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The effect of green coffee extract supplementation on anthropometric measures in adults: A comprehensive systematic review and dose-response meta-analysis of randomized clinical trials

Omid Asbaghi[a], Mehdi Sadeghian[b,c], Sepideh Rahmani[d], Mahnaz Mardani[a], Mahmoud Khodadost[e,f], Vahid Maleki[g], Aliyar Pirouzi[h], Sepide Talebi[i], Omid Sadeghi[h,j,k,*]

[a] Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran
[d] Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[e] Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[f] Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
[g] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[h] Gerash University of Medical Sciences, Gerash, Iran
[i] Student Research Committee, Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[j] Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
[k] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background and aim: Two meta-analyses summarized data on the effects of green coffee extract (GCE) supplementation on anthropometric measures. However, the accuracy of those meta-analyses is uncertain due to several methodological limitations. Therefore, we aimed to conduct a comprehensive systematic review and dose-response meta-analysis to summarize all available evidence on the effects of GCE supplementation on anthropometric measures by considering the main limitations in the previous meta-analyses.

Methods: We searched available online databases for relevant publications up to January 2020, using relevant keywords. All randomized clinical trials (RCTs) investigating the effects of GCE supplementation, compared with a control group, on anthropometric measures [including body weight, body mass index (BMI), body fat percentage, waist circumference (WC) and waist-to-hip ratio (WHR)] were included.

Results: After identifying 1871 studies from our initial search, 15 RCTs with a total sample size of 897 participants were included in the systematic review and meta-analysis. We found a significant reducing effect of GCE supplementation on body weight (weighted mean difference (WMD): −1.23, 95 % CI: −1.64, −0.82 kg,$P < 0.001$), BMI (WMD: −0.48, 95 % CI: −0.78, −0.18 kg/m^2, $P = 0.001$), and WC (WMD: −1.00, 95 % CI: −1.70, −0.29 cm, $P = 0.006$). No significant effect of GCE supplementation on body fat percentage and WHR was seen. In the dose-response analyses, there was no significant association between chlorogenic acid (CGA) dosage, as the main polyphenol in green coffee, and changes in anthropometric measures.

Conclusion: We found that GCE supplementation had a beneficial effect on body weight, BMI and WC. It provides a cost-effective and safe alternative for the treatment of obesity. Additional well-designed studies are required to further confirm our findings.

Abbreviations: GCE, green coffee extract; CGA, chlorogenic acid; RA, randomized; DB, double-blind; SB, single-blind; BMI, body mass index; BFP, body fat percentage; WC, waist circumference; WHR, waist-to-hip ratio; IGT, impaired glucose tolerance; M, male; F, female; NAFLD, non-alcoholic fatty liver disease

* Corresponding author at: Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, P.O. Box 14155-6117, Iran.

E-mail addresses: Asbaghi.omid@lums.ac.ir (O. Asbaghi), sadeghian.m@ajums.ac.ir (M. Sadeghian), ssv.rahmani@gmail.com (S. Rahmani), mardani.m@lums.ac.ir (M. Mardani), m.khodadost@behdasht.gov.ir (M. Khodadost), malekiv@tbzmed.ac.ir (V. Maleki), Pirouzi@gerums.ac.ir (A. Pirouzi), s.talebi@nutr.mui.ac.ir (S. Talebi), osadeghi@razi.tums.ac.ir (O. Sadeghi).

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1. Introduction

Obesity is one of the main problems of public health which is associated with increased risk of many chronic diseases including diabetes, hyperlipidemia, high blood pressure, atopy, and allergic symptoms and coronary artery disease.[1–4] According to the world health organization (WHO) reports, in 2015, around 3.2 billion adults worldwide were overweight and more than 700 million adults were obese.[5–7]

Several therapeutic approaches including diet modification, pharmaceutical methods, and surgery have been used to control obesity.[8,9] Recently, nutraceuticals have been increasingly used in weight loss programs. Nutraceutical is any substance that might be a food or part of food with medical or health benefits.[10] Soybeans, cranberry juice, green tea, onions, garlic, and tomatoes are examples of nutraceuticals.[10–12] Green coffee is considered as a nutraceutical containing high levels of polyphenols. Chlorogenic acid (CGA) is a major polyphenol compound in green coffee that is acknowledged as a protective agent against chronic degenerative diseases.[13,14] There are the two main forms of green coffee including roasted and unroasted, from which unroasted green coffee contains a higher amount of CGA than roasted one because much of the CGA is lost during the roasting process.[15,16]

It has been shown that intake of green coffee, in the form of extract or beverage, provides beneficial effects on glucose homeostasis, lipid profile, blood pressure, and nerve-related disease.[17] Green coffee may stimulate fatty acid oxidation and inhibit lipogenesis and body fat accumulation through the down-regulation of adipogenesis-related genes.[18,19] Therefore, it might affect obesity measures. However, findings from the previous clinical trials regarding the effect of green coffee extract (GCE) intake on obesity measures are conflicting.[20–34] For example, two studies indicated a reducing effect of GCE supplementation on body weight,[22,27] while others did not find any significant effect.[21,26] Although a recent meta-analysis, conducted by Gorji et al., summarized available data on the effects of GCE supplementation on obesity,[35] the accuracy of its findings was uncertain due to several methodological limitations. For instance, investigators in that meta-analysis included a clinical trial in which a potentially active comparator such as coffee was administered for the control group rather than a placebo supplement.[36] Also, Gorji et al. missed three studies that were eligible according to their inclusion criteria.[20,29,32] The authors also included a quasi-experimental study in which there was no control group and findings in the first phase of the study might be carried over to the second phase.[37] Therefore, a comprehensive meta-analysis examining the effects of GCE supplementation on obesity measures by summarizing all available studies is necessary. Overall, the current comprehensive systematic review and meta-analysis was performed to summarize available findings on the effects of GCE supplementation on anthropometric measures in adults.

2. Methods

This study was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) protocol.[38]

2.1. Literature search

A systematic search was performed in four databases including PubMed, the Cochrane Library, Scopus and Web of Sciences until January 2020. We searched for clinical trials investigating the effects of GCE supplementation on anthropometric measures in adults. The electronic search was conducted using suitable keywords (Supplemental Table 1). There was no limitation in terms of the time and language of publications. Also, we conducted a manual search in reference lists of all relevant studies to avoid missing any eligible study.

2.2. Inclusion criteria

A study had to meet the following criteria for inclusion: (1) Randomized clinical trials (both parallel and cross-over designs); (2) studies that administered GCE in the forms of supplement or powder added to a food or beverage; (3) those that performed on adult subjects ($\geq$18 years old), and (4) studies providing means and standard deviations (SDs) for anthropometric measures, or any other effect sizes from which the calculation of mean and SD was possible. If >1 articles were found for one dataset, the more complete paper was included. Since the weight can be altered during a one-week intervention,[39] we included those clinical trials with at least a one-week duration of intervention. Clinical trials with 3 eligible arms were considered as 2 separate studies. Two independent investigators searched databases and screened the articles to reach feasible relevant papers. Any disagreement was solved by debate.

2.3. Exclusion criteria

We excluded animal studies, reviews, *in vitro* studies, and those conducted on children. Also, grey literature including thesis, conference abstract, and reports was excluded. We also excluded clinical trials without any placebo or control group.

2.4. Data extraction

The following data were extracted from each study by two independent investigators: name of the first author, publication year, individuals' characteristics (mean age, sex), randomization, blinding, sample size (control and intervention groups), dosage of GCE and CGA, duration of intervention, and mean changes ($\pm$ SDs) of anthropometric measures throughout the trial for the intervention and control groups. When data for anthropometric measures were reported in different units, we converted them to the most frequently used unit.

2.5. Study quality

We examined the risk of bias for the selected studies using the Cochrane quality assessment tool designed for clinical trials.[40] This tool contained seven domains including random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. Each domain was given a "high risk" score if the study comprised methodological defects that may have distorted the results, a "low risk" score if the defect was considered ineffectual and an "unclear risk" score if the information was not sufficient to determine the impact. If a study had "low risk" for all domains, it was labeled as a high-quality study with a totally low risk of bias. The risk of bias assessment was done independently by two reviewers.

2.6. Statistical analysis

Mean changes of anthropometric measures, comparing GCE and control groups, were used to obtain the overall effect sizes. The overall effect sizes were expressed as weighted mean differences (WMDs) and 95 % confidence intervals (CIs). The effect sizes were pooled using a random-effects model by DerSimonian and Laird.[41] If the within-group mean changes were not reported, we subtracted the final mean value from the baseline mean value in the control and intervention groups. Also, to calculate the SD, the following formula was applied: SD = square root $[(SD_{pre\text{-}treatment}^{2} + SD_{post\text{-}treatment}^{2}) - (2 \times R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$.[42–44] In this formula, R = 0.8 was supposed as a correlation coefficient which ranges between 0 and 1.[45] We also converted standard errors (SEs), 95 % confidence intervals (CIs), and interquartile ranges (IQRs) to SDs using the method by Hozo et al.,[46] Between-study heterogeneity was assessed using the I^2 statistic value

and P-value for heterogeneity (using the Cochrane's Q test).[47] I^2 value > 50 % or P < 0.05 was considered as significant between-study heterogeneity.[48,49] To identify factors associated with high heterogeneity, whenever possible, subgroup analysis was performed. In order to find the non-linear potential influence of CGA (mg/d) dosage on anthropometric measures, fractional polynomials modeling was performed. Due to the lack of information on the dosage of GCE in some included studies, we decided to perform the non-linear dose-response analysis for CGA dosage. The sensitivity analysis was conducted using the leave-one-out method (removing a single clinical trial in each time and repeating the analysis) to examine the effect of each trial on the pooled effect size. Any potential publication bias was identified using the Egger test. All statistical analyses were accomplished using the STATA software, version 11.0 (Stata Corp, College Station, TX). *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Findings from the systematic review

A total of 1871 studies were identified after searching PubMed (n = 362), Scopus (n = 699), Cochrane electronic databases (n = 117) and Web of Science (n = 693). After removing duplicate publications, 1076 articles remained from which, 1052 irrelevant studies were excluded after screening based on the title and abstract. Out of the remaining 24 studies, we excluded 2 studies that used GCE or green coffee for both intervention and placebo groups.[36,50] One study in which GCE was administered in combination with carnitine was excluded as well.[51] We also excluded a study by Beam et al.[52] because they evaluated the post-exercise effects of GCE intake. The study of Ochiai et al. [53] was also excluded because the authors did not report any effect sizes for anthropometric measures. Moreover, we excluded two quasi-experimental studies with time-series data in which researchers assessed one group of subjects repeatedly both before and after the administration of treatment without considering any control group.[37,54] The study of Vinson et al. was excluded because it was retracted due to invalid data.[55] Also, two eligible studies were conducted on the same dataset[14,27] and therefore, we included the more complete one in the current meta-analysis to avoid double counting data.[27] Finally, 15 randomized clinical trials (RCTs) were included in the meta-analysis [20–34]; 12 RCTs had presented data on body weight,[21–28,30,32–34] 13 for body mass index (BMI),[20–24,26–28,30–34] 4 for body fat percentage, [20,26,29,34] 5 for waist circumference (WC),[26,27,29,30,32] and 4 for waist-to-hip ratio (WHR).[20,23,26,30] Flow diagram of study selection is presented in Supplemental Fig. 1.

Characteristics of the 15 selected RCTs are illustrated in Table 1. The sample size inthe included articles ranged from 20 to 70 participants with a total sample size of 897 persons. Trials were published between 2005 and 2019. Six studies were conducted in Iran,[20,23,27,28,30,33] 2 trials in Japan,[24,31] 2 trials in Spain,[25,29] 2 studies in Korea,[26,34] and other studies were performed in France,[22] Jordan,[21] and Mexico.[32] Four studies were conducted on female subjects,[20,23,26,34] 2 studies were performed on male subjects,[24,28] and other studies included both male and female participants. The dosage of GCE was between 90 and 6000 mg/d. Intake of CGA ranged from 30 to 1200 mg/d across RCTs. The duration of the intervention was from 1 to 12 weeks. Most studies used GCE supplements for the intervention; however, in five studies, participants in the intervention group received GCE powder which should be added to a beverage or food.[20,24,25,29,31] Most proposed trials were parallel except 4 studies which had cross-over design.[20,21,25,29] Except 2 studies that were performed on normal-weight individuals,[21,31] others included overweight or obese subjects. Although one study was conducted on apparently healthy subjects,[21] other studies included patients with overweight or obesity, dyslipidemia, hypertension, metabolic syndrome, and non-alcoholic fatty liver disease. According to the Cochrane Risk of Bias Assessment tool, only one study could be considered as a high-quality study with a totally low risk of bias for all domains of this tool.[27] Three studies were of moderate-quality in which one or more domains had an unclear risk of bias.[23,26,30] Others had low-quality since they had a high risk of bias for one or more domains (Supplemental Table 2).

Out of fifteen RCTs on body weight, three had shown a reducing effect of GCE supplementation on body weight[22,27,33] and others revealed no significant effect. There were four studies in which GCE supplementation resulted in a significant reduction in BMI compared with the control group.[22,23,27,33] There were 3 studies that examined the effect of GCE supplementation on body fat percentage[20,26,29,34]; all reached non-significant effects. Out of five studies on WC,[26,27,29,30,32] only one showed a significant reduction in WC following GCE supplementation[27] and others did not report any significant effect. None of the four studies on WHR showed a significant effect of GCE supplementation.[20,23,26,30]

3.2. Findings from the meta-analysis

Overall, fifteen RCTs with a total sample size of 897 participants were included in the current meta-analysis. In the study of Kozuma et al., there were three intervention arms with different dosages of GCE which each arm of the intervention was considered as a separate study.[24] Two RCTs were carried out on two separate groups of normocholesterolemic and hypercholesterolemic subjects[25,29] and therefore, we considered each group as a separate study.

3.3. The effect of GCE on body weight

Overall, 15 effect sizes from 12 studies with a total sample size of 735 participants were included in the analysis,[21–28,30,32–34]. Pooled effect sizes indicated that GCE supplementation significantly reduced body weight compared to the control group (WMD: −1.23, 95 % CI: −1.64, −0.82 kg; P < 0.001) (Fig. 1). No evidence of between-study heterogeneity was observed (I^2: 0.0 %, $P = 0.50$). The sensitivity analysis revealed that the overall estimate did not depend on a single study. Also, the Egger test rejected our hypothesis about the presence of substantial publication bias ($P = 0.61$).

The 12 studies on body weight were included in the non-linear dose-response analysis. In this analysis, we considered the dosage of CGA, rather than the dosage of GCE, due to the lack of information on the dosage of GCE in some included studies. From this analysis, we found no significant effect of CGA dosage on body weight ($P_{non\text{-}linearity} = 0.30$) (Supplemental Fig. 2A).

3.4. The effect of GCE on BMI

Combining 15 effect sizes from 13 trials,[20–24,26–2830–34] that included 689 participants, we found a significant reducing effect of GCE supplementation on BMI (WMD: -0.48, 95 % CI: -0.78, -0.18 kg/m^2; $P = 0.001$) with an evidence of moderate heterogeneity among studies (I^2: 59.6 %, $P = 0.002$) (Fig. 2). To find the potential sources of heterogeneity, we performed subgroup analyses based on study design (parallel vs. cross-over), duration of intervention (≥8 weeks vs. < 8 weeks), dosage of CGA (≥400 mg/d vs. < 400 mg/d), baseline values of BMI (overweight/obesity vs. normal weight), participants' compliance (acceptable vs. unacceptable/unclear), and type of outcome variable (primary vs. secondary) (Table 2). Subgroup analysis based on all mentioned variables could explain the observed between-study heterogeneity. From these analyses, we found a reducing effect of GCE supplementation on BMI in all subgroups of studies other than those with a cross-over design, studies that were performed on normal-weight participants, those that administered ≥400 mg/d CGA, and studies with < 8 weeks' duration of intervention. The sensitivity analysis revealed that the exclusion of any single study did not alter the overall effect size. Results from the Egger's test showed no evidence of

Table 1
Characteristics of included studies investigating the effects of GCE supplementation on anthropometric measures.

Author, year	Design	Participants, n	Health condition	Age, year[1]	Intervention		Duration (week)	Outcomes (changes)[1]		Adjust/matching
					Intervention group	Control group		Intervention group	Control group	
Park et al. 2010	RA/DB/ parallel	F: 43, Int: 23, Con: 20	Overweight/ obesity	Int: 33.1 ± 9.20 Con: 33.1 ± 9.79	200 mg/d GCE containing 56.8 mg CGA	Placebo	8	Weight: -0.99 ± 1.58 kg BMI: -0.39 ± 0.62 kg/ m2 WC: -0.71 ± 2.68 cm BFP: -1.41 ± 1.91 % WHR: 0.00 ± 0.05	Weight: -0.6 ± 1.43 kg BMI: -0.23 ± 0.53 kg/ m2 WC: -0.26 ± 2.44 cm BFP: -1.38 ± 1.56 % WHR: 0.00 ± 0.044	No
Dellalibera et al. 2006	RA/ Parallel	F/M: 50, Int: 30, Con: 20	Overweight	Int: 19−75 Con: 19−75	400 mg/d GCE containing 180 mg CGA	Placebo	8	Weight: -4.97 ± 1.75 kg BMI: -1.9 ± 0.54 kg/ m2	Weight: -2.4 ± 1.65 kg BMI: -0.9 ± 0.44 kg/m2	Weight, muscle mass, fat mass
Haidari et al. 2017	RA/DB/ Parallel	F: 64, Int: 30, Con: 34	Obesity	20−45	400 mg/d GCE containing 180 mg CGA	Placebo	8	Weight: -4.84 ± 7.23 kg BMI: -4.09 ± 2.65 kg/ m2 WHR: -0.06 ± 0.6	Weight: -2.6 ± 7.80 kg BMI: -1.01 ± 3.10 kg/ m2 WHR: -0.16 ± 0.60	Fat mass, fiber and energy intake, physical activity
Shahmohammadi et al. 2017	RA/DB/ Parallel	F/M: 44, Int: 22, Con: 22	Overweight and NAFLD	Int: 41.36 ± 7.69 Con: 44.50 ± 5.24	1000 mg/d GCE containing 500 mg CGA	Placebo	8	Weight: -3.13 ± 4.05 kg BMI: -1.03 ± 1.65 kg/ m2 WC: -0.95 ± 5.67 cm WHR: -0.01 ± 0.04	Weight: -1.65 ± 4.33 kg BMI: -0.58 ± 1.37 kg/ m2 WC: -0.62 ± 5.02 cm WHR: 0.00 ± 0.06	No
Roshan et al. 2018	RA/DB/ Parallel	F/M: 43, Int: 21, Con: 22	Metabolic syndrome	Int: 52.76 ± 9.83, Con: 51.95 ± 8.67	800 mg/d GCE containing 368 mg CGA	Placebo	8	Weight: -2.08 ± 2.11 kg BMI: -0.84 ± 0.86 kg/ m2 WC: -2.4 ± 2.54 cm	Weight: -0.92 ± 1.3 kg BMI: -0.37 ± 0.52 kg/ m2 WC: -0.66 ± 1.17 cm	Sex
Zuniga et al. 2018	RA/DB/ Parallel	F/M: 26, Int: 12, Con: 14	IGT	Int: 30−60 Con: 30−60	Daily intake of GCE containing 1200 mg CGA	Placebo	12	Weight: -2.5 ± 6.70 kg BMI: -1.2 ± 1.64 kg/ m2 WC: -2.0 ± 6.32 cm	Weight: 0.0 ± 5.02 kg BMI: -0.1 ± 1.61 kg/m2 WC: -1 ± 4.24 cm	No

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Table 1 (*continued*)

Author, year	Design	Participants, n	Health condition	Age, year[1]	Intervention		Duration (week)	Outcomes (changes)[1]		Adjust/matching
					Intervention group	Control group		Intervention group	Control group	
Aghaei et al. 2018	RA/SB/ Cross-over	F: 30, Int: 15, Con: 15	Overweight	Int: 30.4 ± 26.82, Con: 28.5 ± 20.53	Training plus 90 mg/d GCE added to a 250 mL/d hot water	Training	8	BMI: -0.14 ± 2.70 kg/m2 BFP: -0.35 ± 3.64 % WHR: -0.002 ± 0.03	BMI: 0.01 ± 4.80 kg/m2 BFP: -0.36 ± 4.91 % WHR: -0.008 ± 0.03	No
Kim et al. 2012	RA/DB/ Parallel	F: 20, Int: 10, Con: 10	Obesity	> 18	100 mg/d GCE containing 29.4 mg CGA	Placebo	8	Weight: -0.5 ± 4.05 kg BMI: -0.3 ± 1.44 kg/m2 BFP: -0.2 ± 2.75 %	Weight: -0.2 ± 5.60 kg BMI: -0.1 ± 1.20 kg/m2 BFP: 0.2 ± 2.43 %	No
Kozuma et al. 2005	RA/DB/ Parallel	M: 117, Int 1: 29, Int 2: 28, Int 3: 31, Con: 29	Hypertension	Int 1: 42.9 ± 8.2, Int 2: 43.3 ± 8.3, Int 3: 43.4 ± 8.4, Con: 43.1 ± 9.1	Int 1: 46 mg/d GCE containing 25 mg CGA, Int 2: 93 mg/d GCE containing 50 mg CGA Int 3: 185 mg/d GCE containing 100 mg CGA GCE was added to a cup of hot water	Control drink	4	Int 1: Weight: -0.1 ± 8.54 kg, BMI: -0.1 ± 2.53 kg/m2 Int 2: Weight: -0.1 ± 5.06, BMI: 0.00 ± 1.64 Int 3: Weight: 0.00 ± 8.50, BMI: 0.00 ± 2.28 kg/m2	Weight: -0.2 ± 6.70 kg BMI: -0.1 ± 1.96 kg/m2	Blood pressure
Watanabe et al. 2006	RA/DB/ Parallel	M/F: 28, Int: 14, Con: 14	Hypertension	Int: 52 ± 11, Con: 51 ± 8	480 mg/d GCE containing 140 mg CGA in the form of a drink	Placebo drink	12	BMI: 0.1 ± 2.03 kg/m^2	BMI: 0.00 ± 2.27 kg/m^2	No
Lopez et al. 2019	RA/SB/ Cross-over	M/F: 52,: Int: 26, Con: 26	Normocholesterolemics (n = 25) Hypercholesterolemics (n = 27)	18−45	Daily intake of roasted/ unroasted green coffee beverage containing 445.2 mg CGA	Control drink	8	Weight: -0.5 ± 7.13 kg Weight: -1 ± 9.11 kg	Weight: -0.2 ± 8.40 kg Weight: -0.1 ± 9.20 kg	No
Sarria et al. 2018	RA/SB/ Cross-over	M/F: 52,: Int: 26, Con: 26	Normocholesterolemics (n = 25) Hypercholesterolemics (n = 27)	18−45	Daily intake of roasted/ unroasted green coffee beverage containing 445.2 mg CGA	Control drink	8	WC: 0.5 ± 4.29 cm BFP: -1.3 ± 4.21 % WC: -1.2 ± 2.60 cm BFP: -1.8 ± 4.23 %	WC: 0.2 ± 4.30 cm BFP: 0.9 ± 4.42 % WC: -0.2 ± 2.60 cm BFP: -1.0 ± 4.10 %	No
Salamat et al. 2019	RA/DB/ Parallel	M: 70, Int: 35, Con: 35	Dyslipidemia	Int: 39.8 ± 6.4 Con: 38.4 ± 5.6	800 mg/d GCE containing 400 mg CGA	Placebo	8	Weight: -0.64 ± 9.85 kg BMI: -0.19 ± 2.71 kg/m2	Weight: -0.39 ± 4.08 kg BMI: 0.12 ± 1.22 kg/m2	No
Al-Dujaili et al. 2016	RA/SB/ Cross-over	M/F: 32, Int: 16, Con: 16	Healthy	24.6 ± 3.3	1000 mg/d GCE containing 500 mg CGA	Placebo	1	Weight: -0.52 ± 10.40 kg BMI:-0.32 ± 2.73 kg/m2	Weight: -0.06 ± 10.4 kg BMI: -0.08 ± 2.77 kg/m2	Caffeine intake

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Table 1 (*continued*)

Author, year	Design	Participants, n	Health condition	Age, year[1]	Intervention		Duration (week)	Outcomes (changes)[1]		Adjust/matching
					Intervention group	Control group		Intervention group	Control group	
Hosseinabadi et al. 2019	RA/DB/ Parallel	M: 23, F: 21, Int: 21, Con: 23	NAFLD	Int: 41.14 ± 7.87, Con: 41.13 ± 8.47	400 mg/d GCE containing 200 mg CGA	Placebo	8	Weight: -1.64 ± 1.08 kg BMI: -0.57 ± 0.64 kg/ m2	Weight: -0.36 ± 1.32 kg BMI: -0.13 ± 0.44 kg/ m2	Baseline values and energy intake

Abbreviations: GCE: green coffee extract; CGA: chlorogenic acid; RA: randomized, DB: double-blind; SB: single-blind; Int: intervention; Con: control; BMI: body mass index; BFP: body fat percentage; WC: waist circumference; WHR: waist-to-hip ratio; IGT: impaired glucose tolerance; M: male; F: female; NAFLD: non-alcoholic fatty liver disease.

[1] Values are mean ± SD or range (for age).

substantial publication bias ($P = 0.58$).

Out of thirteen RCTs on BMI, twelve studies with complete information on the dosage of CGA were included in the non-linear dose-response analysis,[21–24,26–28,30–32,54,55] Combining 15 effect sizes, no significant non-linear association was seen between CGA dosage and changes in BMI ($P_{non\text{-}linearity} = 0.49$) (Supplemental Fig. 2B).

3.5. The effect of GCE on body fat percentage

Combining 5 effect sizes from 4 studies[20,26,29,34] that included 157 subjects revealed no significant effect of GCE supplementation on body fat percentage (WMD: -0.40, 95 % CI: -1.19, 0.39 percent, P = 0.30, I^2: 0, $P = 0.58$) (Fig. 3). According to the sensitivity analysis, excluding none of the trials had a considerable effect on the overall effect size. Based on the Egger's test ($P = 0.28$), no significant publication bias was observed. Because of the limited number of studies and low variation of CGA dosage, we could not perform the dose-response analysis on body fat percentage.

3.6. The effect of GCE on WC

Overall, there were 5 RCTs with a total sample size of 260 participants in this regard.[26,27,29,30,32] Combining 6 effect sizes from these RCTs, we found that GCE supplementation resulted in a significant reduction in WC compared with the control group (WMD: -1.00, 95 % CI: -1.70, -0.29 cm; $P = 0.006$). There was no evidence of between-study heterogeneity (I^2: 0.0 %, $P = 0.62$) (Fig. 4). Based on the findings from the sensitivity analysis, the overall estimate for WC did not depend on a particular study. No evidence of substantial publication bias was seen ($P = 0.15$). In the non-linear dose-response analysis, we observed that the CGA dosage did not affect WC non-linearity ($P_{non\text{-}linearity} = 0.81$) (Supplemental Fig. 2C).

3.7. The effect of GCE on WHR

Four effect sizes from 4 studies,[20,23,26,30] including 181 people, were included in this meta-analysis. Combining these effect sizes, we found no significant effect of GCE supplementation on WHR (WMD: -0.00, 95 % CI: -0.02, 0.02, $P = 0.97$) with no significant between-study heterogeneity (I^2: 0.0 %, $P = 0.77$) (Fig. 5). The sensitivity analysis revealed that the summary effect size was not influenced by a particular study. There was no evidence of substantial publication bias ($P = 0.46$). Due to the limited number of studies on WHR and low variation of CGA dosage, conducting the dose-response analysis was not possible.

3.8. Adverse events

None of the studies included in the current meta-analysis reported adverse events following GCE supplementation. It seems that the dosages used in the studies are safe for clinical interventions.

4. Discussion

Findings from our meta-analysis showed that GCE supplementation had a significant reducing effect on body weight, BMI, and WC. However, this effect was not significant for body fat percentage and WHR. In the non-linear dose-response analysis, we found no significant association between CGA dosage and changes in anthropometric measures. To the best of our knowledge, this study is the first comprehensive meta-analysis that summarizes earlier RCTs on the effects of GCE supplementation on anthropometric measures.

A large number of observational studies have shown an inverse association between coffee consumption and the risk of obesity.[56,57] In line with prior observational studies, we found that GCE supplementation resulted in a significant reduction in general obesity indicators including body weight and BMI. Such a beneficial effect of GCE

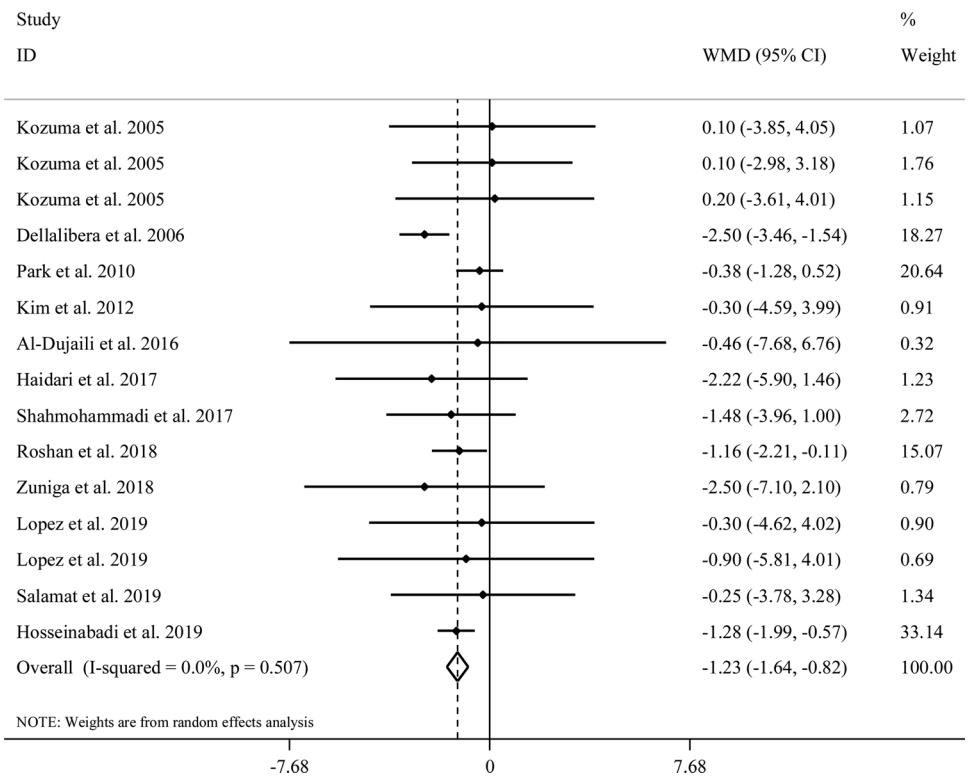

Fig. 1. Forest plot for the effect of GCE supplementation on body weight, expressed as mean differences between intervention and control groups. Horizontal lines represent 95 % CIs. Diamonds represent pooled estimates from the random-effects analysis. GCE: green coffee extract, CI: confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

supplementation on body weight was also reported in an earlier meta-analysis of three RCTs conducted by Onakpoya et al.[58] However, the conclusion drawn by that meta-analysis might be misleading due to some methodological limitations. For instance, Onakpoya et al. included two clinical trials in which participants in the control group received coffee rather than a placebo supplement.[24,53] Also, they included RCTs that examined the efficacy of GCE among participants with overweight or obesity which yields a result that cannot be extrapolated. Another old review on 4 RCTs concluded a minimal reduction in weight following GCE supplementation.[59] In contrast with our findings, a recent meta-analysis, conducted by Gorji et al.[35] revealed no significant effect of GCE supplementation on body weight. However, the presence of several methodological limitations in that meta-analysis made its finding doubtful. For example, Gorji et al. inadvertently missed 3

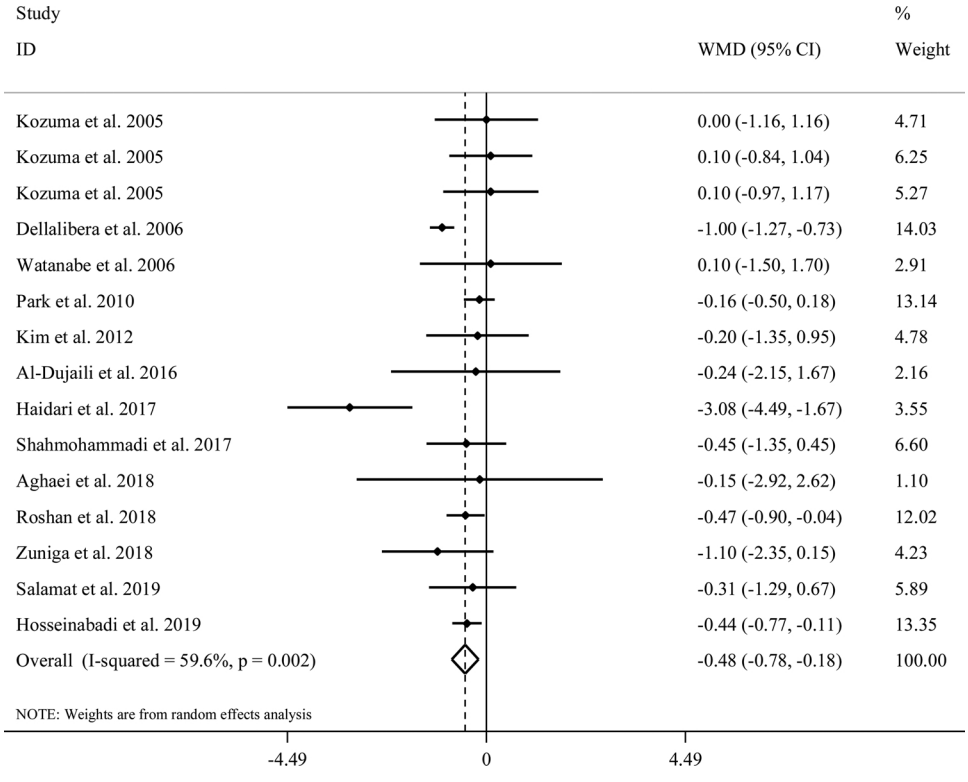

Fig. 2. Forest plot for the effect of GCE supplementation on body mass index, expressed as mean differences between intervention and control groups. Horizontal lines represent 95 % CIs. Diamonds represent pooled estimates from the random-effects analysis. GCE: green coffee extract, WMD: weighted mean difference, CI: confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 2
Subgroup analysis on the effects of GCE supplementation on body mass index.

	Effect size, n	WMD[1]	95 % CI[1]	P-value[2]	Heterogeneity	
					I^2 (%)[3]	P-heterogeneity[4]
Overall effect	15	−0.55	−0.70, -0.40	< 0.001	59.6	0.002
Study design						
Cross-over	2	−0.21	−1.78, 1.36	0.79	0.0	0.96
Parallel	13	−0.56	−0.71, -0.41	< 0.001	65.2	0.001
Intervention duration (week)						
≥8	11	−0.60	−0.75, -0.44	< 0.001	66.7	0.001
< 8	4	0.04	−0.53, 0.62	0.87	0.0	0.99
CGA dosage (mg/d)						
≥400	4	−0.52	−1.08, 0.04	0.07	0.0	0.77
< 400	11	−0.56	−0.71, -0.40	< 0.001	70.2	< 0.001
Baseline BMI						
Overweight and obese	13	−0.56	−0.71, -0.41	< 0.001	64.6	0.001
Normal	2	−0.04	−1.26, 1.18	0.95	0.0	0.79
Compliance						
Acceptable	7	−0.40	−0.63, -0.17	0.001	0.0	0.71
Unacceptable/Unclear	8	−0.67	−0.87, -0.47	< 0.001	74.7	< 0.001
Type of outcome variable						
Primary	7	−0.66	−0.84, -0.47	< 0.001	77.9	< 0.001
Secondary	8	−0.35	−0.61, -0.10	0.007	0.0	0.78

Abbreviation: GCE: green coffee extract, WMD: weighted mean difference; BMI: body mass index; CI: confidence interval; CGA: chlorogenic acid.
[1] Obtained from the fixed-effects model.
[2] Refers to the mean (95 % CI).
[3] Inconsistency, percentage of variation across studies due to heterogeneity.
[4] Obtained from the Q-test.

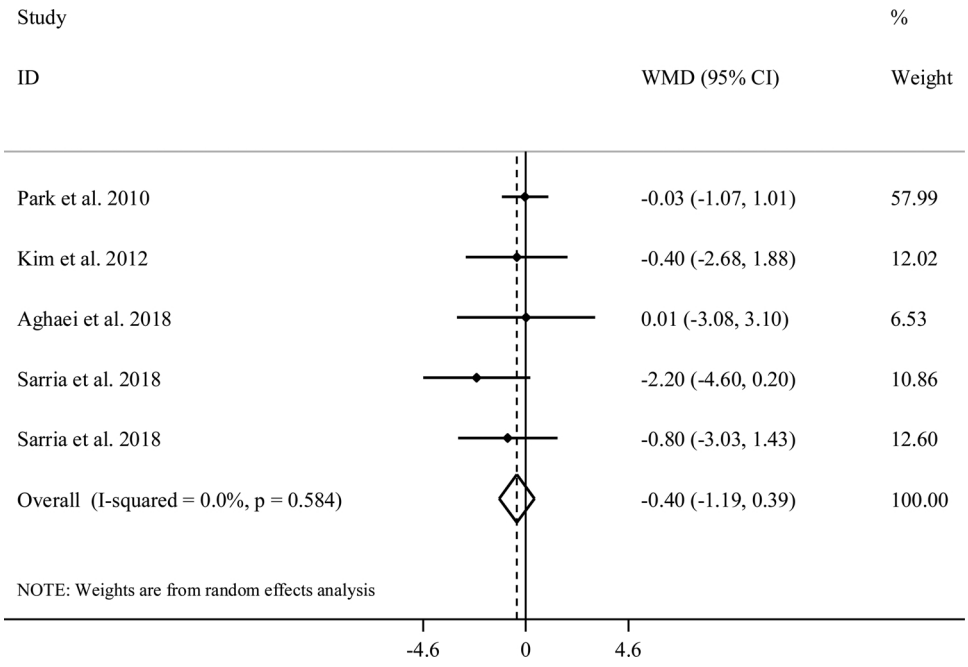

Fig. 3. Forest plot for the effect of GCE supplementation on body fat percentage, expressed as mean differences between intervention and control groups. Horizontal lines represent 95 % CIs. Diamonds represent pooled estimates from the random-effects analysis. GCE: green coffee extract, WMD: weighted mean difference, CI: confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

relevant studies.[20,29,32] They also included one study which used CGA in both intervention and placebo groups[53] and one study with quasi-experimental design.[37] These limitations produced a very high between-study heterogeneity in that meta-analysis, unlike ours, and therefore, the results cannot be accurately interpreted. The lack of significant effect of GCE supplementation on body fat percentage might be due to the minimal influence of green coffee on fat-free mass. This effect prevents a large reduction in body fat percentage. However, the limited number of RCTs in this issue, short duration of intervention and administration of low dose GCE in most studies are other reasons for the lack of significant effect of GCE supplementation on body fat percentage. Some clinical trials have shown that GCE supplementation improves clinical outcomes in patients with obesity-related disorders such as diabetes and non-alcoholic fatty liver disease (NAFLD).[33] Hosseinabadi et al. reported that GCE supplementation improved lipid profile in patients with NAFLD.[33] Chei et al. showed that drinking coffee < 1 cup/wk or ≥3 cups/day was associated with a lower risk of hypertension compared with drinking one cup/day.[60] Overall, it seems that green coffee consumption beneficially affects the clinical outcomes that are directly associated with obesity.

Importantly, a significant reducing effect of GCE supplementation on WC was found in our meta-analysis. In agreement with our findings, a meta-analysis on roasted coffee, not green coffee (which is unroasted), revealed a significant effect of coffee consumption on reduced WC.[56] However, our finding was not consistent with the meta-analysis of Gorji et al.[35] in which GCE supplementation had no significant effect on WC.

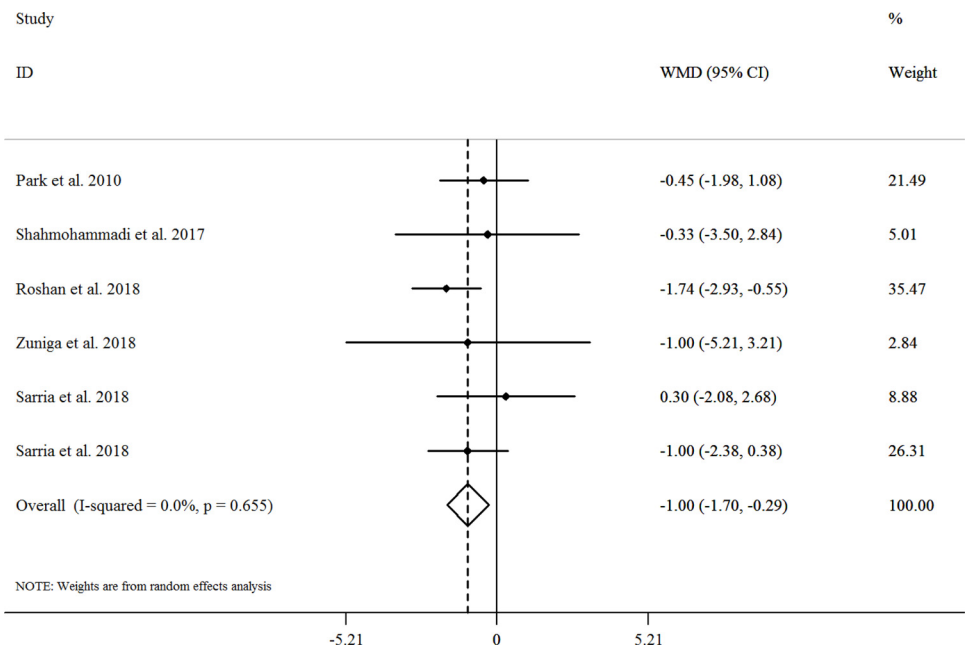

Fig. 4. Forest plot for the effect of GCE supplementation on waist circumference, expressed as mean differences between intervention and control groups. Horizontal lines represent 95 % CIs. Diamonds represent pooled estimates from the random-effects analysis. GCE: green coffee extract, WMD: weighted mean difference, CI: confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

It must be kept in mind that Gorji et al. missed 3 RCTs which reported significant reductions in WC following supplementation with GCE.[20,29,32] Furthermore, other methodological defects of Gorji et al. meta-analysis such as the inclusion of quasi-experimental studies make the results of the meta-analysis uncertain. Unlike WC, we found no significant effect of GCE supplementation on WHR. Although both WC and WHR are indicators of abdominal obesity, WC was shown as a simple and more accurate predictor of abdominal obesity.[61] Since strategies for reducing body weight not always lead to reduced abdominal obesity,[62] reduced WC along with body weight following GCE supplementation are of much importance.

Chlorogenic acid is the main polyphenol compound of green coffee that may provide its possible anti-obesity effects.[13,14] Also, other beneficial effects of green coffee are mostly attributed to its chlorogenic acid content. Among the clinical trials included in the current meta-analysis, green coffee was administered in different forms including extract or beverage. Also, the dosage of green coffee was unclear in some studies. Therefore, dose-response analysis using green coffee dosages was impossible. However, all studies had reported the amount of chlorogenic acid present in the green coffee prescribed and therefore, we decided to conduct the dose-response analysis on the dosage of chlorogenic acid.

Green coffee, as a dietary supplement, refers to raw, unroasted coffee containing a considerable amount of caffeine similar to regular brewed coffee.[25] Green coffee contains a high amount of CGA which is known as a natural antioxidant.[63] Individuals drinking coffee often receive a daily amount of CGA from 0.5 to 1 g.[64] The amount of CGA which was supplemented in the studies included in the current meta-analysis ranged from 57 to 500 mg/d. In animal studies, CGA has been reported to modulate glucose metabolism *via* a reduction in glucose absorption and inhibition of hepatic glucose-6-phosphatase.[36,65] The anti-obesity effect of CGA is mediated by suppressing the accumulation of hepatic triglycerides.[66] The effect is also mediated *via* alteration in levels of plasma adipokines and downregulation of genes associated with adipogenesis and upregulation of genes involved in fatty acid oxidation.[18,19]

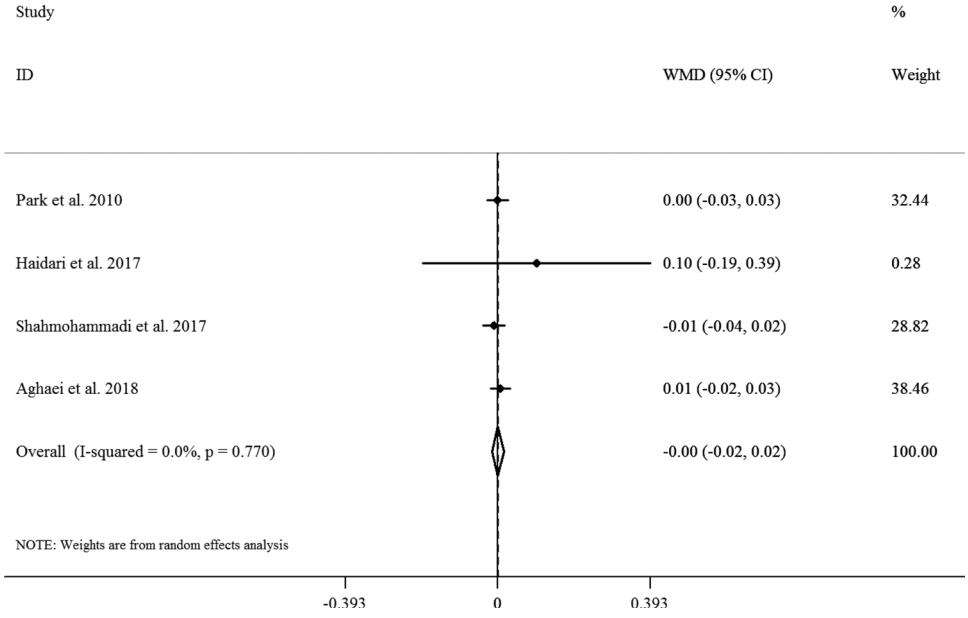

Fig. 5. Forest plot for the effect of GCE supplementation on waist-to-hip ratio, expressed as mean differences between intervention and control groups. Horizontal lines represent 95 % CIs. Diamonds represent pooled estimates from the random-effects analysis. GCE: green coffee extract, WMD: weighted mean difference, CI: confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

The strengths of this study were the inclusion of all clinical trials, written in all languages, investigating the effects of GCE supplementation on anthropometric measures. Lack of publication bias, the presence of low to moderate between-study heterogeneity, and high quality of the most included studies are other strengths of our meta-analysis. However, some limitations should be considered when interpreting our findings. For instance, the lack of evaluation of participants' compliance in a limited number of RCTs, considering anthropometric indices as the secondary outcome variables in some studies, the lack of controlling for baseline values of anthropometric measures in some others, and different study designs should be taken into account.

5. Conclusion

As a whole, findings from this meta-analysis demonstrated a beneficial effect of GCE supplementation in reducing body weight, BMI, and WC. However, it had no significant effect on body fat percentage and WHR. Based on our findings, it seems that consuming the low dosages of GCE (< 400 mg/d) for a long time (≥ 8 weeks) is more effective than the high dosages in a short time. However, clinical trials included in the current meta-analysis revealed no side effects following the consumption of high dosages of GCE. More research is required to evaluate the effects of GCE on fat mass and fat-free mass as well as its effects on controlling appetite. Also, future studies should assess the effect of green coffee on clinical outcomes related to obesity.

Implications for the clinical practice

Surprisingly, GCE reduced body weight by 1.23 kg and BMI by 0.48 kg/m^2 which is half the effect of orlistat on body weight (2.9 kg) and BMI (1 kg/m^2).[67] Therefore, GCE provides a cost-effective and safe alternative for reducing body weight and more importantly abdominal obesity.

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Authors' contributions

OA, MS, SR, MM, and OS contributed to systematic search and data extraction. MK, AP and OS contributed to statistical analyses and data interpretation. OS, VM, ST and MS contributed to manuscript drafting and data interpretation. All authors approved the final manuscript for submission.

Availability of data and materials

All data generated or analyzed are included in the results of the manuscript.

Consent for publication

Not applicable.

Declaration of Competing Interest

All authors declared no personal or financial conflicts of interest.

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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.2020.102424.

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