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Review

Effect of green tea on plasma leptin and ghrelin levels: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Objective: The purpose of this study was to conduct a meta-analysis of randomized controlled trials (RCTs) to assess the effect of green tea on serum leptin and ghrelin concentrations.
Methods: We searched PubMed, ISI Web of Science, Scopus, and Google scholar databases up to December 2016. The searches included RCTs conducted in human adults, and studies on the effect of green tea and green tea extract on serum leptin and ghrelin concentrations as outcome variables. Weighted mean differences (WMDs) and standard errors (SEs) of changes in serum ghrelin and leptin levels were calculated. The random effects model was used to derive the summary mean estimates with their corresponding SEs.
Results: Eleven RCTs were eligible to be included in the systematic review and the meta-analysis. Our analysis indicated that green tea did not significantly affect leptin and ghrelin concentrations in comparison to placebo (WMD = 1.28 ng/mL, 95% confidence interval: −0.49 to 3.05; $P = 0.156$, and WMD = 21.49 pg/mL, 95% confidence interval: −40.86 to 83.84; $P = 0.499$, respectively). However, green tea was associated with an increase in leptin concentration in studies that lasted for more than 12 wk and an increase in ghrelin in women and non-Asians.
Conclusions: Green tea or green tea extract might not be able to change circulatory leptin and ghrelin levels, especially with short-term interventions. More RCTs with longer duration of treatment and higher doses are necessary to assess green tea's effect on fat mass and obesity hormones.

Introduction

Obesity is the most common health problem worldwide. More than 50% of Americans are overweight [1–3]. Obesity increases the risk of many chronic diseases such as diabetes mellitus, cancer, osteoarthritis, cardiovascular disease, and hyperlipidemia [4–7]. Increased energy intake or decreased energy expenditure is the main cause for the development of obesity; therefore, reducing energy intake and sustaining energy expenditure is a solution to lose weight [8].

Losing 5% to 10% of the initial body weight leads to beneficial health effects [9,10]. For most obese subjects, modest weight loss is a realistic goal, but long-term weight maintenance might be unsuccessful, because people do not easily change their diets and activities adequately [11,12]. Therefore, finding some helpful strategies for weight maintenance is relevant. Natural herbal supplements, like green tea, may be a useful agent in this regard [13,14].

Green tea (GT) has the most significant effects on chronic diseases such as cardiovascular disease [15] because it contains antioxidants such as catechins [16]. Several studies have indicated that drinking tea, especially GT, can protect against chronic diseases like obesity [17]. GT may reduce adiposity through several mechanisms: 1) by inhibiting catechol-O-methyl transferase enzyme (COMT) and, consequently, increasing thermogenesis and fat oxidation [13]; 2) by reducing adipocyte

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differentiation and proliferation during lipogenesis [14]; and 3) by changing obesity-related hormones such as leptin and ghrelin. Leptin is produced by brown adipose tissue, skeletal muscle, ovaries, pituitary glands placenta, stomach, bone marrow, liver, and mammary epithelial cells, but is primarily secreted by the adipocytes in white adipose tissue [18]. Leptin helps to regulate energy balance by inhibiting hunger. In obesity, sensitivity to leptin decreases, resulting in an inability to detect satiety; however, recent evidence has indicated that in obese animals, leptin can increase lipolysis by promoting phosphorylation of the enzyme hormone-sensitive lipase (HSL) [19]. Furthermore, leptin can have an affect on the circulatory system, lung surfactant activity, fertility, the brain, and bones [20]. Ghrelin is another novel hormone secreted mainly by the stomach, and regulates energy metabolism, feeding behavior, and gastrointestinal function [21,22]. Ghrelin stimulates appetite, increases food intake, and promotes lipogenesis. In humans, ghrelin can increase food intake by circulating in the bloodstream at the hypothalamus [22]. Some randomized clinical trials (RCTs) have assessed the effect of GT or green tea extract (GTE) on leptin and ghrelin levels; however, the results are inconsistent. In one study, GTE intake for 16 wk increased ghrelin concentration, but leptin concentration did not change significantly [23]. In another study, 12 wk of GTE intake decreased leptin concentration significantly [8], but Westerterp-Plantenga et al. [24] reported that GTE for 48 wk did not change leptin and ghrelin concentrations.

According to our research results, no systematic review or meta-analysis has tried to assess the effect of GT consumption on ghrelin and leptin concentrations. Because the data published on such an association are conflicting, we attempted a systematic review to summarize the results from RCTs conducted on human adults. The purpose of our review was to determine whether GT or GTE protects against obesity in humans by changing obesity hormones and, if possible, to perform a meta-analysis to quantify the effects.

Materials and methods

Systematic searches using PubMed, EMBASE, Scopus, and Google scholar were conducted for the period up to October 2016 using the following key words: "green tea," "green tea extract," "green tea extract AR25," "catechin," "catechins," "EGCG," "camellia sinensis," "tea polyphenols," "Catechinic Acid," "Acid, Catechinic," "*sinenses*, *Camellia*," "*Thea sinensis*," "*sinenses*, *Thea*," "tea polyphenols," "Adipokines," "leptin," "adipocytokines," and "ghrelin." For searching exact terms and group search terms, quotation marks and parentheses were used, respectively. Asterisks were used to search all words deriving from one key word, and Boolean operators (AND and OR) were used for designing search strategies. To find additional relevant articles, reference lists of related studies were also checked. Our objective was to determine the potential effect of taking GT or GTE on leptin and ghrelin. We did not have any restrictions on language, publication time, and study design. To find relevant studies, M.H. and F.N. screened titles and abstracts; M.H., F.N., and F.H. solved discrepancies through group discussions.

Inclusion criteria

The included studies met the following criteria: 1) original article, 2) clinical trial, 3) adult subjects, 4) use of GT or GTE as an intervention, and 5) assessment of serum ghrelin and leptin levels as outcome measures.

Exclusion criteria

Articles with at least one of the following characteristics were excluded: 1) unclear data, 2) use of other food or food supplements with GT or GTE, and 3) studies of short duration (<1 wk).

Quality assessment

The quality of articles was scored on a 5-point Jadad scale [25]. Clinical trials were evaluated on randomization, double blinding, and reporting of withdrawals and dropouts with numbers and reasons. With a maximum possible score of 5, articles with scores >2 were defined as high quality, and those with scores ≤2 were defined as low quality.

Data extraction

We extracted the names of the lead authors, sample size, study design (randomized parallel, crossover, or non-randomized intervention trial), participants' sex, age, body mass index (BMI), numbers of subjects in intervention and control groups, study duration, and means ± SD of ghrelin and leptin for intervention and control groups before and after the intervention period. One study reported the mean with standard error (SE), and we calculated the SD values by multiplying the SE by the square root of the sample size in each group [26]. Two studies expressed the results as means with 95% confidence intervals [27,28].

Statistical analysis

We performed this meta-analysis on the mean difference of changes and their corresponding SE values for leptin and ghrelin. To calculate the summary mean estimates and SE, we used the DerSimonian and Laird random effects model, which takes in account between-study variations [29]. To examine the heterogeneity between studies, we used Cochran's Q test and I^2 [30]. Subgroup analysis was done to identify the source of heterogeneity. The heterogeneity of subgroups was evaluated by using the fixed effect model. Sensitivity analysis was performed to explore the extent to which inferences might be attributed to a particular study or a group of publications. Publication bias was assessed by visual inspection of funnel plots [31]. Egger's regression asymmetry test and Begg's adjusted rank correlation test were used to carry out formal statistical examination of funnel plot asymmetry [30]. We performed all statistical analyses using Stata, Version 11.2 (Stata, College Station, TX, USA). P values <0.05 were considered to indicate significance.

Results

Our search retrieved 607 articles, and 366 were duplicate articles. After removing the duplicate articles, there remained 241 articles, 19 of which were selected after screening titles and abstracts [8,23,24,26–28,32–44] (Fig. 1). After reading the full texts, we excluded 8 articles because they did not meet the inclusion criteria: Six articles used other supplements or diets besides GT and GTE [38,39,41–44], and 2 articles had unclear data [37,40]. Eleven articles were eligible to be included in the systematic review and meta-analysis. Eleven articles assessed the effect of GT on leptin, and 7 articles assessed the effect of GT on ghrelin (Table 1). The studies included 927 adults ages

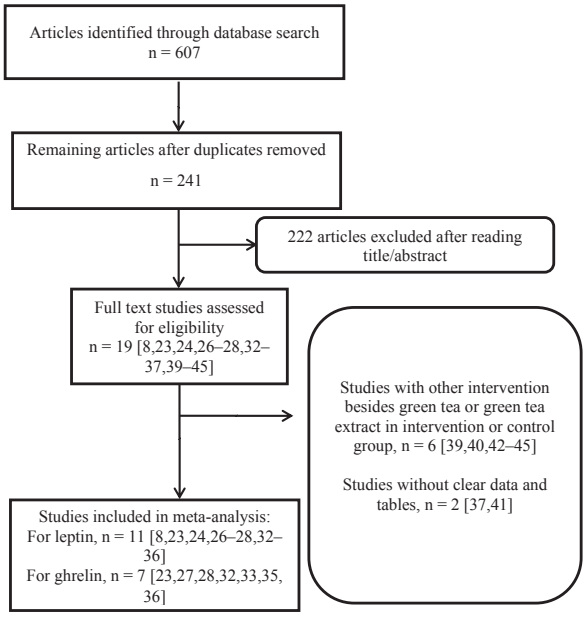

Fig. 1. Study selection process.

Table 1
Randomized controlled trial studies included in meta-analysis

First author (y), country	Sex	Age (y)	Study design	Duration	Intervention	Control	Subjects	Jadad score	Results
Hsu (2011), Taiwan [23]	44 F, 24 M	51.35 ± 9.1*	Randomized, double-blind, placebo-controlled clinical trial	16 wk	500 mg GTE 3×/d	500 mg placebo (cellulose) 3×/d	Obese individuals with type 2 diabetes	3	Serum leptin did not change significantly; however, serum ghrelin increased significantly
Hsu (2008), Taiwan [32]	78 F	43.45 ± 11.85	Randomized, double-blind, placebo-controlled clinical trial	12 wk	400 mg GTE 3×/d	400 mg placebo (cellulose) 3×/d	Obese women	2	Serum leptin did not change significantly; however, serum ghrelin increased significantly
Hursel (2009), Netherlands [8]	22 F, 18 M	44.6 ± 2	Randomized, placebo-controlled, double-blind parallel trial	13 wk	45 mg GTE and 25 mg caffeine/capsule, 6 capsules/d	Placebo (450 mg vegetable oil/capsule; 6 capsules/d)	Overweight and moderately obese subjects	3	Serum leptin decreased significantly
Liu (2014), Taiwan [33]	45 F, 32 M	54.25 ± 6.8	Double-blind, randomized placebo-controlled clinical trial	16 wk	500 mg GTE 3×/d	500 mg placebo (cellulose) 3×/d	Patients with type 2 diabetes mellitus and lipid abnormalities	1	Serum leptin and ghrelin did not change significantly
Dostal (2016), USA [27]	237 F	60.9 ± 0.45	Randomized, double-blind, placebo-controlled trial	48 wk	4 GTE capsules (328 catechin, 211 mg EGCG)/d	Placebo capsules (816 mg maltodextrin, 808 mg cellulose, 8 mg magnesium stearate)	Overweight/obese postmenopausal women	3	Serum leptin and ghrelin did not change significantly
Dostal (2016), USA [28]	121 F	60.0 ± 0.65	Randomized, double-blind, placebo-controlled clinical trial	48 wk	GTE: 843 mg EGCG/d	816 mg maltodextrin, 808 mg cellulose, 8 mg magnesium stearate	Overweight/obese postmenopausal women	2	Serum leptin and ghrelin did not change significantly
Westerterp-Plantenga (2005), Netherlands [24]	38 F/M	18–60	Randomized placebo-controlled double-blind parallel trial	13 wk	GTE: 270 mg EGCG and 150 mg caffeine/d	450 mg placebo (vegetable oil)	Overweight/moderately obese subjects; habitual low-caffeine consumers (caffeine consumption <300 mg/d)	2	In low-caffeine intake: Serum leptin decreased significantly after GTE consumption
	38 F/M	18–60	Randomized placebo-controlled double-blind parallel trial	13 wk	GTE: 270 mg EGCG and 150 mg caffeine/d	450 mg placebo (vegetable oil)	Overweight and moderately obese subjects. habitual high caffeine consumers (caffeine consumption >300 mg/d)	2	In high-caffeine intake: Serum leptin decreased significantly after GTE or placebo consumption
Auvichayapat (2008), Thailand [34]	42 F, 18 M	48.95 ± 4.96	Randomized placebo-controlled double blind parallel trial	12 wk	250 mg GTE 3×/d	Placebo (cellulose)	Overweight adults	3	Serum leptin did not change significantly
Basu (2011), USA [26]	17 F, 5 M	42.5 ± 10	Single-blind randomized clinical trial	8 wk	GTE: 2 capsules and 4 cups water/d	4 cups water/d	Obese subjects with metabolic syndrome	2	Serum leptin did not change significantly
	20 F, 5 M	42.5 ± 10	Single-blind randomized clinical trial	8 wk	Green tea: 4 cups/d	4 cups water/d	Obese subjects with metabolic syndrome	2	Serum leptin did not change significantly
Chen (2016), Taiwan [35]	77 F	44.5 ± 11.4	Double-blind randomized clinical trial	12 wk	GTE: 856.8 mg EGCG/d	500 mg placebo (cellulose) 3×/d	Women with central obesity	1	Serum leptin did not change significantly; however, serum ghrelin decreased significantly
Diepvens (2006), Netherlands [36]	46 F	41.6 ± 10.0	Double-blind, randomized clinical trial	Leptin: 87 d Ghrelin: 32 d	GTE: 1206.9 mg catechins with low-calorie diet	Placebo (maltodextrin 2790.0 mg/d)	Overweight women	2	Serum leptin and ghrelin did not change significantly

EGCG, epigallocatechin-3-gallate; F, female; GTE, green tea extract; M, male
* Mean ± SD.

Table 2
Subgroup analyses of leptin and ghrelin concentrations stratified by previously defined study characteristics

	No. of trials	Effect size (95% CI)	*P*	I^2 (%)	*P* for heterogeneity	*P* for between-subgroup heterogeneity
Leptin						
Overall	13	1.28 (−0.49 to 3.05)	0.156	96.1	<0.0001	—
Duration						0.003
<12 wk	6	−0.48 (−2.06 to 1.11)	0.556	75.2	0.001	
≥12 wk	7	2.90 (0.17 to 5.62)	0.037	97.8	<0.0001	
Region						<0.0001
Asia	5	−0.11 (−1.13 to 0.91)	0.836	60.3	0.039	
Non-Asia	8	1.91 (−0.95 to 4.77)	0.189	97.5	<0.0001	
Placebo						<0.0001
Cellulose	5	−0.11 (−1.13 to 0.91)	0.836	60.3	0.039	
Oil	3	6.22 (−0.28 to 12.72)	0.061	97.9	<0.0001	
Maltodextrin	3	0.56 (−0.32 to 1.44)	0.211	70.6	0.033	
Water	2	−5.20 (−9.90 to −0.50)	0.030	17.9	0.270	
Sex						<0.0001
Female	8	0.13 (−0.73 to 0.99)	0.763	76.5	<0.0001	
Male and female	5	1.70 (−2.11 to 5.51)	0.763	96.9	<0.0001	
Health status						0.016
T2DM or MetS	4	−0.88 (−3.18 to 1.42)	0.453	60.70	0.054	
Healthy	9	2.22 (−0.02 to 4.47)	0.052	97.3	<0.0001	
Ghrelin						
Overall	7	21.49 (−40.86 to 83.84)	0.499	95.5	<0.0001	—
Duration						<0.0001
<12 wk	3	57.49 (−50.56 to 165.55)	0.297	92.9	<0.0001	
≥12 wk	4	−4.29 (−85.90 to 77.32)	0.918	96.4	<0.0001	
Region						0.001
Asia	4	16.2 (−99.64 to 131.68)	0.786	97.5	<0.0001	
Non-Asia	3	43.93 (20.12 to 67.75)	<0.0001	20.1	0.286	
Placebo						0.001
Cellulose	4	16.02 (−99.64 to 131.68)	0.786	97.5	<0.0001	
Maltodextrin	3	43.93 (20.12 to 67.75)	<0.0001	20.1	0.286	
Sex						<0.0001
Female	5	56.97 (6.99 to 106.95)	0.025	88.0	<0.0001	
Male and female	2	−57.71 (−180.2 to 64.79)	0.356	96.1	<0.0001	
Health status						<0.0001
T2DM	5	56.97 (6.99 to 106.95)	0.025	88.0	<0.0001	
Healthy	5	−57.71 (−180.2 to 64.79)	0.356	96.1	<0.0001	

MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus

18–60 y. The intervention periods ranged from 8 to 48 wk. GTE dose ranged from 270 and 1500 mg/d, and in one article 4 cups of GT was used as the intervention.

Meta-analysis results

Effect of GT on leptin and ghrelin

As outlined in Table 2, GT did not significantly change serum leptin and ghrelin levels. For leptin, one trial examined both GTE and GT compared with the control [26], and another article examined the effect of GTE on participants with habitually low and high caffeine intakes [24]. Therefore, the weighted mean difference change for leptin was calculated from 13 effect sizes, which were extracted from 11 trials. Our results indicated no significant changes in subjects who consumed GT (weighted mean difference = 1.28 ng/mL, 95% CI: −0.49 to 3.05; $P = 0.156$) compared with the control group. Significant heterogeneity was observed between the studies ($I^2 = 96.1$, $P < 0.0001$). The weighted mean difference change for ghrelin was calculated from seven effect sizes. Overall, GT did not significantly affect ghrelin concentrations (weighted mean difference = 21.49 pg/mL, 95% CI: −40.86 to 83.84; $P = 0.499$) compared with the control group. There was substantial heterogeneity between the studies ($I^2 = 95.5\%$, $P < 0.0001$). The meta-regression test based on the dosage of green tea extract did not reveal any dose–response association for serum leptin changes (β coefficient = −0.0039, $P = 0.106$).

Subgroup and sensitivity analysis

Subgroup analyses indicated that the pooled effect of GT on leptin levels was influenced by the duration of the intervention (<12 wk versus ≥12 wk) and the placebo. A significant increase in leptin levels was found in studies that lasted more than 12 wk (weighted mean difference = 2.90 ng/mL; 95% CI: 0.17–5.62; $P = 0.037$), whereas there was a non-significant reduction (weighted mean difference = −0.48 ng/mL; 95% CI: −2.06, 1.11; $P = 0.556$) in studies that lasted less than 12 wk (Fig. 2). Between subgroups, the heterogeneity for duration was significant ($P = 0.003$). In studies in which water was consumed by the control group, leptin decreased significantly in the GT group (weighted mean difference = −5.20 ng/mL; 95% CI: −9.90 to −0.50) compared with the control group (Table 2). The results of more subgroup analyses based on sex, region, and health status are summarized in Table 2.

The subgroup analyses indicated that the pooled effects of GT on ghrelin levels are influenced by the region of study (Asia versus non-Asia) and the placebo. Region-based subgroup analysis revealed that GT significantly increased ghrelin levels in non-Asian countries, but could not significantly affect levels in Asian countries (heterogeneity between subgroups = 0.001) (Fig. 3). In studies in which maltodextrin was consumed by the control group, ghrelin increased significantly in the GT group (weighted mean difference = 43.93 pg/mL; 95% CI: 20.12–67.75) as compared with the control group (Table 2). The results of more subgroup analyses based on sex and study duration are summarized in Table 2.

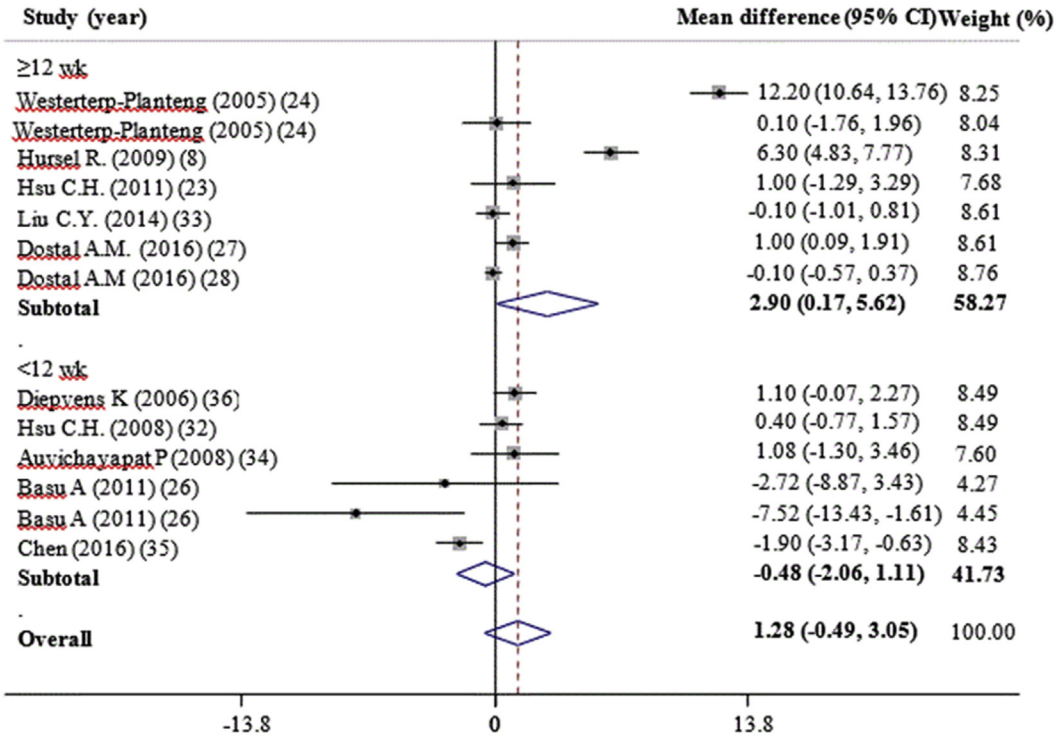

Fig. 2. Forest plot of the effect of green tea consumption on leptin. CI, confidence interval.

The sensitivity analysis revealed that the removal of each trial did not significantly influence the pooled effect of GT on leptin and ghrelin concentrations.

Publication bias

Funnel plots for leptin and ghrelin were visually symmetrical, and the results of Egger's test did not reveal any evidence of publication bias (for leptin: $P = 0.459$, and for ghrelin $P = 0.741$).

Discussion

Our results indicated that GT and GTE cannot change ghrelin and leptin concentrations as compared with placebo, but the

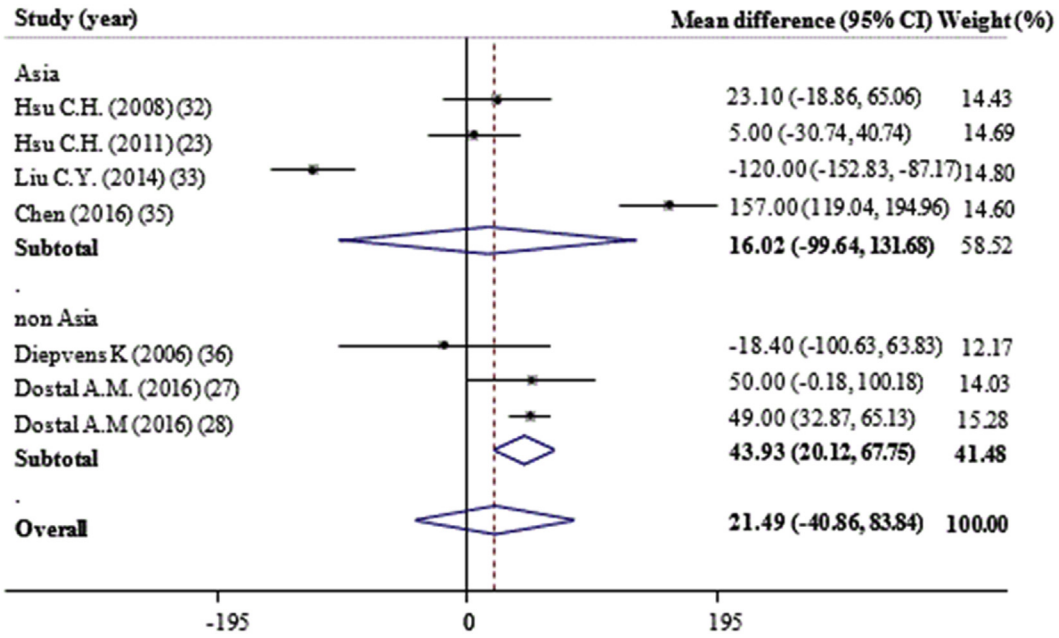

Fig. 3. Forest plot of the effect of green tea consumption on ghrelin. CI, confidence interval.

studies that lasted more than 12 wk increased leptin levels significantly. Our results on ghrelin concentration revealed that GT intake in women and non-Asians increased ghrelin levels significantly. To the best of our knowledge, this is the first meta-analysis to summarize the effects of GT and GTE on leptin and ghrelin concentrations. In their meta-analysis, Li et al. [45] proposed that tea cannot change leptin and ghrelin concentration in patients with type 2 diabetes, but they did not perform subgroup analysis to determine the effect of green tea on ghrelin and leptin levels. Although our subgroup analysis based on health status confirmed the conclusion made by Li et al. on leptin level, green tea increased ghrelin levels significantly in diabetic patients. More trials are needed to confirm our result, because this result was derived from only two articles.

In vitro studies indicated that flavonoid compounds such as catechins can reduce the activity of COMT [24,46]. The reduction of COMT activity can decrease body weight through the increased effect of norepinephrine on fat oxidation and weight reduction by increased energy expenditure [24]. The null relation between GT and ghrelin and leptin concentrations could be due predominantly to the lack of change in BMI, fat mass, and health status. According to the result of a recent Cochrane review evaluating the effects of GT on weight loss, GT is associated with small, non-significant decreases in body weight [47]. Reduction of the risk factors for several diseases related to overweight and obesity requires a loss of 5% to 10% of body weight [48]; and therefore, small losses resulting from GT are not likely to be clinically meaningful in changing obesity-related hormones.

In this meta-analysis, beneficial effects of GT intake on leptin were obtained in studies that lasted more than 12 wk. The reduction of inflammation can increase leptin secretion. In a recent meta-analysis, acute consumption of GT was not found to have any effect on inflammation [49]. According to recent evidence, long-term GT consumption can reduce inflammation, because GT can decrease inflammation by suppressing the inflammatory route activated by nuclear factor-κB [50]. A recent systematic review revealed that GT exerted anti-inflammatory effects only in studies longer than 3 mo [51].

The results of the current meta-analysis indicate that GT can increase ghrelin secretion in non-Asian people. There are several possible explanations for this result. For example, different countries define obesity by different ranges of BMI. In addition, the average consumption of GT differs between Asians and non-Asians. Because of the higher consumption of GT by Asians, it is possible that higher dosages of GT are needed to observe significant changes in these populations as compared with non-Asians.

We observed a significant effect of GT on ghrelin levels in women. Inconsistent with our findings, a recent study revealed a significant increase in ghrelin secretion particularly in women with BMI enhancement [52]. However, it should be kept in mind that this result was derived from only five studies with small samples.

Our meta-analysis has several limitations that must be taken into account. First, there were no separate data for the two genders to analyze separately the effect size on each sex; therefore, the difference in effects of GT on ghrelin and leptin levels in men and women remains unknown. RCTs that try to assess the effects of GT on leptin and ghrelin concentrations in men and women separately are necessary. Second, data on food intake were not included in most articles; therefore, we could not consider these articles in our analysis. We also could not find enough evidence to explain direct significant effect of GT on ghrelin in women. Even though fat mass changes are very important in leptin levels, body composition changes (fat mass, lean body mass, and waist circumference) were not reported in most of the articles. This meta-analysis has some strengths. In our meta-analysis, the studies were conducted in different countries; therefore, differences in habits and lifestyles were included in this study. Most articles in our meta-analysis followed participants for more than 12 wk, and based on recent evidence, continuous ingestion of catechin-rich beverages will be more effective [53]. We also did not impose any limitations for time and language in our meta-analysis.

In conclusion, our meta-analysis on RCTs found that GT and GTE cannot change circulating leptin levels in studies less than 12 wk in duration, but they can increase leptin concentrations in studies longer than 12 wk. GT and GTE cannot change ghrelin concentration in studies less than 12 wk and more than 12 wk, but can increase ghrelin levels in women and non-Asians. There is a need for more RCTs to assess the effect of GT on fat mass and obesity hormones and determine the effect of GT or GTE on different sexes.

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Conflict of interest disclosure

The authors have nothing to declare.

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