The Effect of Green Coffee Bean Extract on Cardiovascular Risk Factors: A Systematic Review and Meta-analysis

Makan Pourmasoumi, Amir Hadi, Wolfgang Marx, Ameneh Najafgholizadeh, Sukhdeep Kaur, and Amirhossein Sahebkar

Abstract

Background and aim: Cardiovascular disease remains the primary cause of noncommunicable disease- related death. The present systematic review and meta-analysis was performed to assess the possible benefit of the green coffee bean extract on cardio-metabolic markers.

Methods: PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched to identify clinical trials that examined the effect of green coffee bean extract on cardio-metabolic risk factors including serum lipid profiles, glycemic status-related markers, blood pressure, and anthropometric indices. Since the included RCTs were carried out in different settings, random effect models were used to conduct all meta-analyses.

Results: Fifteen studies (19 arms) consisting of 637 participants were included. The results indicated that green coffee bean extract significantly reduced levels of total cholesterol (−5.93 mg/dl; 95% CI: −9.21, −2.65; I^2: 0%), fasting plasma glucose (−2.21 mg/dl; 95% CI: −3.94, −0.48; I^2: 32%), systolic blood pressure (−3.08 mmHg; 95% CI: −4.41, −1.75; I^2: 26%), diastolic blood pressure (−2.27 mmHg; 95% CI: −3.82, −0.72; I^2: 61%), body weight (−1.24 kg; 95% CI: −1.82, −0.66; I^2: 15%), and BMI (−0.55 kg/m^2; 95% CI: −0.88, −0.22; I^2: 73%). Although the pooled effect size of

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M. Pourmasoumi
Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

A. Hadi
Halal Research Center of IRI, FDA, Tehran, Iran

W. Marx
School of Medicine, iMPACT, Food & Mood Centre, Deakin University, Geelong, Australia

A. Najafgholizadeh
Department of Microbiology, Naein Branch, Islamic Azad University, Isfahan, Iran

S. Kaur
Department of Food and Nutrition, Punjab Agricultural University, Ludhiana, Punjab, India

A. Sahebkar (✉)
Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
e-mail: sahebkara@mums.ac.ir

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LDL-C, fasting insulin, and waist circumstance were significant, the results were significantly influenced by individual studies. No significant effect was detected for triglycerides, HDL-C, HbA1C, and HOMA-IR. However, the nonsignificant pooled effect size for triglyceride levels was influenced by one individual study.

Conclusion: The present study suggests that green coffee been extract consumption can improve total cholesterol, triglycerides, body weight, blood pressure, and fasting plasma glucose.

Keywords

Cardiovascular disease · CVD · Green coffee · Chlorogenic acid

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1C	Hemoglobin A1C
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
LDL-C	Low-density lipoprotein cholesterol
RCT	Randomized clinical trial
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
WC	Waist circumstance

1 Introduction

Cardiovascular disease (CVD) is the major cause of mortality and morbidity worldwide. In 2016, approximately 31% of all global deaths were due to CVD, with over 75% of these CVD deaths occurring in low- and middle-income countries [1]. Main risk factors associated with CVD are sedentary lifestyle leading to overweight/obesity, unhealthy diet [2], raised blood glucose levels, hypertension [3], dyslipidemia [4], psychosocial factors [5], and smoking [6]. Modifiable lifestyle factors such as diet and physical activity can play an important role in alleviating CVD risk [7]. Several epidemiological and interventional studies have shown that bioactive compounds present in fruits and vegetables, such as polyphenols, carotenoids, flavonoids, and anthocyanins, may have a beneficial effect against the development of CVD [8–11]. Furthermore, there is a growing research interest in the potential beneficial cardioprotective properties of polyphenol-rich beverages such as tea [12–14], wine, beer [15], and coffee [16].

Among these beverages, coffee is one of the most popular drinks in the world [17]. Coffee plants, native to Africa, belong to the genus *Coffea* (family Rubiaceae) and are grown for their seeds (beans) which are roasted, ground, and sold for brewing coffee [18]. Coffee contains bioactive phenolic compound chlorogenic acid, methylxanthines, flavonoids, hydroxycinnamic acid, melanoidin, diterpenes, trigonelline, lignans, and minerals [19–21]. Ample evidence suggests that green coffee beans have anti-inflammatory and antioxidant properties, which are mainly attributed to bioactive compounds including chlorogenic acid, caffeine, diterpene, and trigonelline [22]. Chlorogenic acid has been inversely associated with metabolic syndrome, obesity [23], and chronic liver diseases [24]. Consumption of green coffee bean extract has been shown in both preclinical and emerging clinical trials to ameliorate the risk of diabetes mellitus type 2, ischemic stroke, and CVD [25] through reduction in high serum lipid concentrations [26], appetite level [27], abdominal obesity [28], oxidative damage [29], as well as high fasting blood sugar levels, fasting glucagon, insulin sensitivity [30], high blood pressure [31], arterial elasticity [32], and endothelial dysfunction [33].

The cardioprotective properties of green coffee bean extract have been investigated in human studies [32, 34–37]; however, the results of individual studies have not been consistent. To the authors' knowledge, a systematic review and meta-analysis of these studies has not been previously conducted. Therefore, the present system-

atic review and meta-analysis of clinical trials was designed to assess the overall effect of the green coffee bean extract on cardio-metabolic markers including anthropometric indices, BP, blood glucose, and lipid profile within the adult population.

2 Methods

The present investigation was designed and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [38].

2.1 Search Strategy

Systematic literature searches were conducted using the data sources PubMed, Scopus, ISI Web of Science, and Cochrane Library, from their inception until January 2020. The search strategy texts which were applied for exploring into databases were constituted from two main concepts including "Green coffee" and relevant cardiovascular risk factors. Another search keyword forming from "Green coffee" and "clinical trial" terms was also used to cover those eligible studies in which the outcomes of interest were reported as secondary outcomes and were not mentioned in abstract. The search strategy which was applied based on each database is presented in Supplemental Table 1. An additional manual search was followed by reference lists of selected studies to detect other relevant papers. Two authors (A.H and M.P) separately searched the electronic databases, and disagreements were resolved by group discussion.

2.2 Study Selection

After excluding duplicate publications, studies were independently screened by two reviewers (A.H and A.N) based on their titles, abstracts, and full texts. Articles were eligible for inclusion if they fulfilled the following criteria: (1) the study design was a controlled clinical trial, (2) the population of interest was adults (aged >18 years), (3) the intervention was green coffee supplementation, (4) the outcomes of interest were body weight, body mass index (BMI), waist circumference (WC), glycosylated hemoglobin (HbA1C), fasting plasma glucose (FPG), homeostasis model assessment-estimated insulin resistance (HOMA-IR) index, serum insulin, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), and diastolic blood pressure (DBP). We excluded studies if they lacked a control group (single-arm studies) or with no proper control group (i.e., active agent supplemented as control group), duration of intervention was <2 weeks, green coffee was administrated as complex with other active substances, and age of participants was <18 years. All discrepancies were addressed by consensus or by discussion with a third author (M.P).

2.3 Data Extraction

The following data were extracted from the full text of included studies using a predesigned abstraction form: first author's last name, publication year, location of the study, study design, gender, mean age and BMI of participants, total sample size, study duration, dose and type of green coffee bean extract, and reported outcomes. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. Data extraction was conducted by two authors, independently (A.N and A.H). Subsequently, full-text studies were assessed, and discrepancies were resolved through discussion with a third author (M.P).

2.4 Risk of Bias Assessment and Credibility of Evidence

The risk of bias of the included studies was performed by two reviewers (A.H and M.P) using the Cochrane Collaboration Risk of Bias tool [39]. The main categories consisted of the following six items: (1) sequence generation sufficiency (selection bias), (2) allocation concealment

(selection bias), (3) blinding (performance bias), (4) clarification of failures and incomplete outcome data (attrition bias), (5) selective reporting of the results (reporting bias), and (6) other possible sources of bias. Each domain was assessed as "high risk, " "low risk, " or "unclear." Finally, the overall quality of the studies was categorized into weak or fair if ≥3 or < 3 domains were rated as unclear/high risk, respectively.

The credibility of the present study was evaluated based on GRADE handbook for grading quality of evidence and strength of recommendations [40] by using GRADEpro online software [41]. It assesses the quality of evidence in accordance with several criteria which explore risk of bias, inconsistency, indirectness, impression, and publication bias in each outcome of interests. The rigorous quality of evidences is categorized as very low, low, moderate, and high quality.

2.5 Statistical Analysis

All analyses were performed using STATA software version 12 (StataCorp, College Station, TX, USA). The mean difference and the standard deviation (SD) of intervention and control groups for all the outcomes of interest were extracted to calculate overall effect size. In studies in which mean change was not directly reported in the intervention and control groups, it was calculated by subtracting the post-intervention data from the baseline value. Furthermore, if the SD of change was not provided directly, SD for net changes were imputed according to the method of Follmann et al. [42].

The correlation coefficient used for SD of change calculation was also assessed by studies which provided sufficient data using the following formula: $[R = (SD^2_{Baseline} + SD^2_{Final}\text{-}SD_{Change}) / (2\times SD_{Baseline} \times SD_{Final})]$ [43]. The correlation coefficient (R) for each was the following: triglyceride, 0.74; total cholesterol, 0.68; LDL, 0.70; HDL-C, 0.78; FPG, 0.70; fasting insulin, 0.6; HOMA-IR, 0.61; HbA1C, 0.50; SBP, 0.78; DBP, 0.75; body weight, 0.97; BMI, 0.98; and WC, 0.95. Because of high correlation coefficient calculated for anthropometric indices (body weight, BMI, and WC), the correlation coefficient was assumed 0.9 for these parameters, and sensitivity analysis was also performed to assess whether the results of anthropometric indices are sensitive to different levels of correlation coefficient (0.8 and 0.6).

Since the included RCTs were carried out in different settings, random effect models were used to conduct all meta-analyses. The heterogeneity between studies was examined by the I-squared (I^2) index. The level of heterogeneity across studies was rated as low, moderate, or high corresponding to I^2 value of 0–30%, more than 30–60%, and more than 60%, respectively [39].

We conducted subgroup analysis according to dose of green coffee, duration of study BMI of participants, and/or health condition where possible to assess the impact of heterogeneity on outcomes. Sensitivity analyses were also performed to explore the extent to which inferences might depend on a particular study or group of studies as well as the impact of studies with a high risk of bias. Meta-regression was conducted to detect the effect of potential confounders on changes in outcomes of interest including dose of intervention, duration of study, and baseline measures of outcome of interest. We also assessed publication bias by visual inspection of funnel plot and two formal tests, the Begg-adjusted rank correlation test [44] and the Egger's regression asymmetry test [45]. A P-value <0.05 was accepted as statistically significant, unless otherwise specified.

3 Results

The study selection process, number of removed articles in each steps, and reason for excluding studies are illustrated in Fig. 1. In brief, after primary assessment and discarding irrelevant articles, 21 studies were selected for full-text screening. Of those, six studies were excluded due to a lack of a proper control group (n = 2), use of a combination intervention (n = 1), only reporting postprandial parameters (n = 1), the outcomes which were measured before-after an exercise intervention (n = 1), or the study which

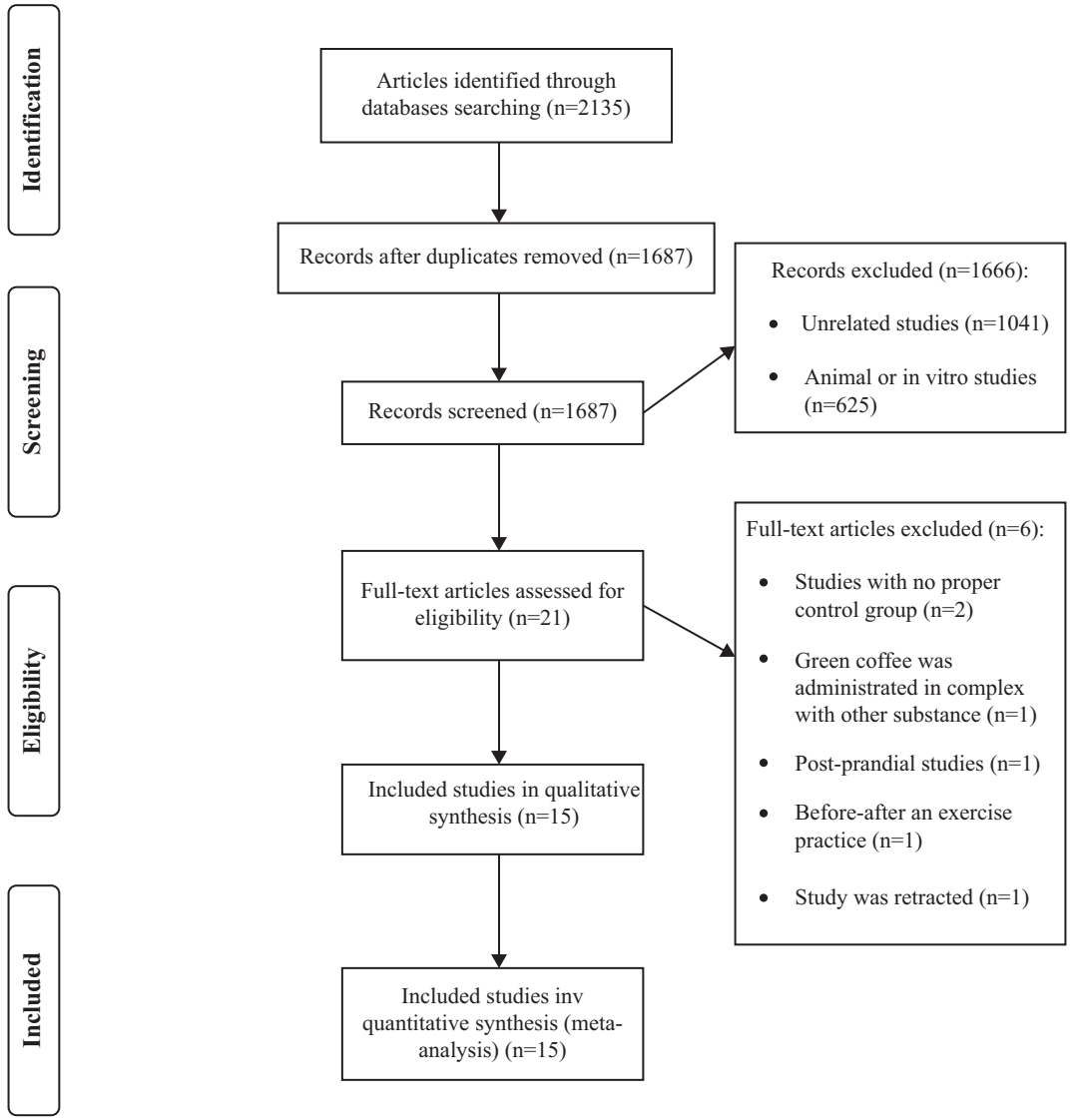

Fig. 1 Flow chart of the process of the study selection

was retracted (n = 1). Finally, 15 studies met eligibility and were included to systematic review. Kozuma et al. [46] administrated three different doses of green coffee bean extract and were considered as three separate active arms. Martínez-Lopez et al. [47] recruited normocholestrolemic and hypercholestrolemic patients and reported the outcomes for each condition independently. In this case, each condition was regarded as separate arm for pooling analysis. In addition, in a study conducted by Naderi et al. [37], participants were divided to four groups, in which green coffee bean extract was administrated to two of the four groups. Therefore, 15 studies including 19 active arms were selected for quantitative analysis.

The main characteristics of included studies are presented in Table 1. Fifteen clinical trials [31, 32, 34, 36, 37, 46–55] comprising a total of 637 participants were included to meta-analysis. The mean age of included participants was 38, and the average BMI was 27.5. Studies were conducted in different countries including Japan [31, 46, 48, 51, 53], Iran [32, 36, 37, 49], South Korea

Table 1 Study characteristics

First author (publication year)	Country	Number and gender	Mean age (Years)	BMI (kg/m^2)	Clinical trial design/ randomized/ blinding	Duration (days)	Comparison group	Type and amount of green coffee/CGA intake	Notes about participants	Outcomes
Suzuki et al. (2019)	Japan	Intervention: 8	Range: 35–56	Intervention: 21.9 ± 1.7	Parallel/ NR/yes	14	Beverage	Beverage containing CGA	Healthy	TG, TC, HDL, LDL, FPG, SBP, DBP
		Control: 8	Intervention: 44.6 ± 6.2	Control: 21.8 ± 2.2				300 mg/day		
		Males	Control:							
Zuniga et a. (2017)	Mexico	Intervention: 14	Range: 30–60	Intervention: 32.6 ± 24	Parallel/ yes/yes	84	Capsule	Capsule containing CGA	Impaired glucose tolerance	TG, TC, HDL, LDL, FPG, HbA1C, SBP, DBP, body weight, BMI, WC
		Control: 12	Intervention: 43 ± 11	Control: 32.1 ± 25				1200 mg/day		
		Both gender	Control: 45 ± 9							
Ochiai et al. (2004)	Japan	Intervention: 10	Range: NR	Intervention: 24.7 ± 1.6	Parallel/ NR/yes	120	Beverage	Beverage containing green coffee bean	Healthy	TG, TC, HD, LDL, FPG, fasting insulin, SBP, DBP
		Control: 10	Intervention: 37.2 ± 1.6	Control: 23.8 ± 0.6				140 mg/day		
		Males	Control: 34.8 ± 2.3							
Haidari et al. (2017)	Iran	Intervention: 30	Range: 20–45	Intervention: 31.58 ± 4.37	Parallel/ yes/yes	56	Capsule	Capsule containing green coffee bean extract	Obesity	TG, TC, HDL, LDL, FPG, fasting insulin, HOMA-IR, body weight, BMI
		Control: 34	Intervention: 36.1	Control: 32.07 ± 4.96				400 mg/day		
		Female	Control: 35.7	Intervention: 31.58 ± 4.37						

First author (publication year)	Country	Number and gender	Mean age (Years)	BMI (kg/m^2)	Clinical trial design/ randomized/ blinding	Duration (days)	Comparison group	Type and amount of green coffee/CGA intake	Notes about participants	Outcomes
Kim et al. (2012)	South Korea	Intervention: 10 Control: 10 Female	Range: NR Intervention: 44.7 ± 10.10 Control: 46.2 ± 10.91	Intervention: 25.6 ± 0.73 Control: 25.1 ± 0.61	Parallel/ yes/yes	56	Capsule	Capsule containing green coffee bean extract 100 mg/day	Overweight/ obese adults	TC, FPG, SBP, DBP, body weight, BMI WC
Fukagawa et al. (2017)	Japan	Intervention: 23 Control: 26 Female	Range: 25–40 NR	Range: 18–25 NR	Parallel/ yes/yes	56	Beverage	Beverage containing green coffee been extract 270 mg/day	Healthy	TG, TC, HDL, LDL, FPG, fasting insulin, HbA1c
Roshan et al. (2017)	Iran	Intervention: 21 Control: 22 Both gender	Range: 18–70 Intervention: 52.76 ± 9.83 Control: 51.95 ± 8.67	Intervention: 31.60 ± 3.58 Control: 31.16 ± 4.88	Parallel/ yes/yes	56	Capsule	Capsule containing green coffee bean extract 400 mg/day	Metabolic syndrome	TG, TC, HDL, LDL, FPG, fasting insulin, HOMA-IR, HbA1C, SBP, DBP, WC, body weight, BMI
Shahmohammadi et al. (2017)	Iran	Intervention: 22 Control: 22 Both gender	Rnge:20–70 Intervention: 41.36 ± 7.69 Control: 44.50 ± 5.24	Intervention: 31.27 ± 2.58 Control: 31.45 ± 2.18	Parallel/ yes/yes	56	Capsule	Capsule containing green coffee bean extract 1000 mg/day	Nonalco-holic fatty liver disease	TG, TC, HDL, LDL, FPG, fasting insulin, HOMA-IR, body weight, BMI, WC

(Continued)

Table 1 (continued)

First author (publication year)	Country	Number and gender	Mean age (Years)	BMI (kg/m^2)	Clinical trial design/ randomized/ blinding	Duration (days)	Comparison group	Type and amount of green coffee/CGA intake	Notes about participants	Outcomes
Kozuma et al. (2005)	Japan	Intervention: Group I: 29 Group II: 28 Group III: 31 Control: 29 Male	Range: 30–50 Intervention: Group I: 42.9 ± 8.2 Group II: 43.3 ± 8.3 Group III: 43.4 ± 8.4 Control: 43.1 ± 9.1	Intervention: Group I: 25.2 ± 4.0 Group II: 24.4 ± 2.6 Group III: 25.1 ± 3.6 Control: 24.0 ± 3.1	Parallel/ yes/yes	28	Low-sodium soy sauce plus soup without green coffee	Low-sodium soy sauce plus soup containing green coffee bean extract Group I: 46 mg/day Group II: 93 mg/day Group III: 185 mg/day	Mild hypertension	TG, TC, HDL, LDL, body weight, BMI
Martínez-López et al. (2018)	Spain	Normocholesterolemics: 25 Hypercholesterolemics: 27 Both gender	Range: 18–45 Normocholesterolemics: F: 26.6 ± 7.7 M: 24.7 ± 5.8 Hypercholesterolemics F: 33.3 ± 10.2 M: 34.8 ± 9.2	Normocholesterolemics F: 21.9 ± 2.5 M: 24.2 ± 2.8 Hypercholesterolemics F: 21.4 ± 2.5 M: 24.9 ± 2.3	Crossover/ yes/ yes	56	Beverage	Beverage containing green/roasted coffee 6 g/ day	Normocholesterolemic/ hypercholesterolemic	TG, TC, HDL, LDL, SBP, DBP, body weight
Watanabe et al. (2006)	Japan	Intervention: 14 Control: 14 Both gender	Range: NR Intervention: 52 ± 11 Control: 51 ± 8	Intervention: 23.8 ± 3.3 Control: 25.0 ± 3.5	Parallel/ yes/yes	84	Beverage	Beverage containing green coffee bean extract 140 mg/day	Mild hypertension	TG, TC, LDL, HDL, BMI
Hasani et al. (2017)	Iran	Intervention: 7 Control: 10 Female	Range: NR Intervention: 24.5 ± 3.06 Control: 24.57 ± 2.98	Intervention: 28.89 ± 2.95 Control: 29.10 ± 4.05	Parallel/ yes/no	42	Exercise	Green coffee plus exercise 250 mg/day	Overweight/ obese women	Body weight, BMI, WC

First author (publication year)	Country	Number and gender	Mean age (Years)	BMI (kg/m^2)	Clinical trial design/ randomized/ blinding	Duration (days)	Comparison group	Type and amount of green coffee/CGA intake	Notes about participants	Outcomes
Naderi et al. (2017)	Iran	Intervention: 12 Control: 12	Range: NR Intervention: 32.23 ± 5.44 Control: 32.25 ± 7.03	Intervention: 33.2 ± 1.37 Control: 32.56 ± 1.5	Parallel/ yes/no	56	Aerobic and resistance trainings	Green coffee capsule plus aerobic And resistance trainings 400 mg/day	Obese women	FPG, insulin, HOMA-IR, BMI
		Intervention: 12 Control: 12 Female	Range: NR Intervention: 30.15 ± 5.58 Control: 31 ± 5.27	Intervention: 31.58 ± 1.67 Control: 32.71 ± 1.68			No training/ supplementation	Green coffee capsule 400 mg/day		
Park et al. (2010)	South Korea	Intervention: 23 Control: 20 Female	Range: NR Intervention: 33.1 ± 1.92 Control: 33.1 ± 2.19	Intervention: 26 ± 0.45 Control: 26.3 ± 0.77	Parallel/ yes/yes	56	Capsule	Green coffee capsule 50 mg/day	Overweight/ obese women	TG, TC, HDL, LDL, FPG, fasting insulin, body weight, BMI, WC, SBP, DBP
Dellalibera et al. (2006)	Italy	Intervention: 30 Control: 20 Both gender	Range: 19–75 NR	NR	Parallel/ yes/yes	60	Capsule	Capsule containing green coffee bean extract 200 mg/day	Overweight	Body weight, BMI

Abbreviations: *CGA* chlorogenic acid, *TG* triacylglycerol, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *FPG* fasting plasma glucose, *HbA1C* hemoglobin A1C, *HOMA-IR* homeostasis model assessment of insulin resistance, *BMI* body mass index, *WC* waist circumstance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NR* not reported

[50, 52], Mexico [54], Italy [55], and Spain [47]. Three studies recruited only male participants [46, 51, 53], six studies enrolled only female participants [36, 37, 48–50, 52], and six remaining studies included both sexes [31, 32, 34, 47, 54, 55]. Except for Martínez-Lopez et al. [47], which had crossover design, all studies were parallel studies. The duration of included interventions spanned from 14 to 120 days, with an average of 56 days. Six studies recruited obese/overweight adults [36, 37, 49, 50, 52, 55], three trials enrolled healthy participants [48, 51, 53], two studies involved patients with mild hypertension [31, 46], one study enrolled participants with normocholesterolemic and hypercholesterolemic conditions separately [47], one study included nonalcoholic fatty liver disease-diagnosed patients [34], one study included participants with metabolic syndrome [32], and one study included participants with impaired glucose tolerance [54]. The dose of green coffee bean extract ranged from a minimum of 100 mg to a maximum of 6 g. Nine studies provided an encapsulated green coffee bean extract [32, 34, 36, 37, 49, 50, 52, 54, 55], fives trials provided a beverage containing green coffee [31, 47, 48, 51, 53], and one study administrated green coffee as part of a soup [46]. All studies were published between 2004 and 2019.

4 Risk of Bias Assessment and Credibility of Evidence

Thirteen studies were randomized [31, 32, 34, 36, 37, 46–50, 52, 55]; however, the method of randomization and allocation concealment was sufficiently addressed in six trials [32, 34, 36, 50, 52, 54]. Eleven studies were blinded [31, 32, 34, 36, 46, 48, 50, 51, 53–55], and 13 trials provided sufficient information around attrition bias [31, 32, 34, 46–55]. Nine studies acknowledged public, commercial, or industry financial support as well as any relation of authors with external agency which might influence the results [32, 34, 36, 47–49, 52–54]. The risk of bias summary is presented in Table 2.

The credibility of evidence for some outcomes of interest including triglyceride, TC, LDL-C, HDL-C, FPG, SBP, and body weight was high and reliable. However, quality of evidences for the rest of them was moderate in fasting insulin, DBP, and BMI, low in HbA1C and WC, and very low in HOMA-IR. Overall, there is a moderate confidence in estimated effects (Supplemental Table 2).

5 Meta-analysis

5.1 Effect of Green Coffee Bean Extract on Lipid Profiles

The results of the included meta-analysis demonstrated a significant reduction in total cholesterol (−5.93 mg/dl; 95% CI: −9.21, −2.65; I^2 = 0%) and LDL-C (−4.41 mg/dl; 95% CI: −7.55, −1.27; I^2 = 7%) levels after green coffee bean extract consumption. No significant effect was detected on triglycerides (−6.25 mg/dl; 95% CI: −13.34, 0.84; I^2 = 20%) and HDL-C (0.95 mg/dl; 95% CI: −0.46, 2.37; I^2 = 31%) serum levels (Fig. 2a–d).

Subgroup analysis based on the duration of intervention indicated that triglyceride levels were significantly reduced in studies with ≥84-day duration (−26.93 mg/dl; 95% CI: −53.11, −0.76; I^2 = 0%), while no significant difference was observed in studies with <84-day follow-up (−4.57 mg/dl; 95% CI: −11.35, 2.21; I^2 = 15%). No favorable effect was detected for triglycerides in further stratified analyses. When studies were stratified according to BMI of participants (>25 or ≤ 25), type of intervention (capsule or beverage), duration of administration, or dosage of administration, a greater reduction on total cholesterol levels was observed in subgroups including studies with mean BMI > 25 (−7.11 mg/dl; 95% CI: −12.69, −1.52; I^2 = 18%), green coffee bean extract administration as capsule (−8.65 mg/dl; 95% CI: −14.96, −2.34; I^2 = 20%), duration ≥84 day (−17.25 mg/dl; 95% CI: −29.63, −4.86; I^2 = 0%), and dosage ≥400 mg/days (−7.56 mg/dl; 95% CI: −13.38, −1.73; I^2 = 38%) (Table 3). Subgroup analyses for LDL-C and HDL-C were skewed by one study with a large weighting [36].

Table 2 The summary of review authors' judgments about each risk of bias item for included studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Suzuki et al. (2019)	U	U	L	L	L	U
Zuniga et a. (2017)	L	L	L	L	L	L
Ochiai et al. (2004)	U	U	L	L	U	U
Haidari et al. (2017)	L	L	L	U	L	U
Kim et al. (2012)	L	L	L	L	U	U
Hasani et al. (2017)	L	U	H	L	L	U
Fukagawa et al. (2017)	L	U	L	L	L	U
Roshan et al. (2017)	L	L	L	L	L	L
Shahmohammadi et al. (2017)	L	L	L	L	L	L
Kozuma et al. (2005)	L	U	L	L	U	L
Martínez-López et al. (2018)	L	U	H	L	L	L
Watanabe et al. (2006)	L	U	L	L	U	U
Naderi et al. (2017)	L	U	H	U	U	H
Park et al. (2010)	L	L	U	L	L	L
Dellalibera et al. (2006)	L	U	L	L	U	U

H high risk of bias, *L* low risk of bias, *U* unclear or unrevealed risk of bias. Criteria defined for risk of bias assessment are according to the Cochrane guidelines

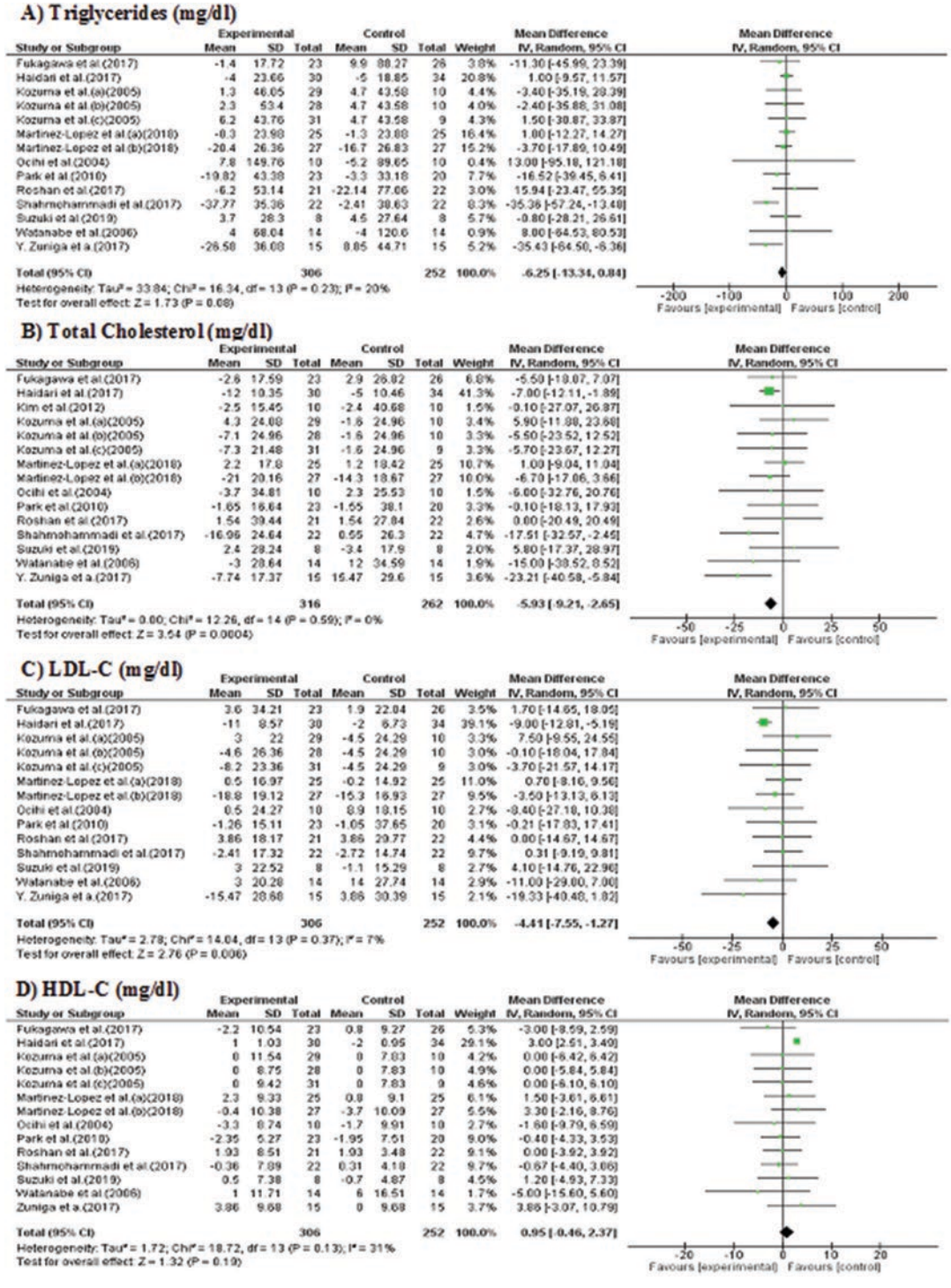

Fig. 2 The meta-analysis results of the effect of green coffee administration on lipid profiles

Table 3 Subgroup analyses

Variables	Subgroup analysis based on		Number of trials	Mean difference (95%CI)	Within study heterogeneity I^2	Between study heterogeneity (P-value)
Triglycerides (mg/dl)	Participants' condition	BMI > 25	7	−6.26 (−13.35, 0.84)	58%	0.29
		BMI ≤ 25	7	−1.62 (−10.08, 6.84)	0%	
	Duration	≥84	3	**−26.93 (−53.11, −0.76)**	0%	0.09
		<84	11	−4.57 (−11.35, 2.21)	15%	
	Dose (mg/day)	≥400	6	−8.52 (−21.10, 4.07)	66%	0.84
		<400	8	−6.04 (−17.84, 5.76)	0%	
Total cholesterol (mg/dl)	Participants' condition	**BMI ≥ 25**	8	**−7.11 (−12.69, −1.52)**	18%	0.34
		BMI < 25	7	−3.83 (−9.27, 1.62)	0%	
	Duration (day)	≥84	3	**−17.25 (−29.63, −4.86)**	0%	0.06
		<84	12	**−5.07 (−8.48, −1.67)**	0%	
	Dose (mg/day)	≥400	6	**−7.56 (−13.38, −1.73)**	38%	0.28
		<400	9	−3.01 (−9.31, 3.29)	0%	
Fasting plasma glucose (mg/dl)	Participants' condition	BMI ≥ 25	8	**−3.03 (−5.67, −0.39)**	54%	0.37
		BMI < 25	4	−0.93 (−3.36, 1.50)	0%	
	Duration (day)	≥84	3	**−4.02 (−7.21, −0.84)**	0%	0.15
		<84	9	−1.87 (−3.84, 0.10)	36%	
	Dose (mg/day)	≥400	6	−3.36 (−6.86, 0.14)	56%	0.66
		<400	6	−1.57 (−3.46, 0.32)	0%	
Systolic blood pressure (mmHg)	Participants' condition	**Elevated blood pressure**	5	**−4.19 (−5.95, −2.43)**	43%	0.02
		Other conditions	7	−1.23 (−3.23, 0.77)	0%	
	Duration (day)	≥84	3	−3.79 (−8.24, 0.65)	64%	0.28
		<84	9	**−2.89 (−4.10, −1.68)**	1%	
	Dose (mg/day)	≥400	4	−2.65 (−5.38, 0.08)	29%	0.56
		<400	8	**−3.23 (−4.84, −1.61)**	32%	
Diastolic blood pressure (mmHg)	Participants' condition	**Elevated blood pressure**	5	**−3.09 (−4.94, −1.25)**	58%	0.10
		Other conditions	7	−1.53 (−4.11, 1.05)	60%	
	Duration (day)	≥84	3	**−5.90 (−7.80, −4.01)**	0%	<0.001
		<84	9	**−1.42 (−2.76, −0.08)**	33%	
	Dose (mg/day)	≥400	4	**−2.08 (−3.85, −0.31)**	0%	0.47
		<400	8	**−2.35 (−4.49, −0.22)**	71%	

Table 3 (continued)

Variables	Subgroup analysis based on		Number of trials	Mean difference (95%CI)	Within study heterogeneity I^2	Between study heterogeneity (P-value)
Body weight (kg)	Participants' condition	**BMI ≥ 25**	10	**−1.32 (−2.01, −0.63)**	30%	0.32
		BMI < 25	3	−0.34 (−2.23, 1.55)	0%	
	Duration (day)	≥60	2	**−2.52 (−3.43, −1.60)**	0%	0.002
		<60	11	**−0.78 (−1.34, −0.22)**	0%	
	Dose (mg/day)	≥400	6	**−1.34 (−2.11, −0.56)**	0%	0.79
		<400	7	−0.92 (−2.09, 0.25)	51%	
BMI (kg/m^2)	Participants' condition	**BMI ≥ 25**	12	**−0.63 (−0.98, −0.28)**	75%	0.05
		BMI < 25	2	0.10 (−0.63, 0.83)	0%	
	Duration (day)	≥60	3	**−0.85 (−1.37, −0.33)**	43%	0.001
		<60	11	**−0.48 (−0.86, −0.11)**	69%	
	Dose (mg/day)	≥400	6	**−0.91 (−0.88, −0.22)**	80%	0.002
		<400	8	−0.27 (−0.70, 0.16)	67%	

-Due to substantial heterogeneity in some subgroups, all analysis was performed based on random effect methods

5.2 Effect of Green Coffee Bean Extract on Glycemic Status-Related Markers

Green coffee bean extract significantly improved FPG (−2.21 mg/dl; 95% CI: −3.94, −0.48; I^2 = 32%) and fasting insulin (−0.33 μU/ml; 95% CI: −0.62, −0.04; I^2 = 0%) concentration. However, no significant influence was observed in either HbA1C (−0.02%; 95% CI: −0.19, 0.16; I^2 = 27%) or HOMA-IR (−0.22 mg/dl; 95% CI: −0.69, 0.24; I^2 = 57%) (Fig. 3a–d). Subgroup analysis based on participants' mean BMI demonstrated a significant reduction in FPG levels in a subset of studies with an average participant BMI >25 (−3.03 mg/dl; 95% CI: −5.67, −0.39; I^2 = 54%) but not in studies with an average BMI ≤25 subgroup (−0.93 mg/dl; 95% CI: −3.36, 1.50; I^2 = 0). When studies were stratified according to study duration, FPG levels had a greater decrease in studies with ≥84-day follow-up (−4.02 mg/dl; 95% CI: −7.21, −0.84; I^2 = 0%) (Table 3). Due to low number of included studies, subgroup analysis was not performed for HbA1C, fasting insulin, and HOMA-IR.

5.3 Effect of Green Coffee Bean Extract on Blood Pressure

The results indicated a significant effect of green coffee bean extract on SBP (−3.08 mg/dl; 95% CI: −4.41, −1.75; I^2 = 26%) and DBP (−2.27 mg/dl; 95% CI: −3.82, −0.72; I^2 = 61%). This reduction was more pronounced in studies that included patients with elevated blood pressure for both SBP (−4.19 mmHg; 95% CI: −5.95, −2.43; I^2 = 43%) and DBP (−3.09 mmHg; 95% CI: −4.94, −1.25; I^2 = 58%) (Fig. 4a, b). Stratified analysis indicated SBP lowering effect of green coffee bean extract is greater in subgroups with a duration <84 days (−2.89 mmHg; 95% CI: −4.10, −1.68; I^2 = 1%) or dosage of administration <400 mg/day (−3.23 mmHg; 95% CI: −4.84, −1.61; I^2 = 32%) than the subset with ≥84-day follow-up (−3.23 mmHg; 95% CI: −4.84, 0.65; I^2 = 32%) or ≥ 400 mg/day green coffee intervention

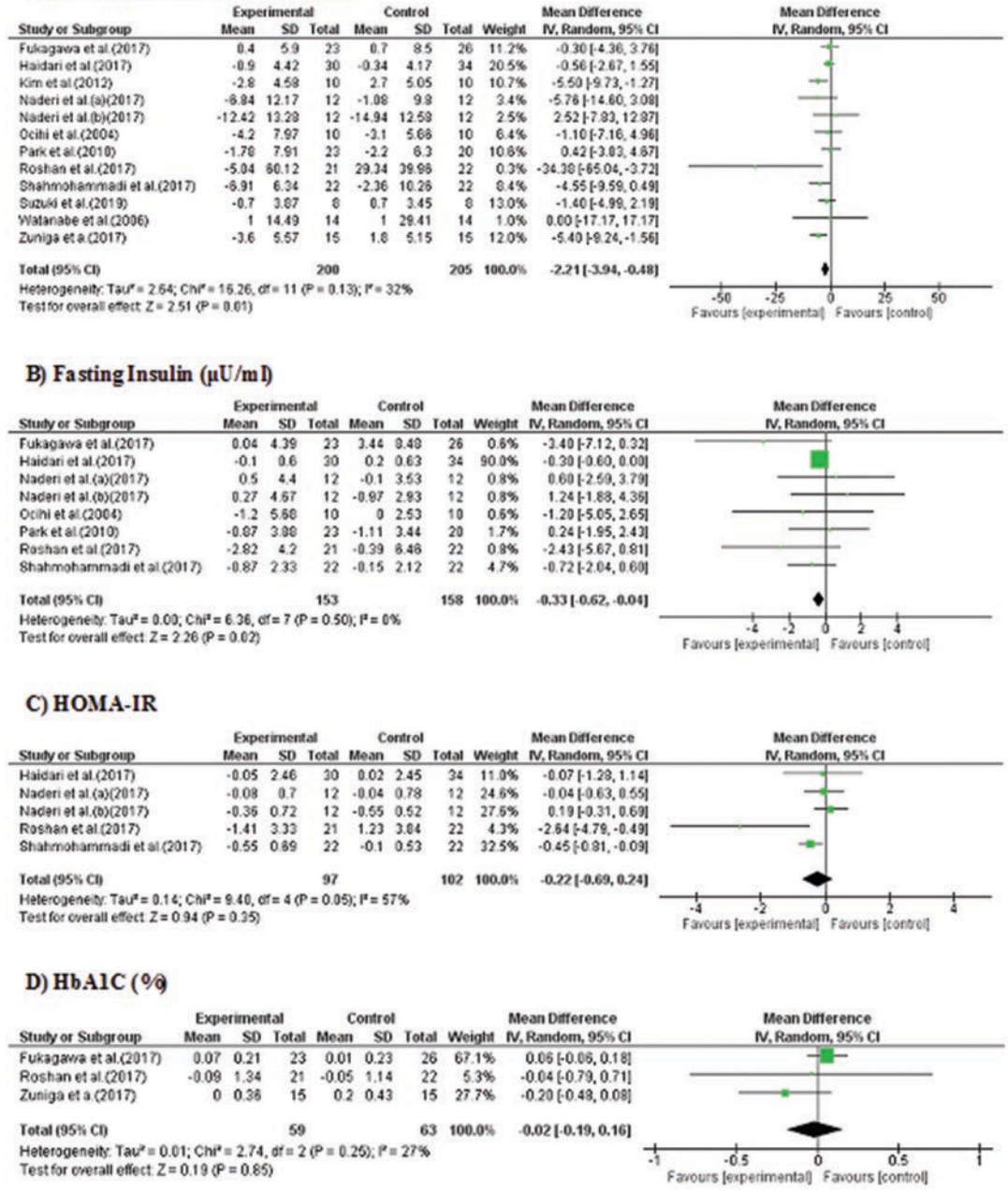

Fig. 3 The meta-analysis results of the effect of green coffee administration on glycemic-related factors

(−3.79 mg/dl; 95% CI: −8.24, 0.08; I^2 = 29%). Furthermore, the effect of green coffee bean extract on DBP levels was more robust in studies that were ≥ 84 days in duration (−5.90 mmHg; 95% CI: −7.80, −4.01; I^2 = 0%). No remarkable difference was detected in other subgroups for DBP (Table 3).

5.4 Effect of Green Coffee Bean Extract on Anthropometric Indices

The pooled results demonstrated that green coffee bean extract significantly decreased body

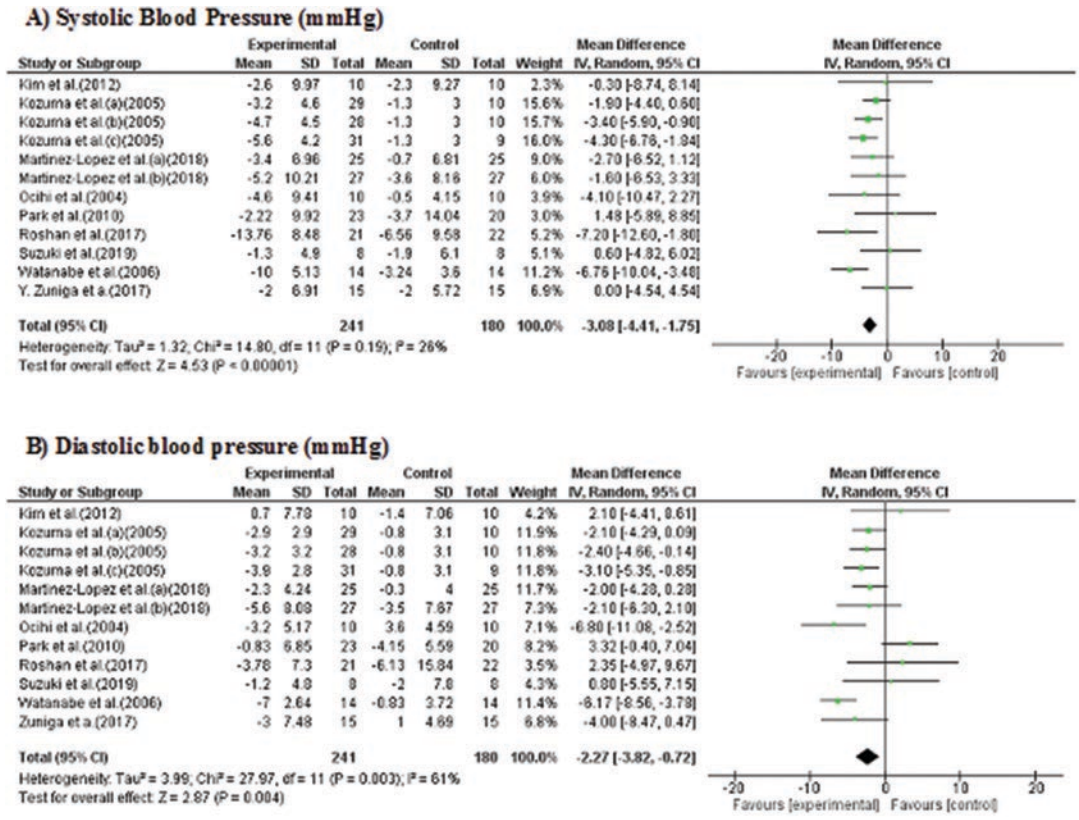

Fig. 4 The meta-analysis results of the effect of green coffee administration on blood pressure

weight (−1.24 kg; 95% CI: −1.82, −0.66; I^2 = 15%), BMI (−0.55 kg/m^2; 95% CI: −0.88, −0.22; I^2 = 73%), and WC (−1.01 cm; 95% CI: −1.78, −0.23; I^2 = 0%) (Fig. 5a–c). A higher level of body weight loss by green coffee bean extract consumption was found in subgroups with mean BMI ≥25 (−1.32 kg; 95% CI: −2.01, −0.63) and ≥ 400 dose of intervention (−1.34 kg; 95% CI: −2.11, −0.56), while no favorable effect on body weight was found in subgroup with mean BMI < 25 (−0.34 kg; 95% CI: −2.23, 1.55) or < 400 dose of intervention (−0.92 kg; 95% CI: −2.09, 0.25). Similarly, a greater BMI reduction was observed in subgroups with a mean BMI ≥25 (−0.63 kg/m^2; 95% CI: −0.98, −0.28) and ≥ 400 dose of intervention (−0.91 kg/m^2; 95% CI: −0.88, −0.22) (Table 3). Due to the low number of studies that reported waist circumference as outcomes, subgroup analysis was not conducted.

6 Sensitivity Analysis

In a sensitivity analysis that removed individual studies at a time, the removal of Haidari et al. [36] from the triglyceride pooled effect size changed the result to significant (−8.19 mg/dl; 95% CI: −16.5, −0.13; I^2 = 18%). The LDL-C overall effect size became nonsignificant after removing Haidari et al. [36] (−1.42 mg/dl; 95% CI: −5.29, 2.44; I^2 = 0%). Similarly, fasting insulin pooled effect size was also sensitive to Haidari et al. [36] with the removal of this study resulting in a non-significant pooled effect (−0.60 µU/ml; 95% CI: −1.51, 0.30; I^2 = 0%). When Haidari et al. [36] was discarded from the BMI pooled effect size, the heterogeneity changed from 73% to 48%, while the results remained significant (−0.44 kg/m^2; 95% CI: −0.69, −0.19). In addition, by excluding of Roshan et al. [32] from WC result, the pooled effect size became nonsignificant (−0.47 cm; 95% CI: −1.49, 0.54; I^2 = 0%). Pooled

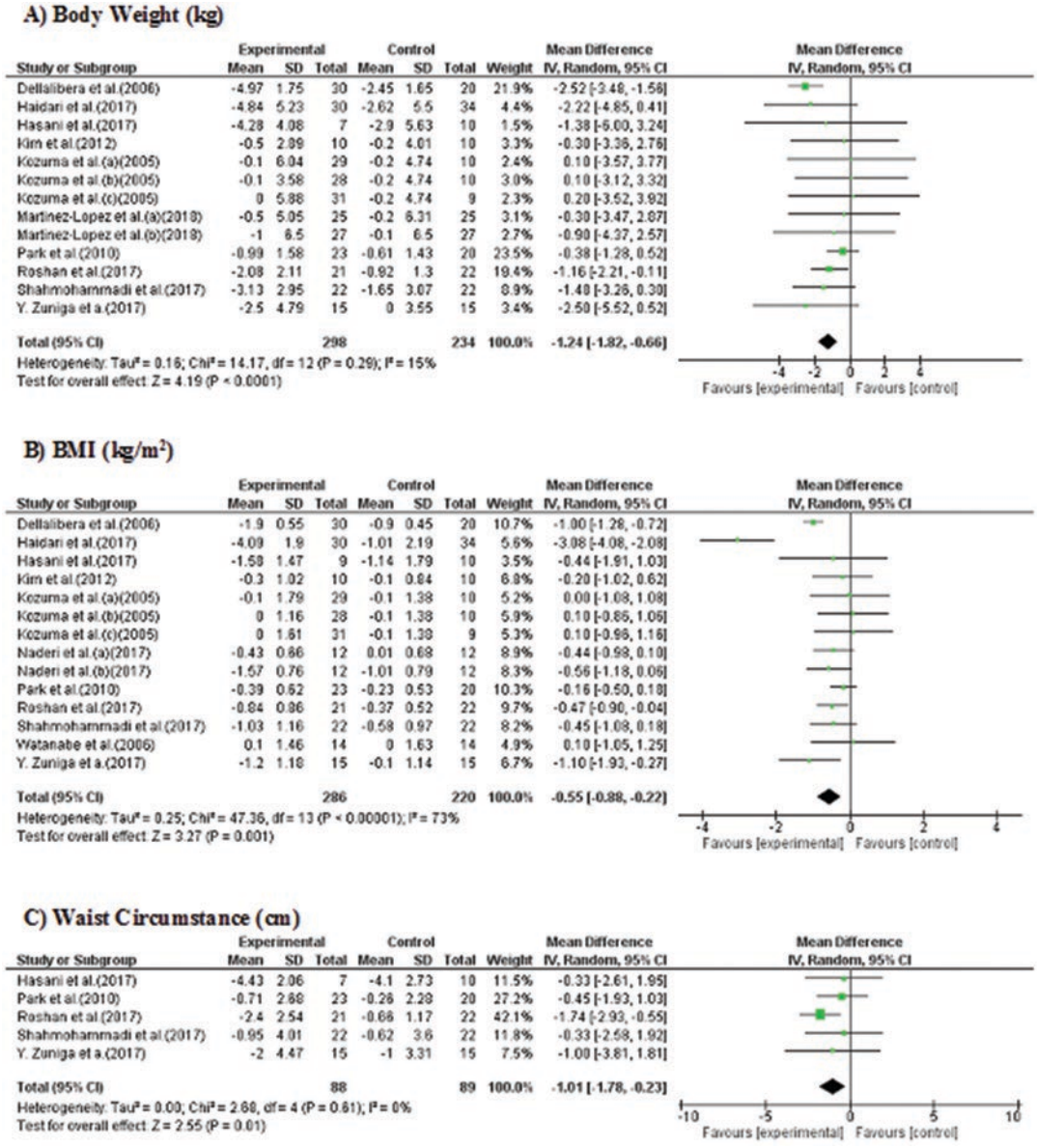

Fig. 5 The meta-analysis results of the effect of green coffee administrations on anthropometric measures

results did not reveal any sensitivity to individual study in other variables including total cholesterol, FPG, SBP, DBP, BMI, and body weight.

Sensitivity analysis by excluding high risk of bias studies [31, 37, 49, 51, 53, 55] indicated that removing studies with high risk of bias did not alter the overall effect size for triglycerides (−5.30 mg/dl; 95% CI: −11.17, 0.56; I^2 = 38%), total cholesterol (−5.99 mg/dl; 95% CI: −9.37, −2.62; I^2 = 0%), LDL-C (−5.27 mg/dl; 95% CI: −8.07, −2.46; I^2 = 21%), HDL-C (1.11 mg/dl; 95% CI: −0.39, 2.61; I^2 = 35%), FPG (−1.99 mg/dl; 95% CI: −3.40, −0.59; I^2 = 59%), SBP (−2.86 mmHg; 95% CI: −4.05, −1.68; I^2 = 0.6%), DBP (−1.86 mmHg; 95% CI: −2.85, −0.87; I^2 = 35%), body weight (−0.83 kg; 95% CI: −1.39, −0.23; I^2 = 0%), and BMI (−0.42 kg/m^2; 95% CI: −0.62, −0.21; I^2 = 77%). Because of the high correlation coefficient (r) calculated for body weight and BMI (0.9), we also performed

sensitivity analysis for alternative levels of correlation coefficient for imputing SD of change. The pooled effect sizes of both BMI (r = 0.8; −0.61 kg/m^2; 95% CI: −0.78, −0.44; I^2 = 58%; r = 0.6; −0.62 kg/m^2; 95% CI: −0.80, −0.44; I^2 = 43%) and body weight (r = 0.8; −1.28 kg; 95% CI: −1.80, −0.77; I^2 = 2%; r = 0.6; −1.30 kg; 95% CI: −1.83, −0.77; I^2 = 0%) were not sensitive to different levels of correlation coefficient.

7 Publication Bias

Visual inspection of funnel plot suggested a mild-to-moderate asymmetry in estimating the influence of green coffee bean extract on nearly all outcomes of interest (Supplemental Fig. 1). However, except for HDL-C, no potential evidence of publication bias was detected by Egger's regression asymmetry test and Begg's rank-correlation methods test for any outcome [triglycerides (Begg's test P = 0.69; Egger's test P = 0.73), total cholesterol (Begg's test P = 0.11; Egger's test P = 0.13), LDL-C (Begg's test P = 0.20; Egger's test P = 0.06), FPG (Begg's test P = 0.33; Egger's test P = 0.19), SBP (Begg's test P = 0.30; Egger's test P = 0.31), DBP (Begg's test P = 0.45; Egger's test P = 0.27), BMI (Begg's test P = 0.78; Egger's test P = 0.70), and body weight (Begg's test P = 0.32; Egger's test P = 0.53)]. Although Begg's rank correlation method test did not show any significant evidence of publication bias (P = 0.82), Egger's regression asymmetry test was significant for HDL-C (P < 0.001). After excluding Haidari et al. (2017), which the HDL-C pooled effect size was sensitive to, the Egger test changed to nonsignificant (P = 0.88). Due to the low number of study (<10) included in the meta-analysis for waist circumference, fasting insulin, HbA1C, and HOMA-IR, the publication bias test was not applicable.

8 Meta-regression

Meta-regression was performed to evaluate the influence of potential covariates, including dose of intervention, duration of study, and baseline measures of outcome of interest, on changes of CVD risk factors in response to green coffee bean extract. The results indicated that changes in FPG serum concentrations were associated with its baseline value (FPG: coefficient = −0.21; P = 0.01). Furthermore, a trend toward a significant association was detected for BMI changes following green coffee bean extract consumption and BMI baseline measures (BMI: coefficient = −0.11; P = 0.05). No other relation was observed between change in BMI and FGP and dose of green coffee bean extract as well as duration of intervention. Furthermore, the effect of green coffee bean extract on all other included CVD risk factors was independent of the potential covariates. Supplemental Table 3 shows the meta-regression results in detail.

9 Discussion

The present systematic review and meta-analysis suggests that green coffee bean extract consumption can be beneficial for controlling total cholesterol, FPG, blood pressure, and body weight. Although the results indicated a significant effect of green coffee bean extract on LDL-C, fasting insulin, and WC, these variables were sensitive to one study and should be interpreted with caution. Similarly, the pooled effect size for triglyceride levels became significant after one study was excluded. Furthermore, while the results of the included meta-analyses reported green coffee bean extract to provide significant improvements in a number of CVD-related outcomes, many of the improvements were relatively small (e.g., a significant body weight decrease of −0.84 kg). However, a relatively minor decrease in CVD risk factors can provide a marked reduced in overall risk of CVD. For example, a 2-mmHg reduction in SBP results in a reduced incidence of mortality related to stroke and ischemic heart by 10% and 7%, respectively [56–58].

The meta-analysis also indicated that the results of all outcomes of interest were robust after excluding studies with high risk of bias methodology. However, the credibility of evidence was only sufficient for some outcomes,

which implied that more studies are needed to make evidence-based conclusion. In addition, meta-regression analysis showed an association between changes in FPG concentration in response to green coffee consumption and FPG baseline measures, but not in case of dose or duration of study. This finding implied that the FPG-lowering effect of green coffee might be more visible in subjects with higher blood glucose levels and could be promising for controlling diseases with impaired glucose metabolism especially diabetes. Furthermore, we conducted a series of subgroup analyses to explore factors that may influence treatment response. While the subgroup analyses were not consistent for each outcome, the subgroup analyses generally suggest that chronic administration of green coffee bean extract (>60 or 84 days) in doses >400 mg may be more effective. In addition, green coffee bean extract may be more effective in populations with cardiovascular risk factors (e.g., BMI >25 or elevated blood pressure).

The mechanisms of action by which green coffee bean extract may improve CVD risk factors require further exploration in human intervention studies. Preclinical animal and cell-culture studies suggest that chlorogenic acid, the primary polyphenol compound within green coffee extract, may improve blood pressure via the stimulation of nitric oxide, antioxidant activity, and the inhibition of angiotensin-converting enzymes [59, 60]. Furthermore, chlorogenic acid may improve glycemic control and lipid profile via its effect on expression of peroxisome proliferator-activated receptor-ɣ and AMP-activated protein kinase [22]. Additional compounds such as caffeine and other polyphenol compounds may also exert a beneficial effect. Several reports have shown a beneficial impact of polyphenols on health condition, and its cardioprotective effect have been frequently suggested [61, 62]. Further studies that utilize techniques such as metabolomic analysis may provide further information regarding the relevant pathways in humans.

Furthermore, interindividual differences in the absorption and bioavailability of green coffee bean extract has not been well-explored in humans. Polyphenol absorption is highly dependent on gut microbiota composition. Monteiro et al. [63] explored the absorption of chlorogenic acid isomers and metabolites in humans and reported significant interindividual differences. This has also been reported for other polyphenol compounds such as Urothillin A, a polyphenol present in pomegranates, which appears to be differentially absorbed based on microbiota composition [64]. Further exploration regarding factors that influence absorption may inform future trials and reduce the possible influence of these factors on treatment response.

In this area, a few meta-analyses have investigated the effect of green coffee on only some of CVD risk factors such as lipid profiles [65] and anthropometric measures [66] and reported a positive influence on these outcomes. Although they supported the hypotheses behind the beneficial effect of green coffee, they only reported a simple influence without any investigation on quality of evidence, and these studies could be considered as primary outcomes. In this case, we put one step forward to clarify the quality of evidences across outcomes by performing adjustments for multiple confounders and exploring risk of bias for each finding. It made our results more reliable to decide whether using green coffee could be practical in prevention/treatment of CVD or there is still a lack of sufficient evidence to make any final conclusion. On the other hand, as these risk factors are known as the surrogate factors for CVD and are not hard outcomes of interest, there is a need to consider all risk factors as far as possible to make an evidence-based decision.

The comparative efficacy of green coffee bean extract compared to standard pharmacotherapy has not yet been evaluated. However, due to the demonstrated benefit of current pharmacological interventions for CVD management and prevention, green coffee bean extract may be of greater benefit as an adjunctive intervention by providing additional improvements in CVD markers. Furthermore, the use of an effective adjuvant intervention may allow for a reduction in the dose of pharmacological interventions in participants experiencing side effects. However, the efficacy

of green coffee bean extract as an adjuvant intervention to standard pharmacotherapy has not yet been evaluated.

While no serious adverse events were reported in the included studies, the safety of green coffee bean extract was only reported in seven studies. Zuniga et al. [54] reported that abdominal pain and distention, headache, diarrhea, and polyuria were experienced by participants in both groups. These side effects disappeared at the end of the first week of the intervention. Two participants in a study conducted by Roshan et al. [32] experienced discomfort by green coffee bean extract. One participant with a history of stomach irritation reported stomachaches, and another participant experienced dizziness. Furthermore, there is a lack of sufficient safety data in chronic conditions such as autoimmune conditions and conditions related to the liver and kidney. Further studies in this area are needed to enhance our knowledge about the safety of green coffee bean extract and possible interaction with pharmacological agents.

The current study has the following limitations which should be considered. The number of included studies per outcome was relatively low, especially in subgroups. The amount of the main active component of green coffee bean extract was not reported in all trials, which limited the ability of meta-regression analyses to adjust for dosage. Therefore, the included subgroup analyses that explored dose of intervention should be interpreted with caution. Due to the wide variation in bioactive compounds in herbal and plant-based interventions, future studies are recommended to report the level of key bioactive compounds and/or use of standard extracts to ensure a consistent dose is provided [67]. Several included studies did not control for participant's diet or physical activity, which may have influenced the study results. Finally, the participant population varied across the studies (i.e., participants with chronic diseases vs healthy participants) which might be as source of heterogeneity.

10 Conclusion

The present systematic review and meta-analysis suggests that green coffee bean extract consumption can have beneficial effect on improving triglycerides, total cholesterol, FPG, blood pressure, and body weight. Due to the promising cardioprotective effect and safety profile, further studies should explore the use of standardized green coffee bean extract as adjuvant therapy to conventional medical treatment. Further studies are also required to explore the relevant mechanisms of action and interindividual responses.

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Competing Interests None.

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material This is a review article and there is no raw data.

Authors' Contributions M.P., A.H., W.M., S.K, and A.S. carried out the conceptualization, design, and drafting of this study. A.N., A.H. and M.P. searched databases, screened articles, and extracted data. M.P. and A.H. performed the acquisition, analysis, and interpretation of data. W.M. critically revised the manuscript. All authors approved the final version of the manuscript. A.S. and A.H are the guarantors of this study.

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