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Review

The effect of green-coffee extract supplementation on obesity: A systematic review and dose-response meta-analysis of randomized controlled trials

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ABSTRACT

Background: Given that the most recent systematic review investigating Green-Coffee Extract (GCE) as a weight loss facilitator was nearly a decade ago and that the authors reported there no consensus on the effect of GCE/CGA (Chlorogenic acids) on body composition indices, a comprehensive systematic review and dose-response meta-analysis of all available randomized controlled trial (RCTs) was undertaken to examine the effect of GCE and CGA intervention on body weight (BW), body mass index (BMI) and waist circumference (WC) in adults.
Methods: We conducted a systematic search of all available randomized controlled trials (RCTs) performed up to June 2019 in the following electronic databases: PubMed, Scopus and Google Scholar. RCTs that investigated the effect GCE/CGA Supplementation on BW, BMI and WC in adults were included for final analysis. The pooled weight mean difference (WMD) of included studies was estimated using a random-effects model.
Results: A total of 13 articles with 16 RCTs were included in the meta-analysis. Results revealed significant reduction in BMI (WMD: −0.403 kg/m^2, 95% CI: −0.800, −0.005, p = 0.047) and no significant change in BW (WMD: −0.585 kg, 95% CI: −1.498, 0.329, p = 0.210) and WC (WMD: −0.847 cm, 95% CI: −1.764, 0.071, p = 0.070). In the subgroup analysis, studies that were conducted on baseline BMI ≥25 kg/m^2 revealed a significant greater reduction in body weight and BMI than those performed on baseline BMI <25 kg/m^2. Moreover, short supplementation periods of less than 4 weeks had no effect.
Conclusion: The results of current meta-analysis study support the use of GCE supplementation for the improvement of obesity indices, with sub-group analysis highlighting greater improvements in individuals with a starting BMI ≥25 kg/m^2.

Introduction

Obesity is regarded as a major public health issue, globally (Clark, 2017), and can be defined by irregular fat accumulation or excess amount of body fat in relation to globally established thresholds (Abarca-Gómez et al., 2017). Previous evidence from the World Health Organization (WHO) estimates a total of 1.9 billion overweight and 650 million adults were obese in 2016 (Organization, 2011). Moreover, by 2030, it has been predicted that 58% of world population will be obese (Kelly et al., 2008). Several genetic factors, metabolism, poor diet, lack of physical activity, as well as cultural conditions are major factors which shape the onset of obesity (Kimokoti and Millen, 2011). Obesity and overweight individuals with these chronic circumstances have been strongly linked to many preventable diseases such as diabetes, non-

Abbreviations: BMI, body mass index; BW, body weight; CGA, chlorogenic acids; GCE, Green-Coffee Extract; RCT, randomized controlled trial; WC, waist circumference; WMD, weighted mean difference

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Table 1
Characteristics of eligible studies.

Author, Country, year	Clinical trial design	Population	Sex	Sample size GCE/Placebo	Duration	Outcome	Intervention Intervention group	Placebo group
Kozuma et al., Japan,2005 **(a)**	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	31/29	4 weeks	Weight, BMI	185 mg/d GCBE (Chlorogenic acids = 54%, Caffeine = 12%)	NR
Kozuma et al., Japan,2005 **(b)**	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	28/29	4 weeks	Weight, BMI	93 mg/d GCBE(Chlorogenic acids = 54%, Caffeine = 12%)	NR
Kozuma et al., Japan,2005 **(c)**	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	29/29	4 weeks	Weight, BMI	46 mg/d GCBE(Chlorogenic acids = 54%, Caffeine = 12%)	NR
Dellalibera et al., 2006	randomised double-blind clinical trial/parallel	Volunteers with overweight problem	Both	30/20	8 weeks	Weight, BMI	400 mg/d GCBE svetol(decaffeinated and rich in chlorogenic acids 45%)	400 mg/d Maltodextrin
Watanabe et al., Japan, 2006	randomised double-blind clinical trial/parallel	adults with mild hypertension	Both	14/14	12 weeks	BMI	125 ml/day fruit and vegetable juice mixed with GCE contain 140 mg/d CGA	125 ml/d fruit and vegetable juice only
Thom et al., Norway, 2007	randomised double-blind clinical trial/parallel	overweight people	Both	15/15	8 week	Weight	200 mg/d GCBE(chlorogenic acids 45–50% by weight 90–100 mg)	Nescafé® instant coffee
Park et al., 2010	randomised double-blind clinical trial/parallel	Overweight women	women	23/20	8 weeks	Weight, BMI, WC	200 mg/d GCBE (Caffeine = 12.6%, Chlorogenic acids = 28.4%)	NR
Al-Dujaili et al., Jordan, 2016	randomized single-blind clinical trial/cross-over	healthy volunteers	Both	8/8	1 week	Weight, BMI	1000 mg/d GCBE(containing 500 mg/d of CGAs and 25 mg Caffeine)	25 mg/d tablet of caffeine
Haidari et al., Iran, 2017	randomised double-blind clinical trial/parallel	obese women	Women	30/34	8 weeks	Weight, BMI	400 mg/d GCBE(180 mg of CGA, and caffeine of less than 0.01%)	400 mg/d starch
Shahmohammadi et al., Iran, 2017	randomised double-blind clinical trial/parallel	Non-Alcoholic Fatty Liver Disease	Both	22/22	8 weeks	Weight, BMI, WC	1000 mg/d GCBE(50% chlorogenic acid)	1000 mg/d starch
Roshan et al., Iran, 2018	randomised double-blind clinical trial/parallel	patients with the metabolic syndrome	Both	21/22	8 weeks	Weight, BMI, WC	800 mg/d GCBE((Caffeine = 1.81%, Chlorogenic acids = 46%))	NR
Martínez_López et al., Spain, 2019	randomized single-blind clinical trial/cross-over	Hypercholesterolemic subjects	Both	27/27	8 weeks	Weight	6 g/d coffee contain(445 mg CGA & 121 mg caffeine)	water or an isotonic drink, caffeine and polyphenol free
Martínez_López et al., Spain, 2019	randomized single-blind clinical trial/cross-over	normocholesterolemic subjects	Both	25/25	8 weeks	Weight	6 g/d coffee contain(445 mg CGA & 121 mg caffeine)	water or an isotonic drink, caffeine and polyphenol free
Salamat et al., Iran, 2019	randomised double-blind clinical trial/parallel	patient with dyslipidemia	Men	36/34	8 weeks	Weight, BMI	800 mg of decaffeinated GCBE with 50% chlorogenic acid	placebo capsule contained 400 mg of starch.
Kim et al., Korea, 2012	randomised double-blind clinical trial/parallel	Mildly Obese Women	Women	10/10	8 weeks	Weight, BMI	210 mg/d dextrin +100 mg/d GCBE(Chlorogenic acids = 29.4%, Caffeine = 13.6%)	310 mg/d dextrin
Soga et al., Japan,2013	randomized single-blind clinical trial/cross-over	Healthy male subjects	Men	18/18	4 weeks	Weight, BMI	150 ml/d test beverage contain (329 mg CGA and 50 mg Caffeine)	150 ml/d test beverage contain (51 mg Caffeine)

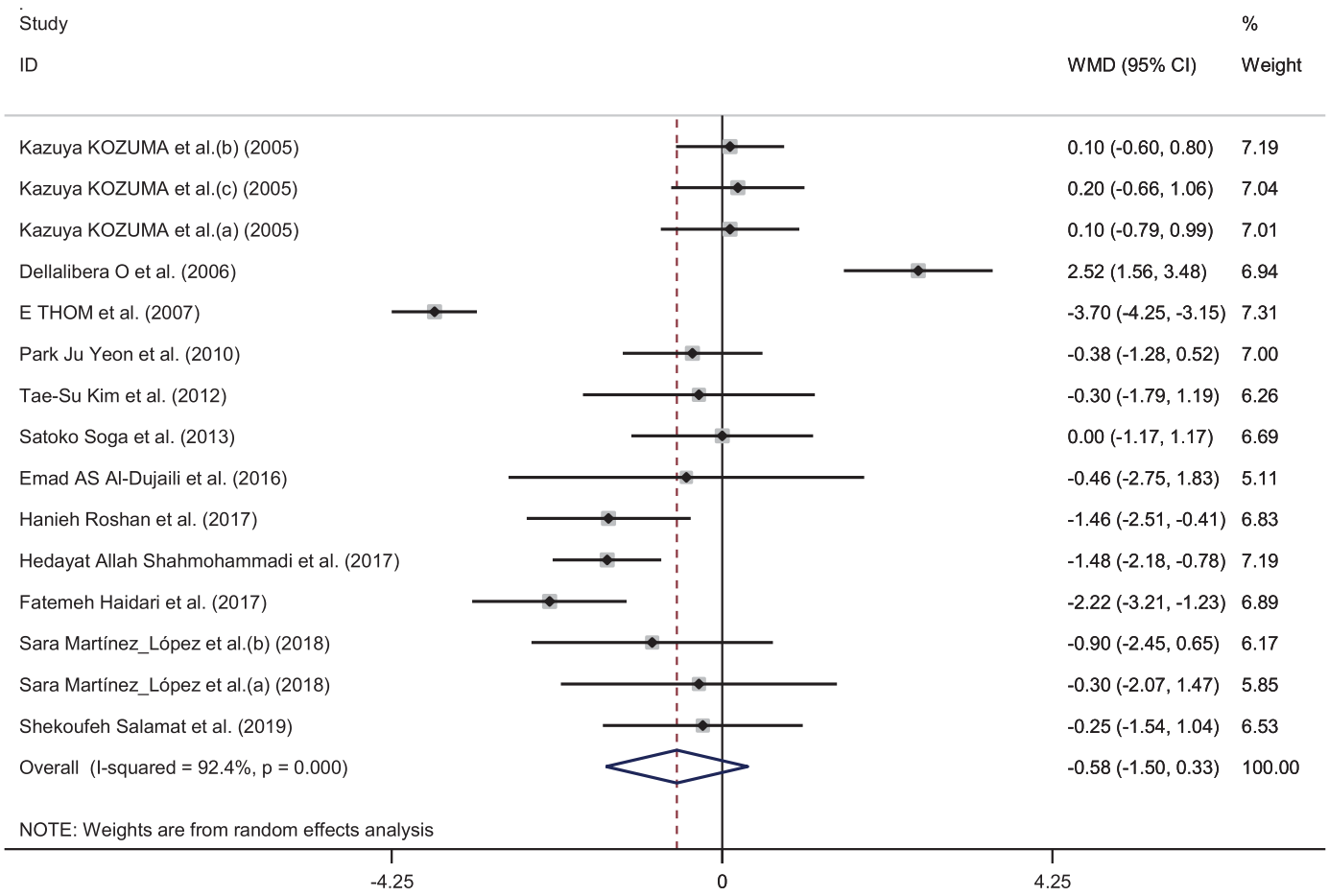

Fig. 1. Forest plot of randomized controlled trials investigating the effects of green coffee extract administration on body weight.

alcoholic fatty liver disease (NAFLD), coronary artery disease, hypertension, various types of cancers, and mental health disorders (Dehal et al., 2011; Faith et al., 2011; Steele et al., 2017; Willey et al., 2011).

Traditional intervention strategies include lifestyle intervention and hypocaloric diets combined with or without exercise, and have been shown inconsistent for treating overweight and obesity long term (MacLean et al., 2015). Recently, herbal supplementation has been shown to be a common method for weight loss; however, the efficacy of many of these supplements remains unclear and needs to be examined more closely. Green coffee bean extract (GCBE) is one such supplement which is purported to elicit positive effects on weight loss (Clifford, 1999). Green coffee bean refers to unroasted mature or immature coffee bean, and are a rich source of polyphenols, particularly comprised of high amounts of chlorogenic acids (CGA) (Clifford, 1999). CGAs are the major phenolic components with antioxidant characteristics exist in GCE; actually, CGA are a family of esters such as quinic acid and several hydroxycinnamic acids (caffeic, ferulic and coumaric acids) (Upadhyay and Mohan Rao, 2013); however, considerable amounts of CGA are destroyed during roasting procedure (Ludwig et al., 2014). Consumption of GCE and CGA has several, putative, positive biological effects, such as inhibition of fat accumulation, the potential to reduce body weight and body mass indices (Haidari et al., 2017; Roshan et al., 2018), mitigation of blood pressure (Onakpoya et al., 2015), and modulation postprandial of glucose metabolism through the reduction of the intestinal absorption (Thom, 2007).

Recent evidence has suggested that CGA is likely to have hypoglycemic and anti-lipidemic effects through mechanisms such as down-regulating the activity of fatty acid synthesis enzymes in the cytosol of the liver cells. This significantly increases the activity of fatty acid oxidative enzymes in the mitochondria of liver cells (Budryn et al., 2017; Tanaka et al., 2009). However, clinical trials on weight loss characteristics of GCE and CGA are controversial and contradictory. Several studies have declared that GCE supplementation is inversely related to indices of body composition (Haidari et al., 2017; Roshan et al., 2018). In contrast, numerous studies did not support these outcomes (Dellalibera et al., 2006; Kozuma et al., 2005). Given that the most recent systematic review investigating GCE as a weight loss facilitator was nearly a decade ago (Onakpoya et al., 2011) and that the authors reported there no consensus on the effect of GCE/CGA on body composition indices, a comprehensive systematic review and dose-response meta-analysis of all available randomized controlled trial (RCTs) was undertaken to examine the effect of GCE and CGA intervention on body weight (BW), body mass index (BMI) and waist circumference (WC) in adults.

Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was employed in writing the present study (Moher et al., 2009).

Search strategy

The literature search was performed in four databases including PubMed/Medline, Scopus, Web of sciences, and Google Scholar to identify clinical trials that examined the effects of GCE supplements on obesity indices from database inception to June 2019. The amalgamation of MESH and non-MESH terms were used as follows: “Chlorogenic

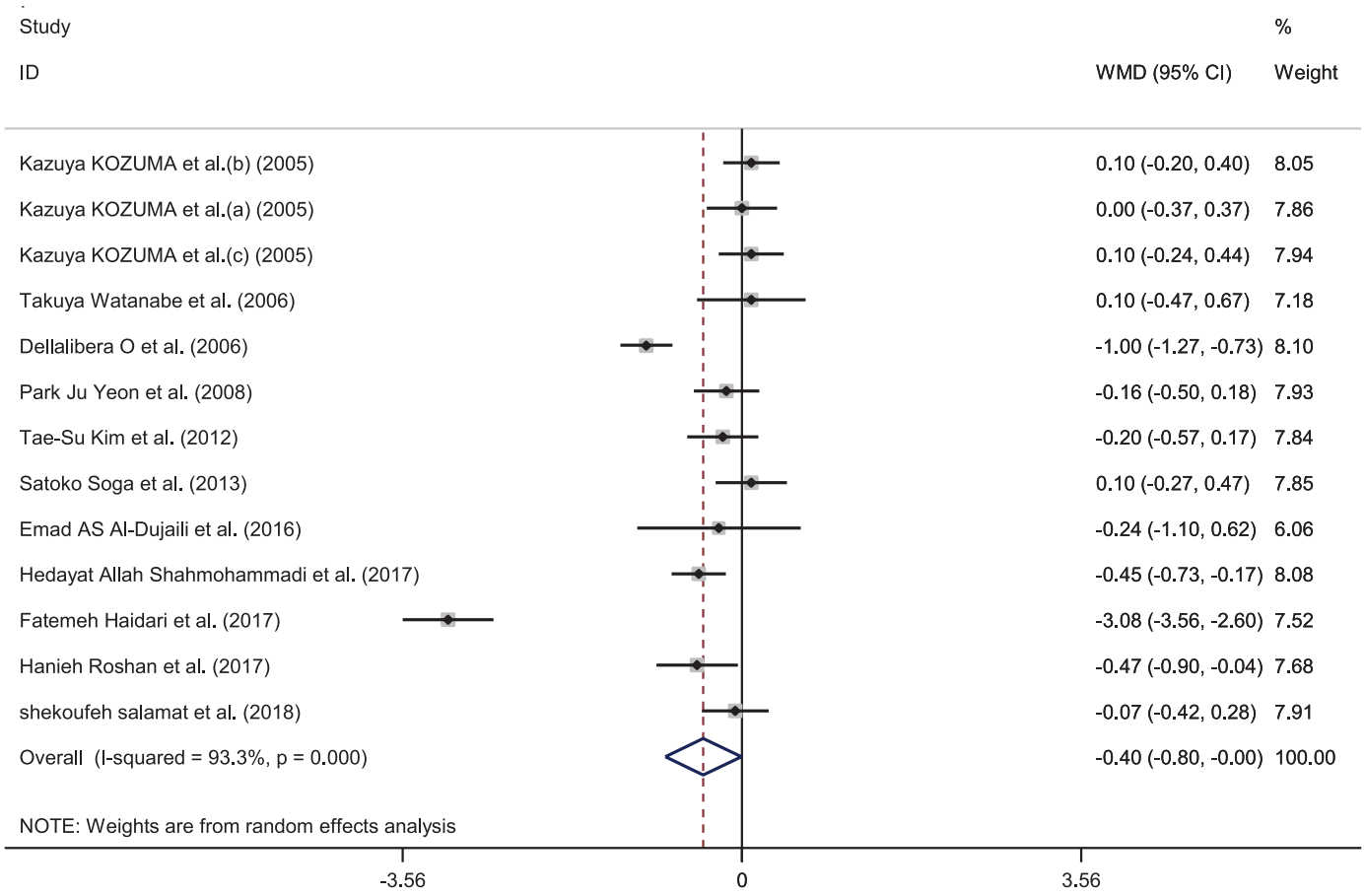

Fig. 2. Forest plot of randomized controlled trials investigating the effects of green coffee extract supplementation on BMI.

Acid"[tiab] OR "Chlorogenic Acid"[Mesh] OR "green coffee"[tiab] OR "green coffee extract"[tiab] AND "Clinical Trials as Topic"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR RCT[Title/Abstract] OR "Intervention Studies"[Title/Abstract] OR "intervention"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR "randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "random"[Title/Abstract] OR "randomly"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "placebo"[Title/Abstract] OR "assignment"[Title/Abstract]. Moreover, we conducted a search by hand in all reference lists of eligible articles, and related reviews in order to avoid omitting any relevant article.

Eligibility criteria

We considered studies that were: (1) randomized placebo-controlled trials with crossover or parallel design (2), publications that were carried out on adult individuals more than 18 years of age (3), studies that report sufficient data on baseline and final trials of BW or/and BMI or/and WC in both GCE/CGA and control groups (4), and studies that conducted the intervention with any green coffee species. Also, we excluded articles if they: (1) were conducted using children, pregnant women or animals (2), were not placebo-controlled trials (3), did not report enough information on the outcomes in GCE or control groups (4), or examined the effects of GCE along with other interventions in combinations. Grey literature such as conference papers, dissertations, and patents were omitted as well.

Data extraction

Two independent investigators (A.N and HKV) did the study selection whereas a chief researcher (Y.Z) was also present to resolve any disagreements. In case of absence of reporting data in the published studies, we emailed the corresponding author to request the required data. The following data was acquire from each study: first study author's name, year of publication, age and sex of subjects, trial duration, study location, type and dosage of GCE supplements, study design, health status of participants, number of participants in each group, mean and SD of outcome measures at baseline, post-trial, and/or changes in outcome measures from baseline to the end-of-study. If a study reported multiple data at diverse time points, only the most recent were included.

Quality assessment

Methodological quality and risk of bias of included studies was determined by combining the Cochrane scoring system (Moher et al., 2009). This tool assesses possible sources of bias in randomized trials, which include: random sequence generation, concealment of allocation to conditions, inhibition of awareness of the allocated intervention,

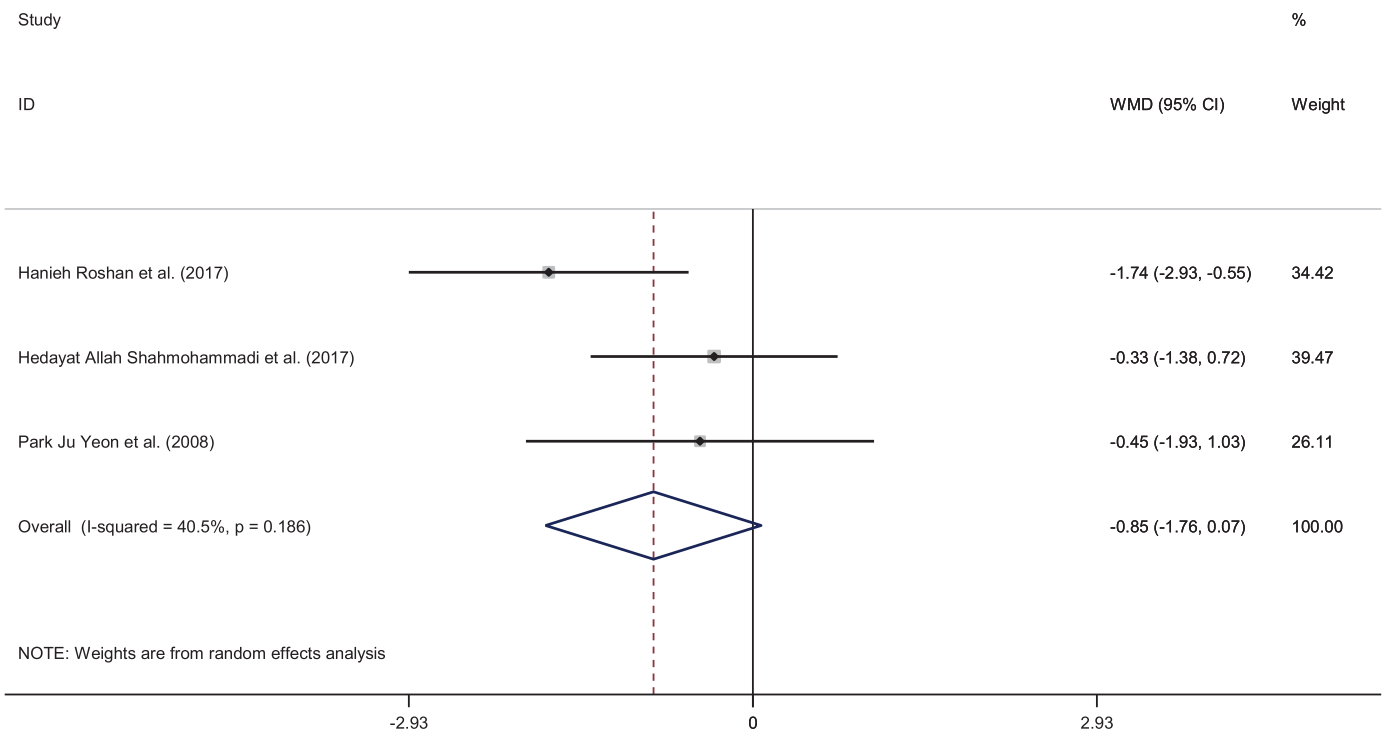

Fig. 3. Forest plot of randomized controlled trials investigating the effects of green coffee extract supplementation on WC.

blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Three scores of yes, no, and unclear could be given to each above-mentioned item, which are referred as high risk, low risk, and unknown risk respectively (Supplemental Table 1).

Data synthesis and statistical analysis

Mean change and standard deviation (SD) of the outcome measures were used to estimate the mean differences between the intervention group and the control group at follow-up. If data was reported in a different format, standard calculations were performed to derive the mean and SD (Higgins, 2011; Hozo et al., 2005). For example, if the SD of the mean difference was not reported in the studies, we acquired it using the following formula: SD_{change} = square root $[(SD_{baseline}^2 + SD_{final}^2) - (2 \times R \times SD_{baseline} \times SD_{final})]$. In order to estimate effect sizes, the random-effects model (using DerSimonian-Laird method) was used and results were provided across weighted mean difference (WMD) and 95% CI. We conducted subgroup analysis to discover potential sources of heterogeneity among the studies. The sensitivity analysis was done by the one-study exclude (leave-one-out) method, to discover the impact of each study on the overall effect size. Publication bias was assessed by means of visual calculation of funnel plots and Egger's tests (Egger et al., 1997). If any publication bias was detected, it was tested via the 'trim and fill' approach (Palmer et al., 2008). All statistical analyses were implemented using Stata software (Stata Corp. College Station, Texas, USA).

Results

Study selection

The initial database search returned 831 articles and 2 articles were recognized by a hand search; after duplicates were removed 646 articles remained. After screening based on the title and abstract 24 articles yielded for full-text review. Finally, 13 articles were included in this meta-analysis (Supplemental Fig. 1). Of 13 included papers, 12 articles with 15 studies reported the effect of GCE on BW (Al-Dujaili et al., 2016; Dellalibera et al., 2006; Haidari et al., 2017; Kim et al., 2012; Kozuma et al., 2005; Martínez-López et al., 2019; Park et al., 2010; Roshan et al., 2018; Salamat et al., 2019; Shahmohammadi et al., 2017; Soga et al., 2013; Thom, 2007), 11 articles with 13 trails on BMI (Al-Dujaili et al., 2016; Dellalibera et al., 2006; Haidari et al., 2017; Kim et al., 2012; Kozuma et al., 2005; Park et al., 2010; Roshan et al., 2018; Salamat et al., 2019; Shahmohammadi et al., 2017; Soga et al., 2013; Watanabe et al., 2006), and 3 articles on WC (Park et al., 2010; Roshan et al., 2018; Shahmohammadi et al., 2017).

Characteristics of the included studies

The characteristics of the included studies are summarized in Table 1. These studies were published between 2005 and 2017 and were conducted in the Iran (Haidari et al., 2017; Roshan et al., 2018; Salamat et al., 2019; Shahmohammadi et al., 2017), Jordan (Al-Dujaili et al., 2016), South Korea (Kim et al., 2012; Park et al., 2010), Japan (Kozuma et al., 2005; Soga et al., 2013; Watanabe et al., 2006), Spain (Martínez-López et al., 2019), Norway (Thom, 2007), France (Dellalibera et al., 2006). The follow-up period ranged from 1 to 12 weeks. Daily recommended dosage of GCE varied between 46 and 6000 mg in these studies. All studies were done on both sexes except for three trials, which were done exclusively on women (Haidari et al., 2017; Kim et al., 2012; Park et al., 2010) and four studies on only men (Kozuma et al., 2005; Salamat et al., 2019). The sample size in the included trials ranged from 20 to 70. Participants in include studies were patients with the metabolic syndrome (Roshan et al., 2018), patients with dyslipidemia (Martínez-López et al., 2019; Salamat et al., 2019), NAFLD (Shahmohammadi et al., 2017), obese and overweight people (Dellalibera et al., 2006; Haidari et al., 2017; Kim et al., 2012; Park et al., 2010; Thom, 2007), healthy volunteers (Al-Dujaili et al., 2016; Soga et al., 2013) and patients with hypertension (Kozuma et al., 2005; Watanabe et al., 2006).

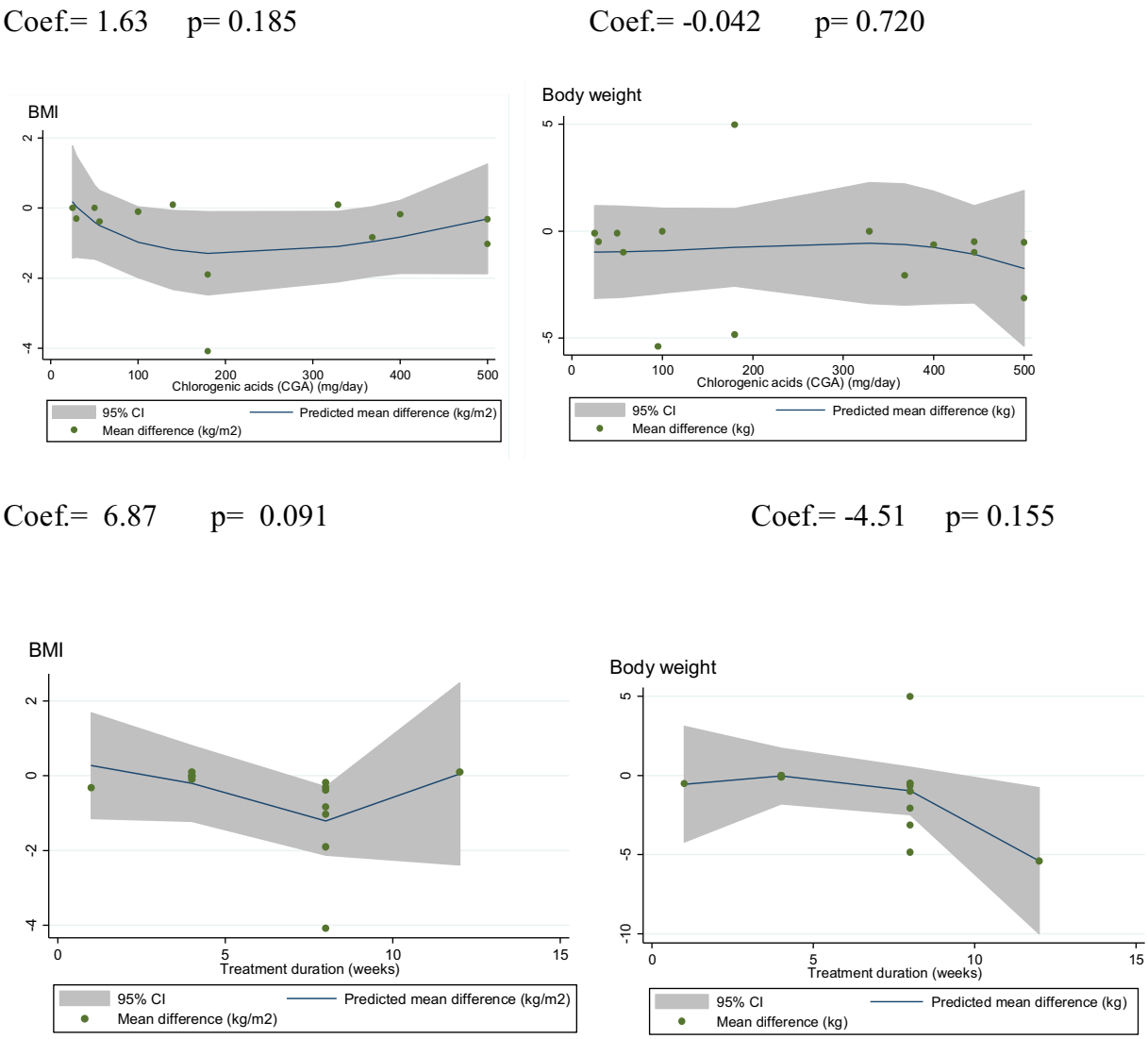

Fig. 4. Non-linear dose-responses between green coffee extract supplementation and unstandardized mean difference in body weight (kg), and body mass index (kg/m^2). The 95% CI is depicted in the shaded regions.

Meta-analysis results

Effect of GCE supplementation on BW

15 studies including a total of 695 participants (case = 353, and control = 342) reported body weight as an outcome measure. Combined results from the random-effects model indicated that body weight did not change significantly following GCE administration (Weighted Mean Difference (WMD): −0.585 kg, 95% CI: −1.498, 0.329, $p = 0.210$) with significant heterogeneity among the studies (I^2 = 92.4%, $p = 0.000$) (Fig. 1). In the subgroup analysis, we found that baseline BMI, study design, intervention duration and sex of study participants explained this heterogeneity. Studies that were conducted on baseline BMI ≥25 kg/m^2 revealed a greater reduction in body weight (WMD: −2.054 kg, 95% CI: −2.377, −1.731; I^2: 90.7%, $p < 0.001$) than those performed on baseline BMI <25 kg/m^2 (WMD: 0.008 kg, 95% CI: −0.389, 0.404; I^2: 0.0%, $p = 0.929$). In addition, based on sex, a significant reduction in body weight was found in trials that were performed on both sexes (WMD: −1.746 kg, 95% CI: −2.093, −1.399; I^2: 95.4%, $p < 0.001$) and women (WMD: −1.057 kg, 95% CI: −1.666, −0.448; I^2: 76.2%, $p = 0.015$) compared with those conducted on men (WMD: 0.129 kg, 95% CI: −0.332, 0.591; I^2: 0.0%, $p = 0.982$). All these findings were provided in Supplemental Table 2.

Effect of GCE supplementation on BMI

13 studies including a total of 589 participants (case = 300 and control = 289) reported BMI as an outcome measure. Overall results from the random-effects model indicated that GCE administration did result in significant change in BMI after GCE supplementation (WMD: −0.403 kg/m^2, 95% CI: −0.800, −0.005, $p = 0.047$) with significant heterogeneity among the studies (I^2 = 93.3%, $p = 0.000$) (Fig. 2). However, the study design, baseline BMI, GCE dosage, intervention duration, sex, and their health status could explain the heterogeneity. Reduction in BMI after GCE consumption was significant in subjects with baseline BMI ≥25 kg/m^2 (WMD: −0.544 kg/m^2, 95% CI: −0.692, −0.397; $p < 0.001$); however, it did not influence BMI in baseline BMI <25 kg/m^2 subjects (WMD: 0.069 kg/m^2, 95% CI: −0.091, 0.229; $p = 0.396$). Among studies with intervention duration more than 4 weeks, GCE administration resulted in a greater reduction in BMI (WMD: −0.611 kg/m^2, 95% CI: −0.737, −0.484; $p < 0.001$) than ≤4 weeks studies (WMD: 0.067 kg/m^2, 95% CI: −0.100, 0.233; $p = 433$). Based on sex, significant reduction in BMI was found in trials that were performed on women (WMD: −0.816 kg/m^2, 95% CI: −1.040, −0.593; $p < 0.001$), in both sexes (WMD: −0.604 kg/m^2, 95% CI: −0.772, −0.437; $p < 0.001$), in comparison with those conducted on only men (WMD: 0.050 kg/m^2, 95% CI: −0.103, 0.203; $p = 0.940$).

Effect of GCE supplementation on WC

Moreover, three studies including a total of 130 (case = 66, and control = 64) participants provided information for WC as an outcome measure. Pooled results from the random-effects model indicated that WC following GCE consumption did not change significantly (Mean Difference (WMD: −0.847 cm, 95% CI: −1.764, 0.071, $p = 0.070$) with no significant heterogeneity among studies ($I^2 = 40.5\%$, $p = 0.186$) (Fig. 3).

Non-linear dose-responses between dose and duration of GCE supplementation and outcomes

Following dose-response evaluation, GCE intake did not change body weight and BMI significantly based on treatment duration or GCE dosage in non-linear fashion (Fig. 4).

Sensitivity analysis

To discover the impact of each single study on the combine effect size, we removed each trial from the analysis, step by step. We observed no significant effect of any individual study on the combine effect sizes of BW, BMI, and WC.

Publication bias

Evolution of publication bias by visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of GCE supplementation on body weight, BMI, and WC (Supplemental Fig. 2). Egger's linear regression test also revealed the same result (body weight: $p = 0.120$, BMI: $p = 0.742$, and WC: $p = 0.964$).

Discussion

Bioactive phytochemicals of coffee have gained prominence due to their reputed biological properties, including; antioxidant and anti-inflammatory activities (Godos et al., 2014), increased fatty acid oxidation and insulin sensitivity, and modulation of glucose absorption and utilization (Sudeep et al., 2016). Although containing innumerable bioactive phytochemicals, the traditional coffee roasting process inhibits significant amounts of the phytochemicals that are purportedly responsible for the biological actions, such as chlorogenic acid (Esquivel and Jiménez, 2012). To ameliorate loss of some compounds with beneficial, health-eliciting effects, coffee can also be used as GCE bean extract (Esquivel and Jiménez, 2012). GCE bean extract is comprised of unroasted coffee beans and contains higher amounts of bioactive phytochemicals than that for the usual roasted coffee that is generally consumed (Esquivel and Jiménez, 2012; Sarriá et al., 2016) . The unroasted variant of coffee, the GCE bean, has been purported to elicit numerous, potential, positive effects on indices of obesity and health (Sarriá et al., 2018). It has been asserted that although GCE supplementation is promising, a systematic review in 2010 highlighted that studies were of poor methodological quality, leading to the recommendation that more rigorous trials are required to assess the efficacy of GCE as a weight loss tool. In the preceding decade, there have been numerous additions to the literature, and thus, we sought to conduct a comprehensive systematic review and dose-response meta-analysis of all available RCTs to examine the effect of GCE and CGA intervention on BW, BMI and WC in adults. In accord with the aims of this study, we found that GCE and CGA intervention resulted in significant reductions in BW and BMI, with no concurrent, significant, reductions in WC. Moreover, sub-group analyses revealed that effects were more pronounced in individuals with a study commencement BMI of $\geq 25\,kg/m^2$.

Polyphenols are abundant secondary metabolites in plants and are asserted to prevent, or at least ameliorate, diseases associated with oxidative stress and its associated complications. The glycosylated derivate forms of polyphenol, chlorogenic acids (ester of caffeic acid and quinic acid) are the principal polyphenol in coffee (Manach et al., 2004). There is proliferative evidence that coffee affects metabolic syndromes such as obesity, type 2 diabetes, atherosclerosis, and insulin-resistance (Dickson et al., 2015; Ding et al., 2014; Ho et al., 2012). Many different pharmacological studies regarding GCE demonstrate that the chlorogenic acids in GCE regulates hypertensive, vasoreactivity, and glucose metabolism (Blum et al., 2007; Kozuma et al., 2005). With respect to weight loss and reduction is BMI following GCE supplementation, the results of the current study are congruent with numerous independent reports; in Haidari et al. (2017), the authors reported a significant weight loss; which was further supported in a meta-analysis of three human studies (Onakpoya et al., 2011), where a mean weight loss of 2.5 kg after the consumption of GCE (180–200 mg GCBE per day) was found. The current meta-analysis improved upon the previous meta-analysis, at minima, by virtue of its' improved sample size. Interestingly, whilst we found a decrease in BMI and BW, there was no concurrent reduction WC. Logically, if BW decreases, then BMI must also decrease, given that BMI is calculated using height and weight. With respect to WC, it is conceivable that the weight loss observed in the included trials was compartmental, i.e., peripheral fat loss may occur earlier than abdominal or visceral fat loss (Molarius and Seidell, 1998). Moreover, this suggests that it would be pragmatic to perform segmental body composition assessments, to better understand what contributes to reductions in BW. Whilst a further avenue for future research would be to assess, longitudinally, weight loss and WC, to establish the length of time likely required to elicit changes in WC.

In Table 1 we reported the variable caffeine content recorded in individual studies; this is an important consideration to have due to the fact caffeine, in isolation, can elicit several metabolic effects. Caffeine is an adenosine-receptor antagonist (Van Soeren and Graham, 1998) and thus, all tissues with adenosine receptors can be affected by caffeine exposure; Spriet et al. suggested that caffeine was able to stimulate fat utilization in muscle tissue during exercise(Spriet et al., 1992). Moreover, Astrup et al. asserted a dose-dependent increase in basal energy expenditure with caffeine intake; attributing this effect to an increase in lactate and triacylglycerol production and increased vascular smooth muscle tone (Astrup et al., 1990). Thus, further work considering the specific contribution of caffeine and other green coffee constituents, respectively is warranted.

Concomitant to human investigation, in animals, GCE has been reported to influence postprandial glucose concentration and blood lipid concentration (Thom, 2007). This is suggested to occur via glucose absorption reduction in the intestine; a mechanism achieved by precipitating dispersal of the sodium electrochemical gradient. The aforementioned dispersal results in an influx of glucose into the enterocytes (Welsch et al., 1989). Moreover, GCE is also believed to inhibit the enzymatic activity of hepatic glucose-6-phosphatase, involved in the homeostasis of glucose (Hemmerle et al., 1997). Various reports from animal studies have suggested it is conceivable that GCE mediates its anti-obesity effect by suppressing the accumulation of hepatic triglycerides (Shimoda et al., 2006). Furthermore, few have also postulated that the anti-obesity effect of GCE may be interceded via alteration of plasma adipokines, distribution of body fat and downregulating fatty acid and cholesterol biosynthesis, concomitant to the upregulation of fatty acid oxidation and peroxisome proliferator-activated receptor alpha expression (Cho et al., 2010). Diets abundant in polyphenols may precipitate prevention of various diseases or comorbidities associated with oxidative stress, including coronary heart disease and various forms of cancer (Adlercreutz and Mazur, 1997; Tijburg et al., 1997). GCE has been shown capable of scavenging free radicals *in vitro*, whilst increasing the antioxidant capacity of plasma *in vivo* (Blum et al., 2007; Monteiro et al., 2007). There is further evidence that certain dietary phenols, such as GCE, conceivably modulates intestinal glucose uptake (Bidel et al., 2006; Lopez-Garcia et al., 2006). This biological activity may provide a basis for putatively explaining its effects on body weight.

The purported weight reducing effect of CGA would have a protective effect against diabetes mellitus, via changes in gastrointestinal hormone secretion (Greenberg et al., 2006). Furthermore, the mechanism by which blood glucose may be reduced by chlorogenic acids is via its activation of AMP-activated protein kinase (AMPK). Activation of AMPK contributes to enhancing GLUT4 translocation to plasma membrane, augmenting glucose transport to cells, resulting in peripheral glucose disposal (Ong et al., 2012). Also, CGA present within GCE can inhibit glucose 6-phosphatase leading to limited glucose production by gluconeogenesis and glycogenolysis (Henry-Vitrac et al., 2010). Clearly, although there is evidence to support the mechanistic action of GCE on metabolism; more experimental work is required to ascertain the pathology related to morphological and structural changes, such as waist circumference.

Strength and limitations

The primary strength of this study was that this meta-analysis provided a comprehensive overview of the effect of GCE supplementation of obesity indices, far beyond evidence thus far, manifest in human-based RCTs; and given the potential influence on obesity treatment or management, this is worthwhile endeavor. The evidence base, prior to this meta-analysis, was relatively bereft of uniformity, with the preceding meta-analysis only including three studies, and thus urgently required a summative, quantitative assessment, which we have provided. We demonstrated that there is sufficient evidence for GCE supplementation to elicit positive effects on BMI and BW. Another strength of the current meta-analysis is the assimilation of the heterogeneous sample of participants, with a range of demographic status', ethnicities and ages. We were also able to stratify analyses based on both duration of supplementation and dosage, in addition to starting weight and BMI, thereby providing foresight into expected outcomes based on such information.

Notwithstanding, the current study has some limitations. The analyses were not restricted to solitarily include patients of one type, where metabolic syndrome (Roshan et al., 2018), NAFLD (Shahmohammadi et al., 2017), obese and overweight (Dellalibera et al., 2006; Haidari et al., 2017; Park et al., 2010; Thom, 2007; Vinson et al., 2012), healthy (Al-Dujaili et al., 2016) and patients with hypertension (Kozuma et al., 2005; Ochiai et al., 2008; Watanabe et al., 2006) were included. Consequently, this permitted a larger number of studies and participants to be included for analyses, however could conceivably impact mechanism of action and effectiveness. Some included trials were small in sample size, as low as 4 participants, and it has been demonstrated by Sterne et al. that it is probable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools (Sterne and Egger, 2001), nevertheless, this was out of the operational control of the meta-analysis.

Conclusion

The results of current meta-analysis study support the use of GCE supplementation for the improvement of obesity indices, with subgroup analysis highlighting greater improvements in individuals with a starting BMI $\geq 25\ kg/m^2$. However, the literature base remains equivocal as to whether significant benefits are incurred for morphological changes, such as waist circumference. Therefore, notwithstanding the positive effect elicited by GCE supplementation for some clinically relevant variables, it is evident that more, well-controlled and randomized studies are needed to confirm the veracity of non-significant and/or equivocal findings, and indeed, further explore mechanism of action in population and disease sub-groups.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2019.153018.

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