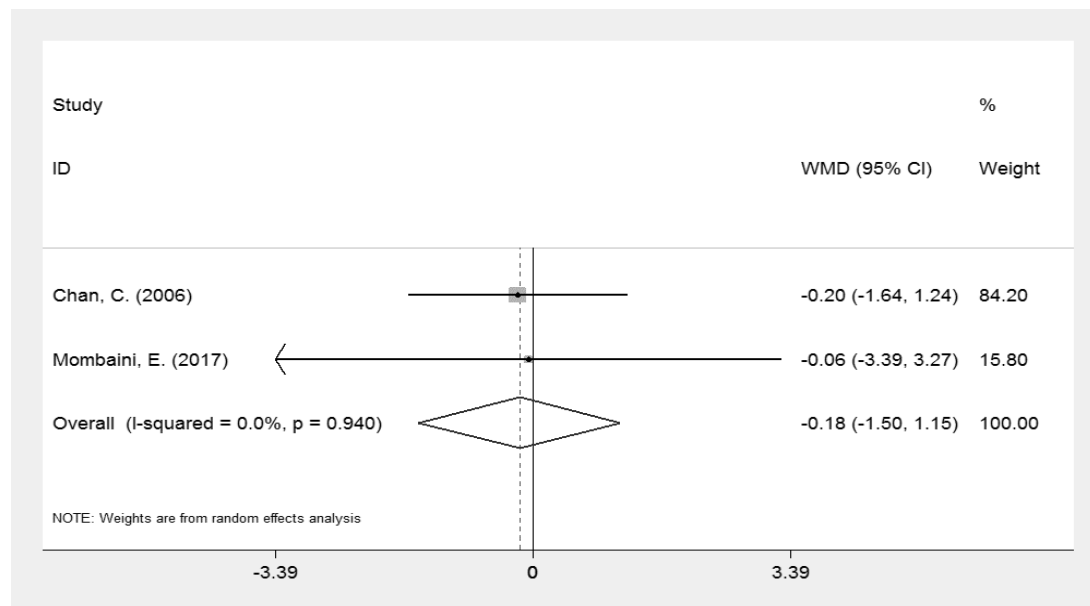


Figure 4. Forest plot for the effect of green tea supplement on BMI

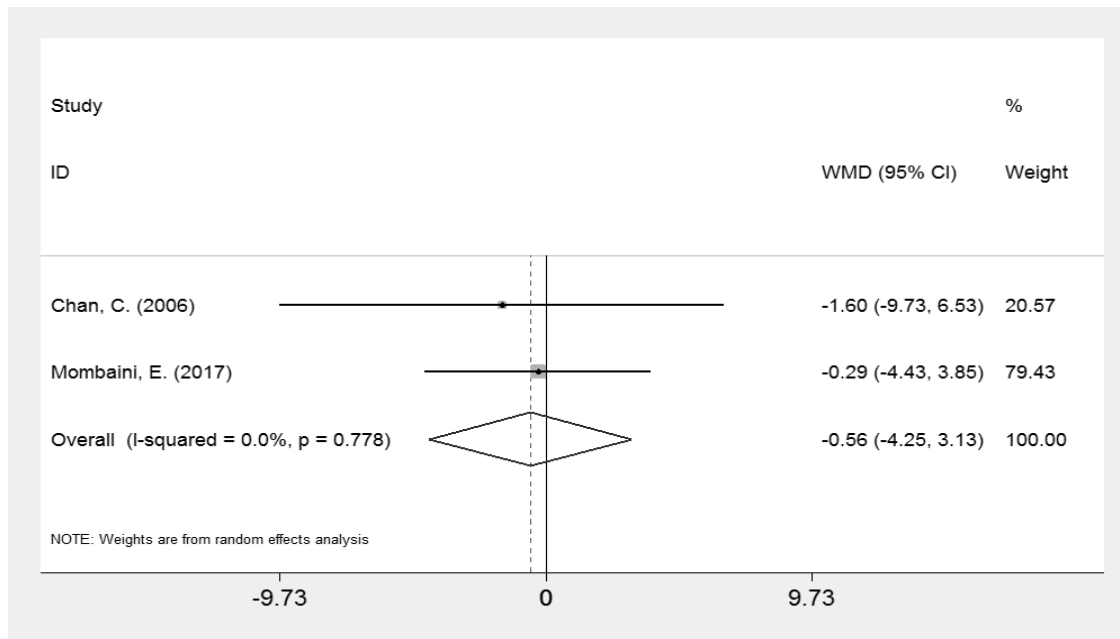


Figure 5. Forest plot for the effect of green tea supplement on body fat percentage

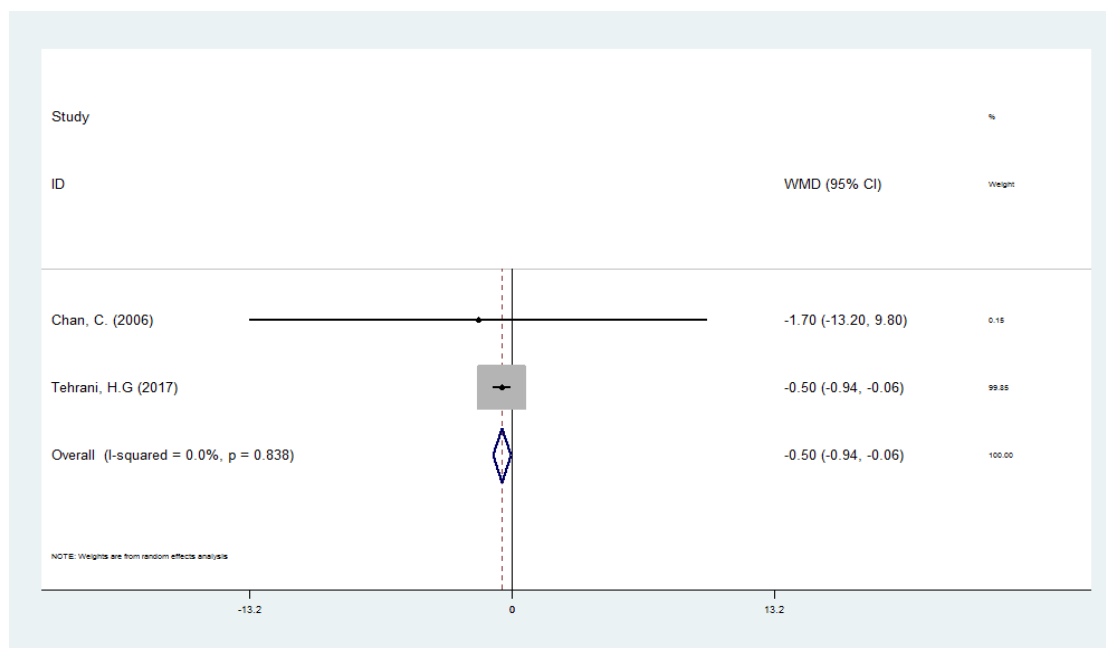


Figure 6. Forest plot for the effect of green tea supplement on fasting insulin

Discussion

The results of current meta-analysis show that green tea supplement significantly reduced body weight, WHR, and fasting insulin, without any beneficial effects on BMI and PBF. To the best of the authors' knowledge, this is the first meta-analysis with pooled effect of green tea extract on

weight, BMI, WHR, and fasting insulin among women with PCOS.

Caffeine and catechins are main compounds of green tea. There are several mechanisms for body weight-lowering effects of green tea. Enzyme catechol-O-methyltransferase (COMT) plays an important role in the degradation of

catecholamines, especially norepinephrine which suppresses the sympathetic nerve system (SNS). Green tea catechins inactivate COMT activity resulted in longer norepinephrine shelf-life, which delays the inhibition of SNS, subsequently stimulating fat oxidation and thermogenesis (Cardoso *et al.*, 2013, Janssens *et al.*, 2013). Another mechanism is known decreasing intestinal fat absorption and increasing fecal fat loss because of reduction in gastric and pancreatic lipase activity (Juhel *et al.*, 2000). Moreover, catechins can increase norepinephrine levels in hypothalamus, which result in suppressing appetite and induction satiety (Auvichayapat *et al.*, 2008). Green tea may upregulate gene expression of enzymes involved in energy expenditure and fat metabolism by stimulating peroxisome proliferator-activated receptor gamma coactivator1-alpha (PGC)-1 α (Roberts *et al.*, 2015). In addition, caffeinated green tea suppresses the enzyme phosphodiesterase (PDE) which may result in weight loss. PDE could degrade cyclic AMP (cAMP) to increase norepinephrine levels then stimulates SNS (Dulloo *et al.*, 1992). Therefore, inactivation of PDE by caffeine increases SNS activity, promoting fat oxidation and thermogenesis (Auvichayapat *et al.*, 2008).

In line with the study findings, a meta-analysis was conducted on 11 studies in 2009 which showed green tea significantly decreased body weight by -1.31 kg (-2.05 to -0.57 , $P < 0.001$) (Hursel *et al.*, 2009) among overweight and obese adults. Another meta-analysis on 14 studies (including 1562 people) reported that there was a significant weight loss after consumption of green tea supplement (-0.95 kg; 95% CI: -1.76 to -0.14) (Jurgens *et al.*, 2012). However, due to high rate of heterogeneity in the latter meta-analysis, authors categorized studies into two subgroups, including Japan and other countries. Their findings revealed that green tea had no effect on weight, BMI, and WC in other countries rather than Japan. In studies conducted in Japan, body weight significantly reduced after green tea supplement (-1.44 kg; 95% CI: -2.38 to -0.51) with no changes in BMI and WC. However, the later study included RCTs

using green tea/green tea extract vs. placebo. These two meta-analyses included studies which applied catechins green tea vs. placebo and high-dose vs. low dose catechins green tea supplements. In addition, they removed studies with a follow-up of less than 12 weeks that may affect results. Another meta-analysis on 5 studies (including 310 people) found no change on weight (-0.78 kg; 95% CI: -2.31 to 0.75); however, BMI reduced (-0.31 kg/m²; 95% CI: -0.88 to 0.27), which were in line with the present study. Another meta-analysis investigated the effect of green tea extract on insulin sensitivity in population at risk of type 2 diabetes in 2014, and fasting serum insulin did not show significant reduction [Standard mean difference (SMD) -0.09 ; 95% CI -0.30 to 0.11] (Wang *et al.*, 2014). In another meta-analysis among type 2 diabetes green tea did not show significant association with fasting insulin (SMD, -0.25 ; 95% CI, -0.64 to 0.15) (Yu *et al.*, 2017). A meta-analysis of cohort studies indicated that green tea consumption more than 4 cups were associated with a reduction of type 2 diabetes risk (RR, 0.96; 95% (CI), 0.92–1.01) (Jing *et al.*, 2009).

Conclusion

The findings showed that consumption of green tea extract may reduce body weight, WHR, and insulin level in women with PCOS.

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This study did not receive any grants from any agencies.

Authors' contributions

Lesani A and Shab-Bidar S contributed to design of the research; Lesani A, Sharafi F and Hatami M contributed to, analysis, or interpretation of the results; Lesani A and Hatami M drafted the manuscript; Shab-Bidar S critically revised the manuscript; and Shab-Bidar S agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Supplementary_Figure 1:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number.	2-3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-8
Risk of bias	22	Present results of any assessment of risk of bias across studies (see Item 15).	8

across studies

Additional analysis 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

DISCUSSION

Summary of evidence 24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). 8

Limitations 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). 9

Conclusions 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research. 9-10

FUNDING

Funding 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. 10

Supplementary Table 1: Search strategy**Search strategy in PubMed**

Concept 1#	Concept 2#	Concept 3#
PCOS [Mesh]	Tea" [Mesh]	Randomized Trials [Mesh]
Syndrome, Polycystic Ovary [Mesh]	EGCG [Mesh]	Randomized Controlled Trial [Mesh]
Syndrome, Polycystic Ovarian [Mesh]	catechin [Mesh]	Random Allocation [Mesh]
Stein Leventhal Syndrome [Mesh]	Tea Polyphenols [Mesh]	Randomised Controlled trials [Mesh]
Ovary Syndrome, Polycystic [Mesh]	Green Tea Extract [Mesh]	Clinical Trial [Mesh]
Sclerocystic Ovary Syndrome [Mesh]	Tea [tiab]	Non-Randomized Controlled Trials as Topic [Mesh]
Polycystic Ovarian Syndrome [Mesh]	Green Tea Oral [tiab]	Controlled Clinical Trials [Mesh]
Ovarian Syndrome, Polycystic [Mesh]	Tea Supplement [tiab]	Randomized Clinical Trial [tiab]
PCOS [tiab]	Green Tea Extract [tiab]	Controlled Clinical Trials [tiab]
Polycystic Ovarian Syndrome [tiab]	Tea Polyphenols [tiab]	Placebo [tiab]
PCOS [tiab]	EGCG [tiab]	Randomised Controlled Trials [tiab]
Stein-Leventhal Syndrome [tiab]	catechin [tiab]	Randomized Trial [tiab]
	"epigallocatechin gallate" [tiab]	Clinical Trial [tiab]
		RCT [tiab]
		Randomised [tiab]