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REVIEW ARTICLE

The effect of green coffee extract supplementation on cardio metabolic risk factors: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose Considering the present controversies on the association between green coffee supplementation and cardio metabolic risk factors, this systematic review and meta-analysis was conducted to evaluate the effect of green coffee supplementation on cardio metabolic risk factors.

Method A systematic literature search was performed throughout the PubMed, Embase, Scopus, and Web of Science databases up to October 2019. As a result, all randomized controlled trials over the effect of green coffee supplementation on fasting blood sugar (FBS), insulin, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C - reactive protein (CRP), and homeostatic model assessment for insulin resistance (HOMA-IR) in adults were examined. Data were extracted from the relevant studies and analyzed using the random-effect or pooled model and standardized mean difference (SMD) with 95% confidence interval (CI).

Results After excluding the irrelevant articles, 27 studies were included in the final analysis. Pooled results revealed that green coffee supplementation significantly reduced FBS (WMD = −2.28, 95% CI: −4.49 to −0.07, $P = 0.043$), insulin (WMD = −0.53, 95% CI: −0.93 to −0.14, $P = 0.008$), and triglyceride (WMD = −9.28, 95% CI: −14.93 to - 3.63, $P = 0.001$). Furthermore, green coffee supplementation increased the HDL levels (WMD = 1.33, 95% CI: 0.08 to 2.58, $P = 0.037$). However, the changes in HOMA-IR, LDL, and CRP levels were not significant ($P > 0.05$).

Conclusion This meta-analysis indicated that green coffee supplementation significantly decreased FBS, insulin, and triglyceride, but improved HDL. No statistically significant improvement was found in HOMA-IR, LDL, and CRP indices following the green coffee supplementation.

Keywords Green-coffee · Cardiometabolic risk factors · Chlorogenic acid · Fasting blood sugar · Meta-analysis

Introduction

In recent years, cardio-metabolic disorders have changed into a major public health issue worldwide. Some underlying risk factors of the cardio metabolic diseases include inflammation, hyperglycemia, dyslipidemia, and endothelial dysfunction. These rampant and burgeoning health issues affect about 20–25% of the world's adult population [1, 2]. Since chemical drugs have several adverse effects, no single treatment has ever been identified for management of the cardio-metabolic disorders [3, 4]. Several studies reported the effective role of nutritional supplements such as antioxidants in prevention and treatment of the cardio-metabolic disorders [5, 6]. A growing number of researchers have been trying to find natural compounds to improve cardio-metabolic treatments [7]. Recently,

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herbal supplementation was found to be effective in treating chronic disorders [8].

Coffee, one of the most popular beverages, contains caffeine [9]. Coffee plays an important role in individuals' diet and health due to its high consumption rate around the world [10]. Coffee is rich in phenolic compounds, which are protective agents against chronic degenerative diseases [11]. Green coffee consists of several bioactive components including chlorogenic acid (CGA), trigonelline, and polyphenols. Chlorogenic acids, the ester of quinic acid and caffeic acid, are the main components of polyphenols with antioxidant abilities [12]. Previous studies demonstrated the anti-diabetic, anti-carcinogenic, anti-inflammatory, and anti-obesity effects of CGA [13–16]. Several animal studies also reported that CGA had anti-diabetes [17], anti-obesity [18], and anti-lipidaemic properties [18, 19] with beneficial effects on insulin resistance [20]. A recent meta-analysis also indicated that green coffee supplements could decrease blood pressure [21]. Despite the confirmed positive effects of green coffee supplementation on cardio-metabolic factors in animal studies, the results of human studies are still inconsistent. Although positive effects of green coffee were reported on cardio-metabolic factors, such as lipid profile in the literature [22], some studies did not find any significant association in this regard [23, 24].

So, this systematic review and meta-analysis aimed to review the available randomized controlled trials (RCTs) to assess the effect of green coffee extract (GCE) supplementation on fasting blood sugar (FBS), insulin, homeostatic model assessment for insulin resistance (HOMA-IR), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and C - reactive protein (CRP) concentrations.

Materials and methods

Data sources and search strategy

The current systematic review was conducted based on the guidelines provided by PRISMA [25]. Online databases including PubMed, Embase, Scopus, and Web of Science were systematically searched to find the related articles over the effect of green coffee supplementation on cardio metabolic risk factors up to October 2019 with no language and time restrictions. In addition, Google Scholar, Cochrane Library, and reference lists of the related papers were manually searched to find any other possible references. The keywords used in this systematic search included: ("green coffee" or "green coffee extract" or "chlorogenic acid") AND ("cardio-metabolic" OR "cardio metabolic" OR "blood sugar" OR "fasting blood sugar" OR "FBS" OR insulin OR glycaemia OR "insulin resistance" OR "insulin sensitivity" OR "HOMAIR" OR "HOMA-IR" OR "triglyceride" OR "TG" or "lipid profile" OR "Low-density lipoprotein" OR LDL OR HDL OR "High – density lipoprotein" OR cholesterol OR "Total cholesterol" OR inflammation OR "CRP" OR "C-reactive protein") AND ("trial" OR "randomi*" OR "control" OR "clinical" OR "intervention" OR "randomized" OR "placebo" OR "blind").

Inclusion and exclusion criteria

Articles were included in our meta-analysis in the case that they: [1] were clinical trials, [2] investigated adults over 18 years of age [3], reported sufficient data on the baseline and final tests of FBS, TG, HDL, LDL, cholesterol, insulin, HOMA-IR, or/and CRP in both green coffee and control groups [4], and conducted the intervention using any green coffee species. Studies were excluded in the case that they lasted less than 2 weeks, were nonrandomized clinical trials, were animal or cross-sectional studies, conducted on children, and examined the effects of green coffee along with other interventions. Grey literature such as conference papers, dissertations, and patents were also removed from the analysis.

Data selection

The data extraction process was completed by two independent reviewers (MM and MR) according to the eligibility criteria (Table 1). Extracted information included: first author's name, paper publication year, sample size, trial design, green coffee extract (GCE) dose, study duration, participants' mean age, research quality, and study outcomes. Any disagreements were resolved by the third reviewer (ER) at this stage.

Quality assessment

Quality of the papers was evaluated by the Cochrane Collaboration's risk of bias assessment tool [26] according to the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each domain was judged to have low, high, or unclear risk of bias. Finally, based on these results, the overall quality of studies was defined as good (low risk in more than three domains), fair (low risk in three domains), and poor (low risk in less than three domains).

Statistical analysis

Statistical analysis was performed by Stata 12. Weighted mean difference (WMD) and 95% confidence interval (CI) were used to evaluate the effect of GCE supplementation on cardio metabolic risk factors. In the case that the changes were not

Table 1 Inclusion and exclusion criteria following the PICOS approach

PICOS	Inclusion and exclusion criteria	Data extraction
Participants	Adult population's ≥ 18 and ≤ 65 y with or without disease. Studies with a median age between these values were eligible. Participants with mean age ≤ 18 y or nonclinical studies were excluded.	Age, sex, gender, sample size, location, inclusion and exclusion criteria
Intervention	Green coffee extract defined as "Green coffee "OR "chlorogenic acid" OR "Green coffee bean" OR "Green coffee extract" or any other compound defined by the author as a green coffee extract if justification for the compound fulfilling criteria as a green coffee extract were explicitly stated. Green coffee extract to be administered at a dose of ≥100 mg/day for ≥2 wk. Trials that included other interventions (e.g., drug use) were included if the effect of the Green coffee extract alone could be isolated. Multiple intervention arms were eligible.	Green coffee type, placebo type, intervention and placebo dosage, duration of intervention
Comparators	Only studies with control group were included, The effect of the green coffee extract alone had to be able to be isolated.	Type and dose of comparator, compliance
Outcomes	Mean changes and SD in FBS, insulin, HOMA-IR, TG, LDL, HDL, cholesterol and CRP	Outcomes measured, Evaluation methods and side effects.
Study design	Only randomized controlled trials, where it was possible to extract data on just the green coffee extract compared with to placebo. We included both the parallel and crossover design	Design of the study, loss of the study, study quality

PICOS, participants, intervention, comparator, outcome, study type

CRP, C-Reactive Protein; *FBS*, Fasting blood sugar; *HOMA-IR*, Homeostatic Model Assessment for Insulin Resistance; *LDL*, Low-Density Lipoprotein; *TG*, Triglyceride

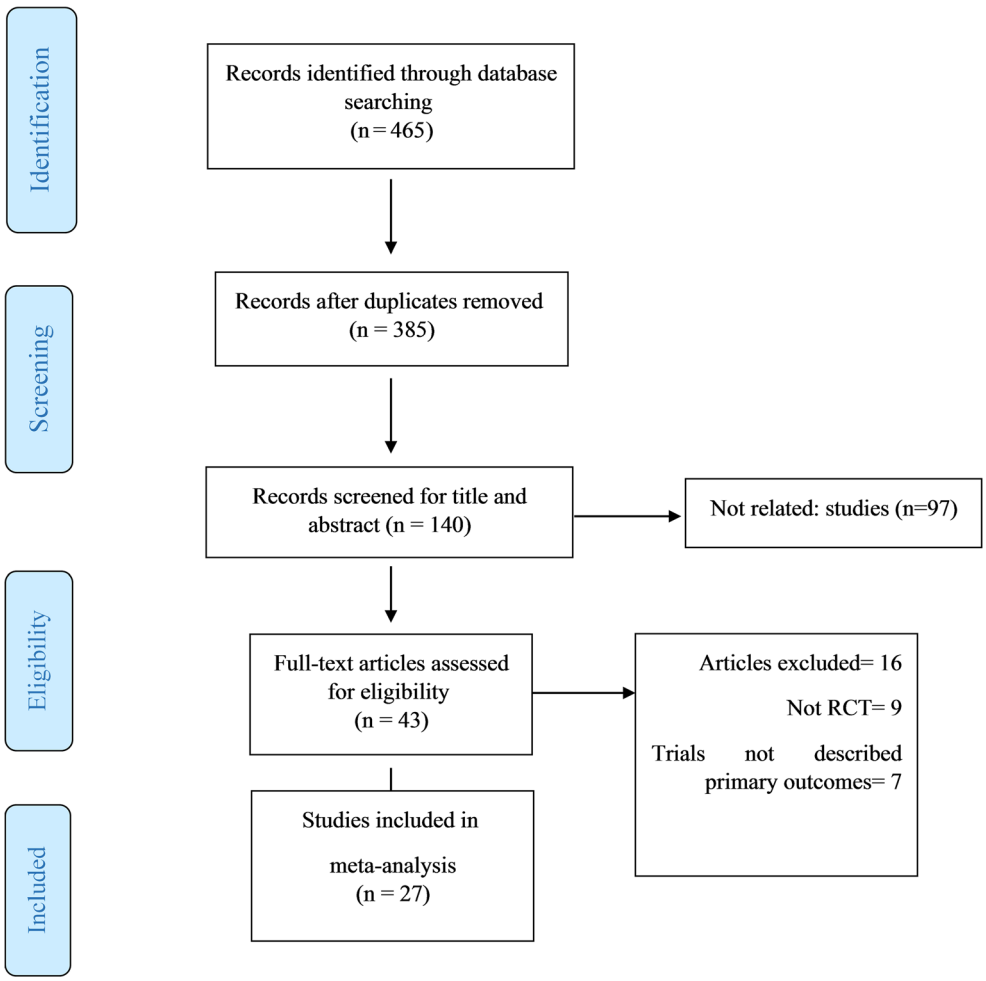

Fig. 1 Flow diagram of literature search according to the PRISMA statement

Table 2 Characteristics of included studies in the systematic-review

First Author, Year	Study design	Country	Age range	Gender	Participants (Intervention/ control)	Intervention Type	Duration/ week	Intervention Dose(mg)	Study quality	outcome
Banitalebi E et al. (2019)	RCT	Iran	30–50	F	15/15	GCBE	8	500	G	TG, HDL, T Chol, LDL, FBS
Fasihi M et al. (2019)	RCT	Iran	53.7	F	22/21	GCBE	8	400	F	TG, HDL, T Chol, LDL, FBS, insulin, HOMA-IR
Mansour A et al. (2019)	RCT	Iran	44.57	F/M	25/23	Chlorogenic Acid	24	200	G	TG, HDL, T Chol, FBS, Insulin, HOMAIR, AST, ALT
Sarria B et al. (2019)	RCT	Spain	29.5	M/F	26/26	GCBE	8	200	G	T Chol, LDL
Suzuki A et al. (2019)	RCT	Japan	45	M	8/8	Chlorogenic Acid	2	300	P	TG, HDL, LDL, T Chol, AST, ALT
Alhamhany N (2018) et al.	RCT	Iraq	36.7	F, M	35/0	GCBE	6	1000	P	T Chol, LDL
Aljamal. A et al. (2018)	RCT	Jordan	>30	M	10/5	GCBE	4	200	P	TG, HDL, LDL, T Chol
Hosseinabadi S et al. (2018)	RCT	Iran	41.5	M/F	22/23	GCBE	8	200	F	TG, HDL, T Chol, LDL, FBS, Insulin, HOMAIR, AST, ALT
Katada S et al. (2018)	RCT	Japan	38	M	15/15	Chlorogenic Acid	4	428	F	TG, HDL, T Chol, LDL, FBS
Martínez S et al. (2018)	RCT	Spain	30	F/M	27/25	GCBE	8	6000	P	TG, LDL, T Chol, AST, ALT
Roshan H et al. (2018)	RCT	Iran	52.3	F, M	21/22	GCBE	8	800	G	TG, HDL, LDL, T Chol, FBS, Insulin, HOMAIR
Salamat Sh et al. (2018)	RCT	Iran	38.9	M	35/35	GCBE	8	800	G	TG, HDL, LDL, T Chol
Zuniga L et al. (2018)	RCT	Mexico	44	F, M	12/14	Chlorogenic Acid	12	1200	G	TG, HDL, LDL, T Chol, FBS
Nikpayam O et al.(2018)	RCT	Iran	43	F,M	22/21	GCBE	8	400	G	CRP
Fukagawa S et al. (2017)	RCT	Japan	25–40	F	23/26	GCBE		270	P	TG, AST, ALT
Haidari F et al.(2017)	RCT	Iran	35.9	F	30/34	chlorogenic acid	8	180 mg	G	TG, HDL, LDL, T Chol, FBS, Insulin, HOMAIR
Shahmohammadi H et al. (2017)	RCT	Iran	42.9	F, M	22/22	GCBE	8	1000	G	TG, HDL, LDL, T Chol, FBS, Insulin, HOMAIR, AST, ALT
Naderi L et al. (2017)		Iran	31.1	F	12/12	GCBE	8	400	P	FBS, Insulin, HOMAIR
Agudelo-Ochoa G et al. (2016)	RCT	Colombia	38.5	F, M	25/25	Chlorogenic Acid	8	420	F	TG, HDL, LDL,T Chol, FBS
Sarria B et al. (2016)	RCT	Spain	29.6	F, M	52/52	GCBE	8	6000	P	FBS, Insulin, HOMAIR
Kim T et al. (2012)	RCT	China	45.4	F	10/10	Chlorogenic acid	8	100	F	T Chol
Park J et al.(2010)	RCT	Korea	33.1	F	23/20	GCBE	8	200	G	TG, HDL, LDL, T Chol, FBS, Insulin
Watanabe T et al. (2009)	RCT	Japan	51.5	F/M	14/14	Chlorogenic Acid	12	140	G	TG, HDL, LDL, T Chol,AST, ALT
Blum J et al.(2007)	RCT	France	18–70	F/M	9/9	Chlorogenic Acid	6	200	P	FBS
Kozuma K et al.(2005)	RCT	Japan		M	28/29	GCBE	4	100	F	TG, HDL, LDL, T Chol,
Ochiai R et al. (2004)	RCT	Japan	36	M	10/10	Chlorogenic Acid	18	140	P	TG, HDL, LDL, T Chol, FBS, Insulin
Van Rooij J et al. (1995)	RCT	Netherlands	19–64	F, M	12/12	GCBE	6	2000	F	TG, HDL, LDL, T Chol,AST, ALT

G, Good quality, *P*, Poor quality, *F*, Fair quality

ALT, Alanine Aminotransferase; *AST*, Aspartate Aminotransferase; *CRP*, C-Reactive Protein; *HOMAIR*, Homeostatic Model Assessment for Insulin Resistance; *FBS*, Fasting Blood Sugar; *GCBE*, green coffee beans extract; *HDL*, High-Density Lipoprotein; *LDL*, Low-Density Lipoprotein; *T Chol*, Total Cholesterol; *TG*, triglyceride

reported in studies, the baseline and final mean values and standard deviations (SDs) were extracted and SD of the mean changes was calculated using the correlation coefficient of 0.5. If the heterogeneity was high, fixed- or random-effects

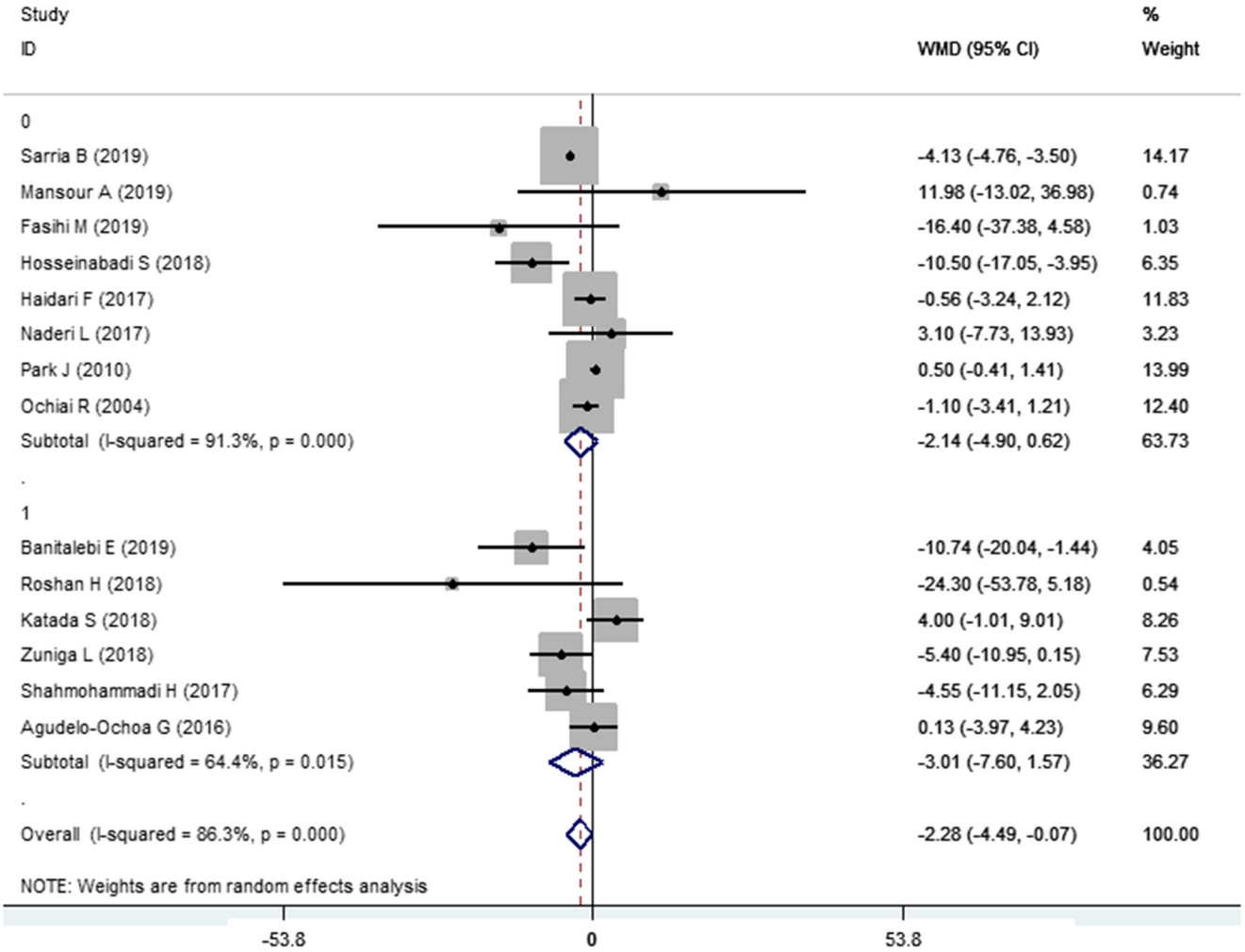

Fig. 2 Forest plot summarizing the association between green coffee extract supplementation on circulating FBS concentrations

models were performed. Significant and high heterogeneity were assessed using p value <0.05 and $I^2 \geq 50\%$, respectively. Sensitivity analysis was conducted to examine the effect of each study on the pooled results. Egger weighted regression test was also performed to identify the potential publication bias. P value <0.05 was considered as statistically significant.

Results

The database searches identified 465 articles. In the first screening phase, after reading the studies' titles and abstracts, 325 articles were removed and 140 studies were retrieved for full-text review. Finally, 27 RCTs met the eligibility criteria [22–24, 27–50]. The study flow diagram is depicted in Fig. 1.

Study characteristics

Table 2 includes the articles examined in this meta-analysis. Of 27 articles that met the eligibility criteria, five had cross-over design and others had a parallel design. Studies were conducted in Spain, Japan, China, Korea, France, Netherlands, Colombia, Mexico, and Iran. The mean dose of GCE or its active compounds varied from 200 to 2000 mg/day and the duration of intervention ranged from 2 to 24 weeks. All evaluated studies were carried out among adults. A total number of 992 participants (565 participants in the intervention groups and 427 participants in the control groups) were included in the final analysis.

Quality assessment

The Cochrane risk-of-bias tool was applied to evaluate quality of the studies. According to the results, 11 articles had good quality, seven had fair quality, and nine had poor quality.

Meta-analysis results over the effect of GCE on glycemic controls

The FBS was investigated and reported in 14 studies among a total of 512 participants. The random-effects' model findings revealed that GCE supplementation caused a significant

Table 3 Results of subgroup-analysis for effect of green coffee extract on cardio metabolic risk factors

	No. of effect sizes	RR (95% CI)	P within[1]	I^2 (%)	P between[2]
Subgroup analyses for FBS and green coffee extract					
Duration of follow up					0.043
More than 8 weeks	3	−2.15 (−6.15, 1.85)	0.211	35.8	
8 weeks and less	11	−2.37 (−4.97, 0.23)	0.342	89.1	
Quality score					
High Quality	9	−3.76 (−6.59, −0.93)	0.009	90.3	
Fair and Poor Quality	5	0.28 (−2.50, 3.07)	0.176	32.8	
Supplement Dose					
≥500 mg/day	6	−3.01(−7.60, 1.57)	0.267	86.3	
<500 mg/day	8	−2.14(−4.90, 0.62)	0.315	64.4	
Subgroup analyses for Insulin and green coffee extract					
Quality score					0.008
High Quality	6	−0.4 (−0.83, 0.04)	0.465	66.8	
Fair and Poor Quality	4	−1.31 (−2.22, −0.4)	0.008	0.0	
Supplement Dose					
≥400 mg/day	4	−1.18 (−2.11, − 0.25)	0.004	0.0	
< 400 mg/day	6	−0.42 (−0.86, 0.01)	0.176	66.7	
Subgroup analyses for HOMA-IR and green coffee extract					
Supplement Dose					0.001
≥400 mg/day	4	−0.2 (−0.95, 0.55)	0.163	62.8	
<400 mg/day	4	−0.25 (−0.28, − 0.22)	0.03	0.0	
Quality score					
High Quality	5	−0.32 (−0.61, − 0.04)	0.032	43.1	
Fair and Poor Quality	3	0.08 (−0.54, 0.7)	0.287	52.5	
Subgroup analysis for TG and green coffee extract					
Duration of follow up0.001					
More than 4 weeks	15	−10.81 (−17.73, −3.89)	0.002	75.5	
4 weeks and less	4	−4.42 (−11.38, 2.53)	0.286	0.0	
Supplement Dose					
≥500 mg/day	9	−10.18 (−20.41, 0.06)	0.181	82.4	
<500 mg/day	10	−9.32(−14.68, −3.95)	0.009	19.9	
Quality score					
High Quality	9	−10.18(−17.77, −2.58)	0.009	0.61	
Fair and Poor Quality	10	−7.86 (−16.17, 0.45)	0.276	55.2	
Subgroup analysis for LDL and green coffee extract					
Supplement Dose0.215					
≥400 mg/day	10	0.92(−5.95, 7.78)	0.234	82.6	
<400 mg/day	9	−2.72(−6.94, 1.50)	0.167	71.9	
Quality score					
High Quality	8	−6.01(−11.30, −0.72)	0.032	76.9	
Fair and Poor Quality	9	2.67(−2.28, 7.62)	0.376	75.2	
Subgroup analysis for HDL and green coffee extract					
Duration of follow up0.037					
4 weeks and less	4	3.26(0.55, 5.96)	0.034	0.0	
More than 4 weeks	14	0.97(−0.44, 2.38)	0.324	0.74	
Quality score					
High Quality	9	0.8 (−0.96, 2.56)	0.465	84.3	
Fair and Poor Quality	9	1.98(0.36, 3.61)	0.003	0.0	
Supplement Dose					
>400 mg/day	10	2.42 (1.26, 3.58)	<0.001	0.0	
≤400 mg/day	8	1.27(−0.49, 3.04)	0.312	78.8	

Table 3 (continued)

	No. of effect sizes	RR (95% CI)	P within[1]	I^2 (%)	P between[2]
Subgroup analysis for total cholesterol and green coffee extract					
Duration of follow up0.14					
8 weeks and less	15	−0.75(−4.73, 3.22)	0.416	50.8	
More than 8 weeks	4	−12.44(−18.44, −5.86)	0.002	18.7	
Quality score					
High quality	9	−8.98(−14.62, −3.34)	0.005	61	
Fair and Poor quality	10	1.58(−3.09, 6.25)	0.265	41.2	
Supplement dose					
8 weeks and less		−1.93(−10.71, 6.84)	0.289	73.4	
More than 8 weeks		−2.94 (−6.63, 0.75)	0.176	36.7	
Subgroup analysis for CRP and green coffee extract					
Supplement dose0.486					
>500 mg/day	3	−0.01(−0.15, 0.12)	0.461	32.6	
≤ 500 mg /day	3	−0.78(−1.98, 0.43)	0.354	88.5	

CRP, C-Reactive Protein; *FBS*, Fasting blood sugar; *HOMA-IR*, Homeostatic Model Assessment for Insulin Resistance; *LDL*, Low- Density Lipoprotein; *TG*, Triglyceride

reduction in the FBS concentration (WMD = −2.28, 95% CI: −4.49 to −0.07, $P = 0.043$) with a significant heterogeneity ($I^2 = 86.3\%$, $P < 0.001$) (Fig. 2). Based on the subgroup analysis, the GCE could decrease the FBS concentration significantly only in studies with good quality (WMD = −3.76, 95% CI: −6.59 to −0.93, $P = 0.009$) (Table 3). The leave-one-out sensitivity analysis revealed that the pooled effect size was not dependent on a single study (Table 1S). No publication bias was found based o9n the funnel plots analysis (Egger's test $P = 0.864$; Begg's test $P = 0.274$) (Fig. 3).

The effect of GCE on insulin levels was examined in 10 articles. According to the meta-analysis, insulin levels decreased significantly after the GCE supplementation (WMD = −0.53, 95% CI: −0.93 to −0.14, $P = 0.008$) (Fig. 4). Heterogeneity was significant between these studies ($I^2 = 53.8$, $P = 0.02$). Considering the subgroup analysis, GCE supplementation decreased the insulin levels in studies with poor and fair quality levels (WMD = −0.53, 95% CI: −0.93 to −0.14, P = 0.008) and in studies that used higher doses of GCE (≥400 mg/day)

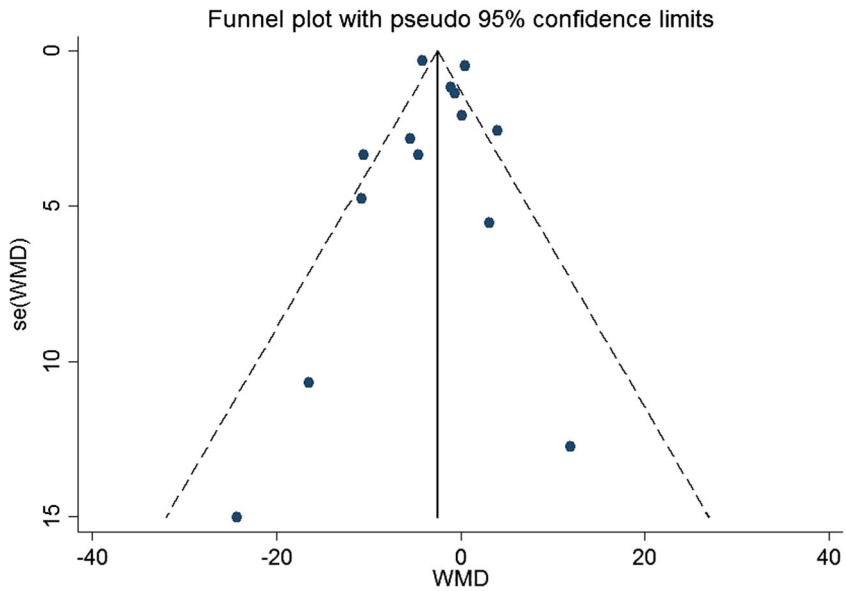

Fig. 3 Funnel plots detailing publication bias in the selected studies of the relation between intakes of green coffee extract and FBS

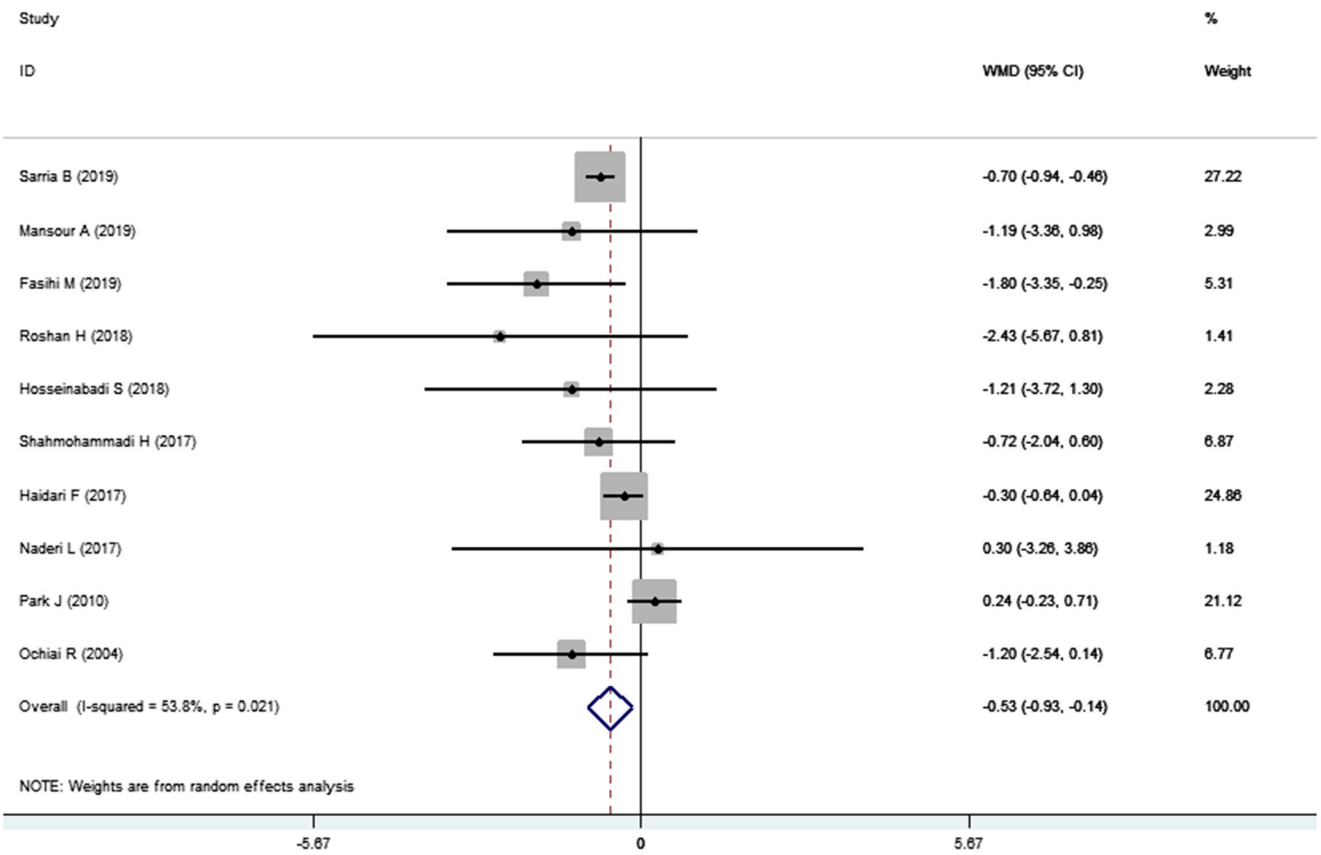

Fig. 4 Forest plot summarizing the association between green coffee extract supplementation on circulating insulin concentrations

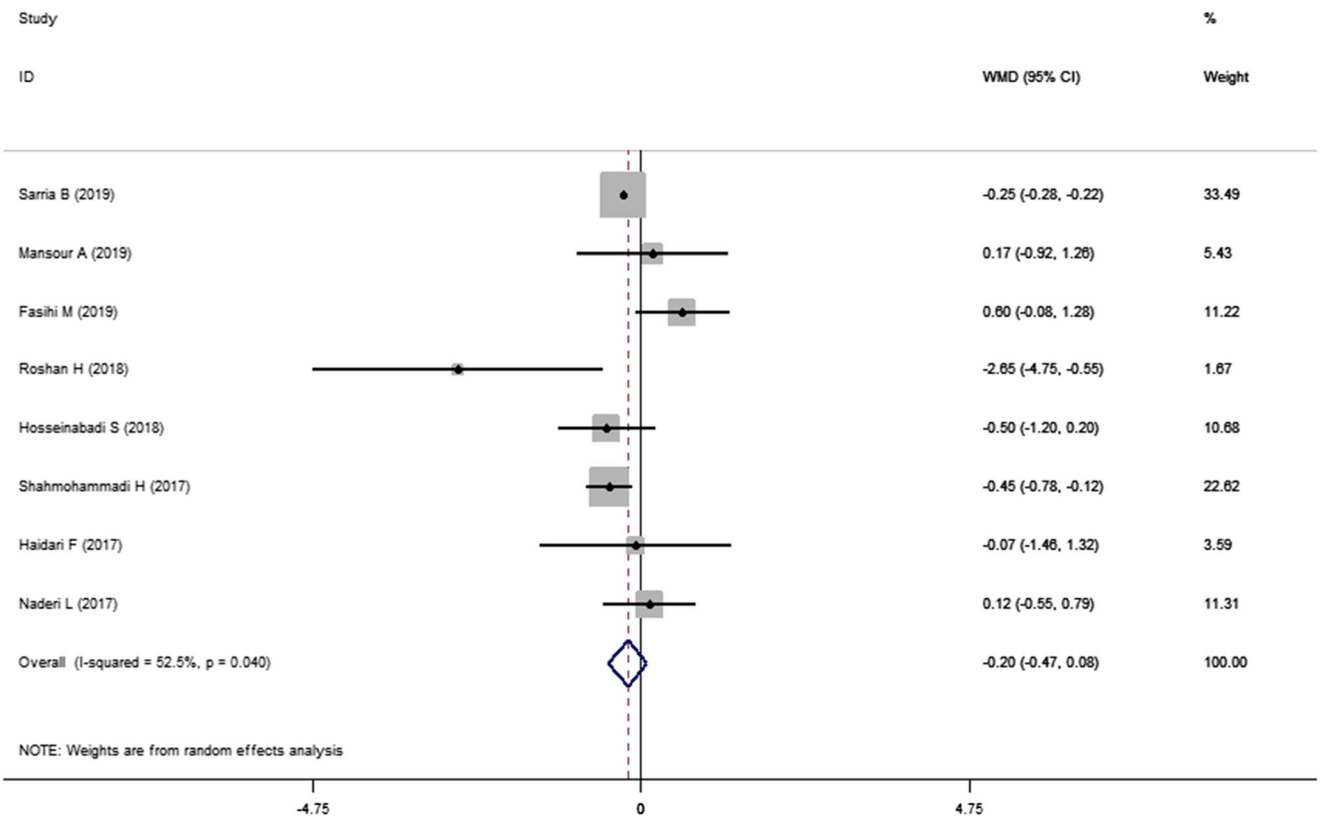

Fig. 5 Forest plot summarizing the association between green coffee extract supplementation on HOMA-IR

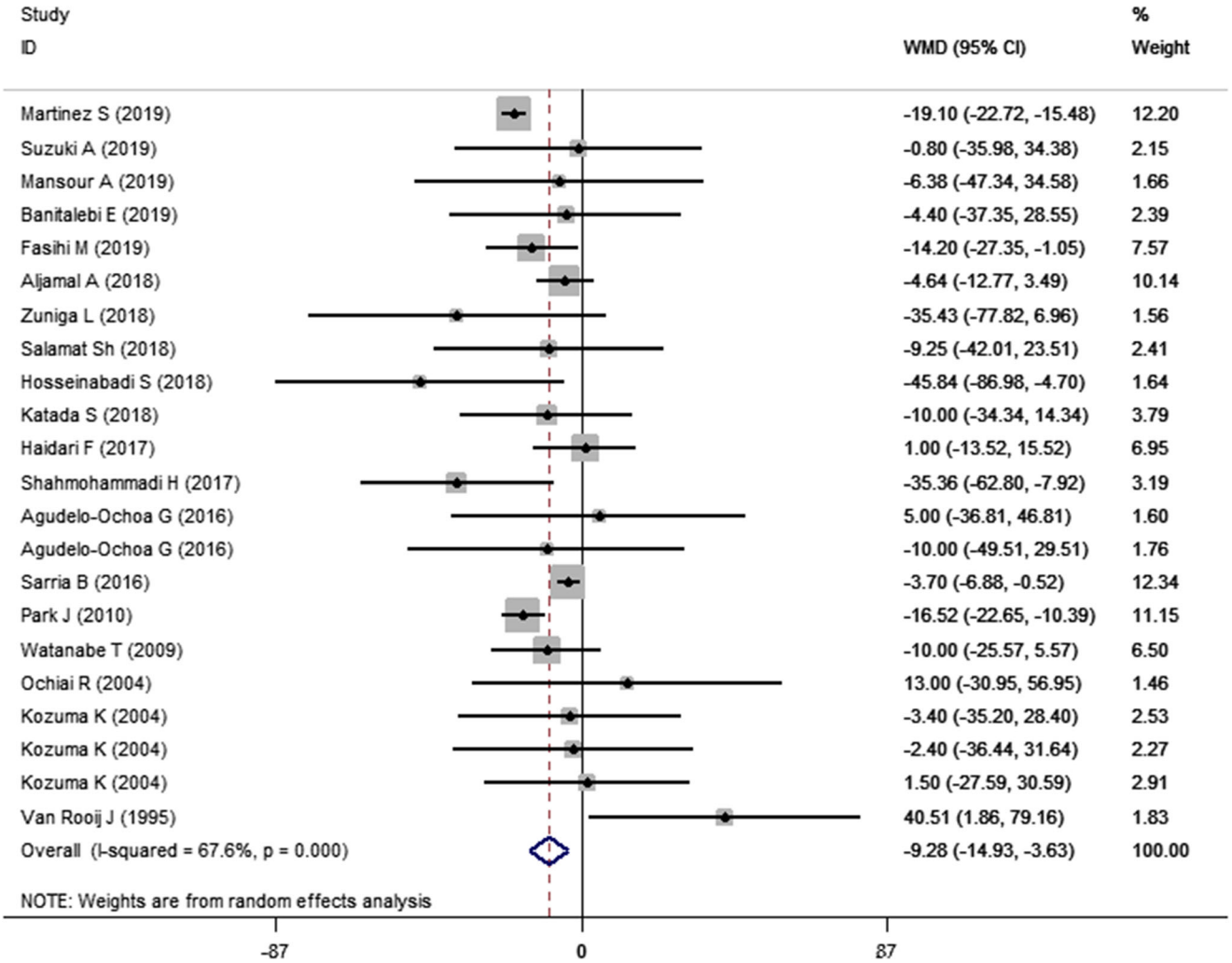

Fig. 6 Forest plot summarizing the association between green coffee extract supplementation on TG

(WMD = −0.53, 95% CI: −0.93 to −0.14, $P = 0.004$) (Table 3). Sensitivity analysis did not reveal alterations in the findings (Table 2S). According to the funnel plot and Egger's statistics, no evidence of publication bias was found among trials (Egger's test $P = 0.485$; Begg's test $P = 0.929$) (**Fig. 1S**).

Meta-analysis of HOMA-IR data showed that GCE supplementation had no significant effect on insulin sensitivity (WMD = −0.2, 95% CI: −0.47 to 0.08, $P = 0.168$) (Fig. 5), but the heterogeneity test was significant ($I^2 = 52.5\%$, $P = 0.04$). According to the subgroup analysis, GCE supplementation could reduce HOMA-IR significantly in studies with good quality (WMD = −0.32, 95% CI: −0.61 to −0.04, $P = 0.03$) (Table 3). Sensitivity analysis did not show any significant differences. Analysis of funnel plots and Egger's statistics did not report any publication bias in the studies (Egger's test $P = 0.920$; Begg's test $P = 0.621$) (**Fig. 2S**).

Meta-analysis over the effect of GCE on lipid profile

After combining the findings from 19 published papers, we found that GCE supplementation had a significant effect on TG levels (WMD = −9.28, 95% CI: −14.93 to - 3.63, $P = 0.001$) (Fig. 6). Considering the high heterogeneity between trials ($I^2 = 67.6\%$, $P < 0.001$), we stratified trials based on the supplementation dose (>400 mg/day vs. ≤400 mg/day), intervention duration (>4 vs. ≤ 4 weeks), and study quality (good quality vs. poor or fair quality). The GCE supplementation significantly reduced TG concentration in studies with good quality (WMD = −10.18, 95% CI: −17.77 to - 2.58, $P = 0.009$) and longer duration (WMD = −10.81, 95% CI: −17.73 to - 3.89, $P = 0.002$) (Table 3). Sensitivity analysis **indicated that removal of** each study from the meta-analysis did not overthrow the result of the present pooled analysis. Moreover, no evidences of publication bias were found in studies (Egger's test $P = 0.920$; Begg's test $P = 0.621$) (**Fig. 3S**).

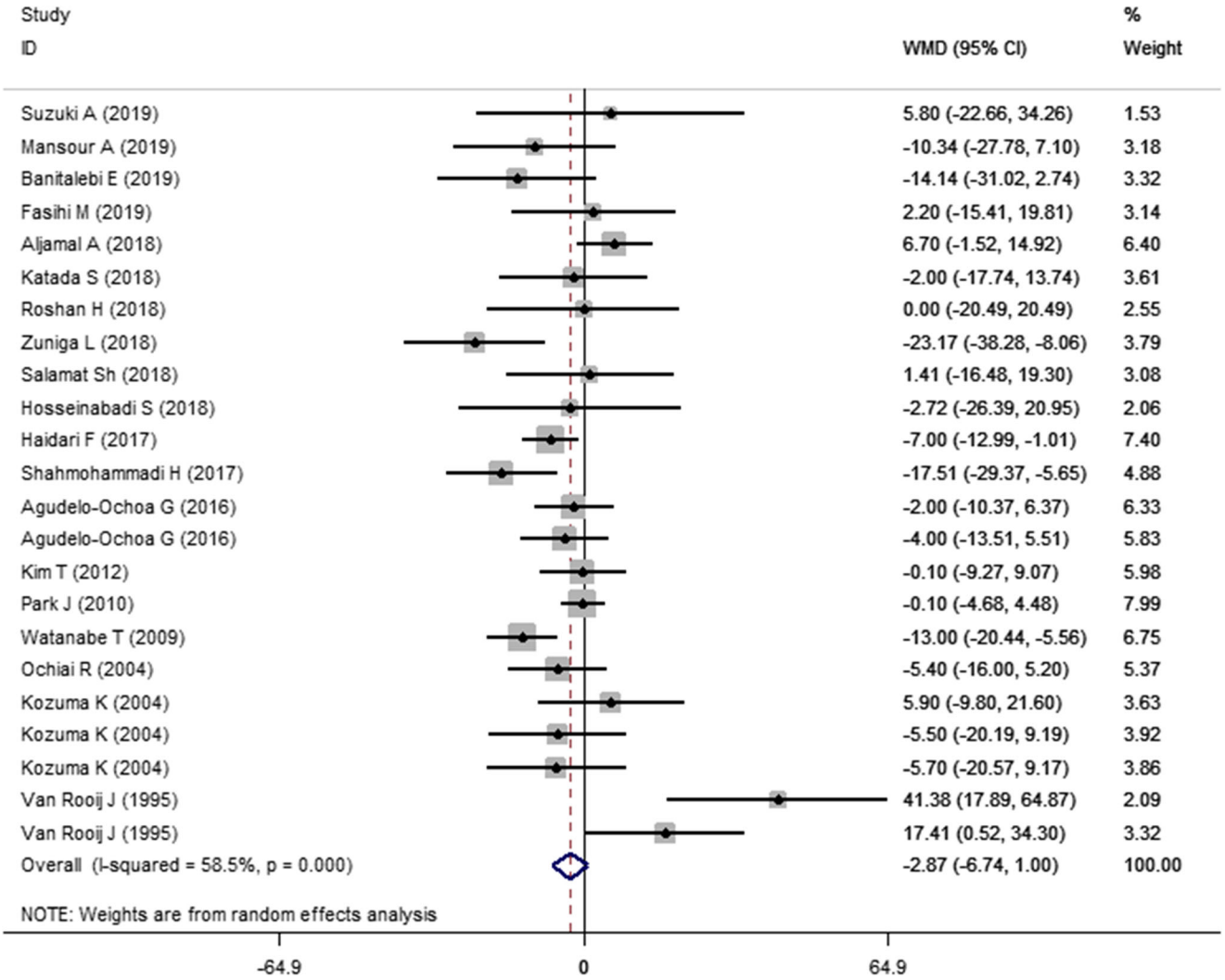

Fig. 7 Forest plot summarizing the association between green coffee extract supplementation on Total cholesterol

Findings of 19 studies showed that GCE supplementation caused a non-significant reduction in the total cholesterol concentration (WMD = −2.87, 95% CI: −6.74 to 1, $P = 0.146$) (Fig. 7), with a high heterogeneity among studies (I^2 = 58.5%, $P < 0.001$). Based on the subgroup analysis, GCE supplementation significantly reduced the cholesterol levels in studies with good quality (WMD = -8.98, 95% CI: −14.62 to −3.34, $P = 0.005$). In addition, longer intervention period (>8 weeks) reduced the cholesterol concentration significantly (WMD = -12.44, 95% CI: −18.44 to −5.86, $P = 0.002$). Subgroup analysis did not show any significant association between GCE supplementation and cholesterol levels (Table 3).

No evidence of publication bias was observed among the studies (Egger's test $P = 0.599$; Begg's test $P = 0.328$) (**Fig. 4S**).

Based on the results collected from 17 studies, GCE supplementation did not have any significant effect on the LDL cholesterol level (WMD = −0.8, 95% CI: −4.61 to 3, $P = 0.215$) (Fig. 8). According to the subgroup analysis, GCE supplementation could decrease LDL concentration significantly in the studies with good quality (WMD = −6.01, 95% CI: −11.30 to −0.72, $P = 0.032$) (Table 3). However, no evidence of publication bias was found in the studies.

In the final analysis, 18 studies examined the effect of GCE supplementation on HDL concentration. The results indicated that green coffee supplementation significantly increased the HDL levels (WMD = 1.33, 95% CI: 0.08 to 2.58, $P = 0.037$) (Fig. 9), with a significant heterogeneity (I^2 = 65.6% $P < 0.001$). According to the subgroup analysis, GCE supplementation could increase the HDL concentration in the studies that administered higher doses (>400 mg/day) (WMD = 2.42, 95% CI: 1.26 to 3.58, $P < 0.001$), had fair and poor quality (WMD = 1.98, 95% CI: 0.36 to 3.61, $P < 0.001$), and lasted <4 weeks (WMD = 3.26, 95% CI: 0.55 to 5.96, $P = 0.018$) (Table 3). Sensitivity and publication bias analyses did not show any changes in the results (**Fig. 5S**).

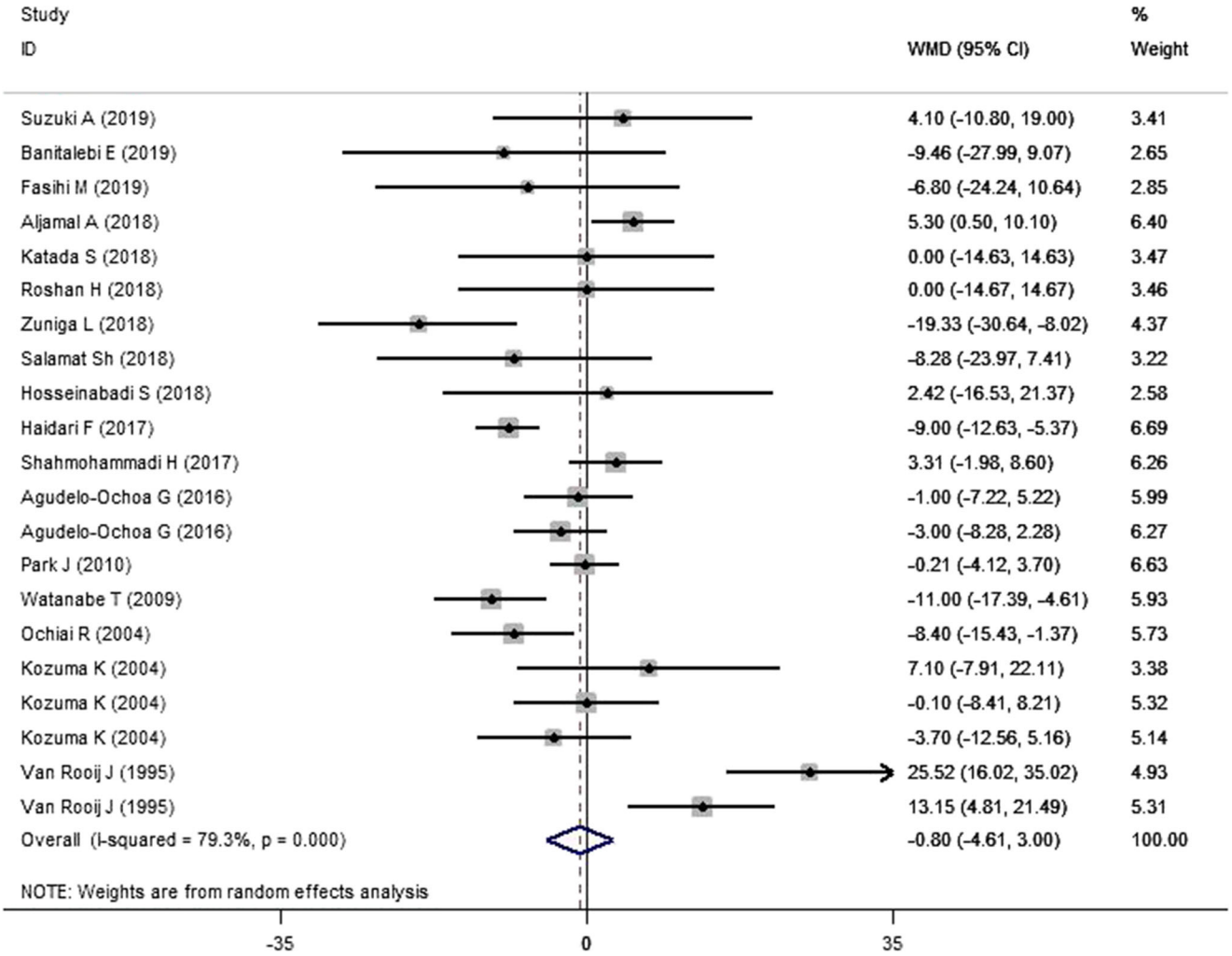

Fig. 8 Forest plot summarizing the association between green coffee extract supplementation on LDL

Meta-analysis over the effect of green coffee on CRP level

Considering the results of 6 studies, green coffee supplementation did not have any significant effect on CRP concentration (WMD = −0.03, 95% CI: - 0.12 to 0.06, $P = 0.486$) (Fig. 10), with a high heterogeneity in studies ($I^2 = 82.3\%$, $P < 0.001$). Subgroup analysis and sensitivity analysis did not show any alteration in the findings. In addition, no evidence of publication bias was found in the studies (Egger's test $P = 0.430$; Begg's test $P = 0.851$) (**Fig. 6S**).

Discussion

Recently, many researchers focused on the effects of supplementation with green coffee and its ingredients on different aspects of human health. The present meta-analysis was conducted on eligible RCTs over the effect of GCE supplementation on serum CRP, lipid, and glycemic profile.

According to the results, GCE supplementation had a considerable effect on the reduction of insulin and FBS concentrations, but it had no significant effect on insulin resistance (measured by HOMA-IR). Based on the subgroup analysis, a significant decrease was observed in HOMA-IR among studies with high quality. Many recent pieces of evidence suggested a beneficial effect of green coffee on blood glucose. Green coffee is a complex beverage containing a wide variety of biologically active compounds [36], such as chlorogenic acid, which is the main bioactive component in coffee and is responsible for potential health effects of green coffee [49]. Inconsistent with our results, some previous studies reported a lowering effect of coffee on serum FBS [51, 52] and insulin [53, 54]. Based on a new review, GCE supplementation reduced FBG, but had no effect on insulin levels and the HOMA-IR status [52]. Mechanisms proposed to explain the glycemic lowering effects of green coffee and chlorogenic acid include: stimulating insulin secretion by increasing glucagon-like peptide-1 [55] and glucose-dependent insulinotropic peptide [56]; enhancing glucose uptake by

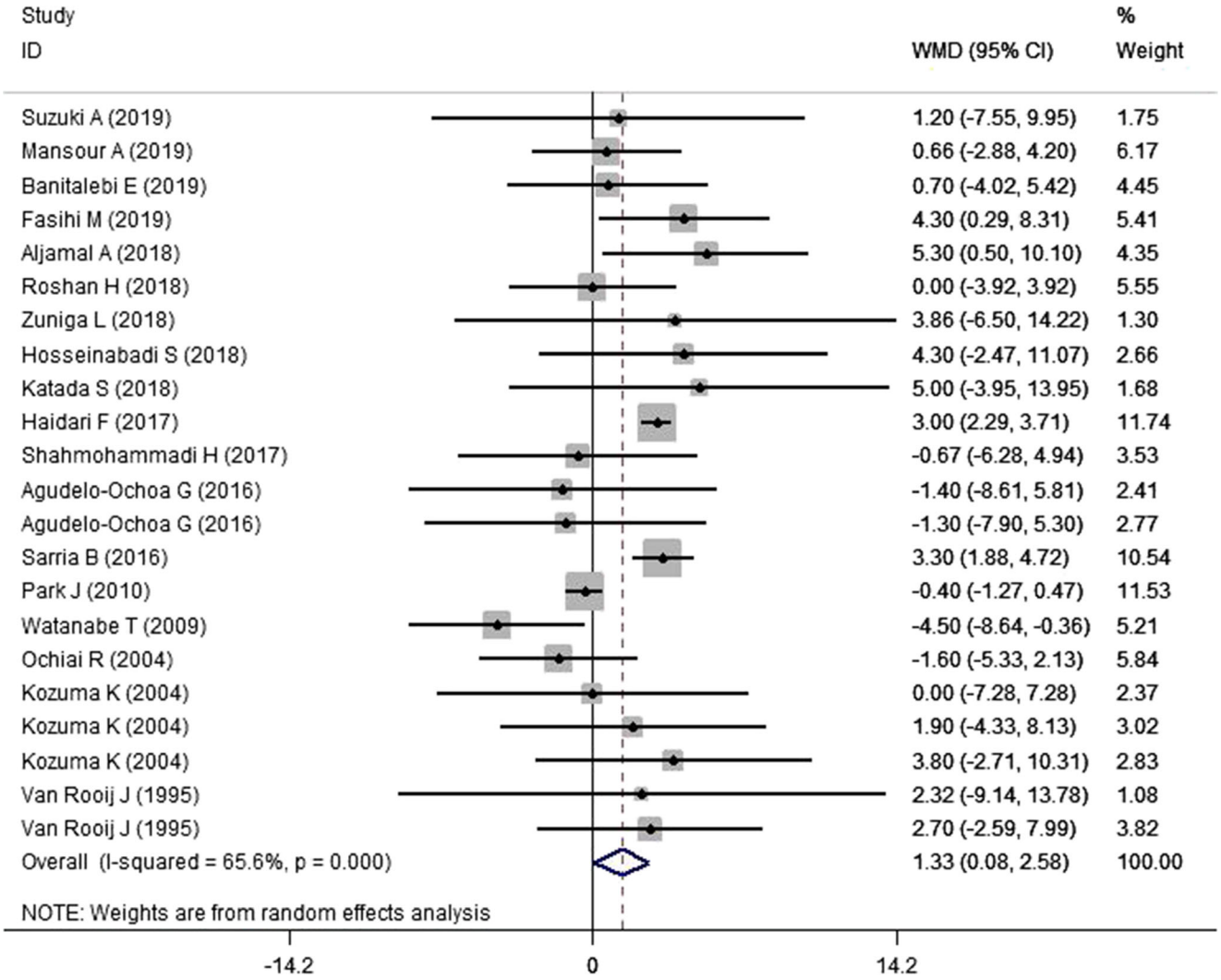

Fig. 9 Forest plot summarizing the association between green coffee extract supplementation on HDL

skeletal muscles using adenosine 5′ monophosphate- protein kinase activation [57]; attenuating adipogenesis and proinflammatory cytokines accompanied with increased translocation of glucose transporter type 4 in muscle and adipose tissue [54]; decreasing intestinal glucose absorption by inhibiting digestive enzymes related to carbohydrates such as α-amylase, α-glucosidase, and pancreatic amylase isoenzymes I and II [58, 59]; up-regulating expression of the hepatic proliferation-activated receptor-α (PPAR-α) that promotes clearing lipids by liver and intensifies insulin sensitivity [60]; inhibiting hepatic glucose-6-phosphatase activity and subsequently less insulin secretion [61]; and destructing the Na + electrochemical gradient and accumulating glucose in enterocytes [62].

Some investigations reported no special effect of the GCE on glycemic parameters [63, 64]. A part of such discrepancies can be due to the short study duration, small sample size, differences in coffee preparing and administrating methods, as well as GCE doses.

The lipid-improving effects of GCE were confirmed by previous studies [60, 65, 66]. In the current study, we found that GCE had significant positive effect on HDL and TG levels, but had no significant influence on LDL and total cholesterol concentrations. Further subgroup analyses revealed significant reductions in the levels of TG, LDL, and total cholesterol in high-quality studies. A recent review reported that GCE supplementation increased HDL-C significantly, but reduced LDL-C and total cholesterol levels. However, the reduction in TG level was not significant [66]. In this regard, some studies indicated that CGA decreased TG, cholesterol, and LDL [60, 65, 67, 68], but increased HDL concentrations [63, 67]. Some mechanisms have been suggested for beneficial effects of green coffee, such as declining intestinal lipid absorption and changing hepatic lipid metabolism [37]. The inhibitory role of CGA was also suggested in cholesterol micelles formation and pancreatic lipase function that resulted in declining intestinal fat absorption [69]. Based on in vitro experiments, CGA had an inhibitory effect on some enzymes

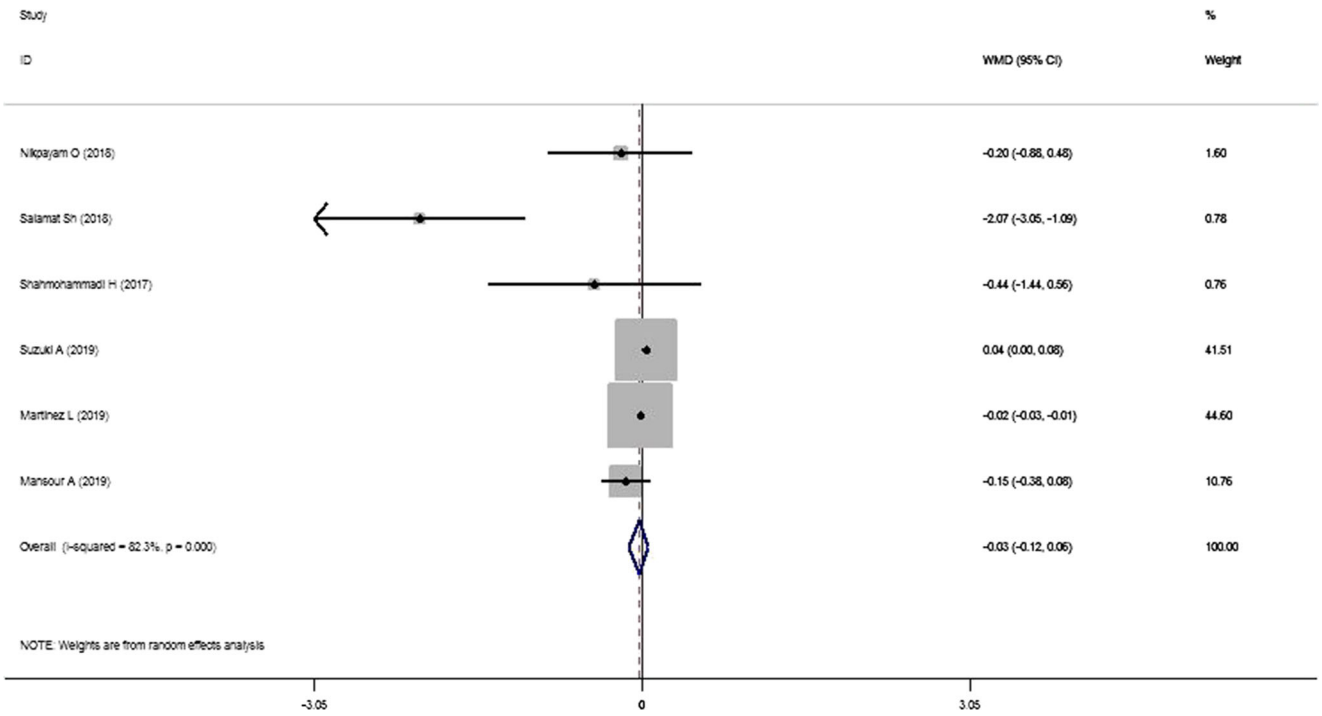

Fig. 10 Forest plot summarizing the association between green coffee extract supplementation on CRP

such as 3-hydroxy-3 -methylglutaryl coenzyme A reductase [69] and acyl-coenzyme A cholesterol acyltransferase, which reduced blood cholesterol [19]. As mentioned previously, CGA increased PPAR-α expression, which increased uptake and catabolism of fatty acids by the liver [19, 60]. However, some other studies found no substantial effect of CGA [67] or even indicated its adverse effects [70, 71] on lipid profile.

Coffee preparing method can be effective on its lipid reducing property; in other words, roasting in high temperatures results in degradation of GCE bioactive components, especially CGA [48], which reduces the health effects of green coffee. Coffee oil was also found to have hyperlipidemic effects due to its monodehydrated fatty acid esters, such as kahveol and cafestol. Coffee oil lipid-rising effect can be reduced by filtering [72].

Some RCTs over the association between green coffee consumption and inflammatory biomarkers, such as CRP showed positive effects of coffee on CRP concentration [73–75]. However, our findings did not show any significant effect of GCBE supplementation on CRP concentration. In our meta-analysis, three studies (of six) found that GCE supplementation had no significant effect on the CRP level [29, 42, 76]. Mansour et al. [29] reported no substantial decline in CRP levels after six months of coffee/ or chlorogenic acid supplementation in type 2 diabetes patients with non-alcoholic fatty liver disease. Nikpayam et al. [42] carried out a study among patients with metabolic syndrome and observed that GCE administration did not decrease oxidative stress, systematic, and vascular inflammation. Moreover, the acute and chronic effects of GCE and its bioactive components on endothelial function were examined in few studies. Cheong et al. investigated the effects of GCE administration on endothelial dysfunction in a mouse model of the metabolic syndrome and showed that GCE did not attenuate endothelial dysfunction induced by high-fat diet in animals [77]. In another study, Priftis et al. examined the protective effects of GCE in myoblasts and endothelial cells and showed that GCE caused a significant improvement in the cell redox status and endothelial function [78]. Kajikawa et al. evaluated the effects of consuming coffee with a high content of CGA on endothelial function among 37 patients with borderline or stage 1 hypertension. They reported a significant improvement in postprandial FMD after CGA supplementation [79]. The effects of GCE ingestion on endothelial function are quite controversial and more studies are required in this area [80]. Variation in participants' characteristics might justify these discrepancies. In other words, some studies were carried out on participants with metabolic disease [36, 37, 42], while some others examined participants without this disease [36, 76]. The observed discrepancy in the findings can also be explained by different methods of GCE administration. For example, Martinez et al. [36] demonstrated that green/roasted coffee blend had beneficial effects on CRP level, while GCE had no substantial effects in other studies [42, 76]. Furthermore, long-term coffee consumption may have a potential effect on improving the systematic inflammation [63] . Most RCTs included in our

meta-analysis were conducted in an 8-week duration, which may be not long enough to make substantial changes in the CRP level.

Our meta-analysis had some limitations. High heterogeneity was observed between the included studies. In addition, a limited number of studies were included regarding some variables, which could affect our results. Most of the included studies were conducted within ≤12 weeks with a small population size.

Conclusion

Based on the results, GCE supplementation improved the serum levels of FBS, insulin, TG, and HDL. As a result, consumption of GCE is recommended to improve the cardiometabolic risk factors. Moreover, no adverse side effects were observed for GCE supplementation. However, further studies are needed to provide enough evidences on the effect of green coffee intake on preventing cardio metabolic disorders.

Author's contribution MR designed the research; MM and ER performed the systematic search and study selection; MR and MJ extracted the data; MR and MM analyzed the data; MJ, ER and AKh wrote the manuscript; MR and AKh edited the manuscript and all authors read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest No conflict of interest was declared.

References

1. Zhang D, Tang X, Shen P, Si Y, Liu X, Xu Z, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. BMJ Open. 2019;9(3):e024476.
2. Takami H, Nakamoto M, Uemura H, Katsuura S, Yamaguchi M, Hiyoshi M, et al. Inverse correlation between coffee consumption and prevalence of metabolic syndrome: baseline survey of the Japan multi-institutional collaborative cohort (J-MICC) study in Tokushima. Japan J Epidemiol. 2013;23(1):12–20.
3. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation. 2007;116(5):480–8.
4. Heidemann C, Scheidt-Nave C, Richter A, Mensink GB. Dietary patterns are associated with cardiometabolic risk factors in a representative study population of German adults. Br J Nutr. 2011;106(8):1253–62.
5. Goodpaster BH, DeLany JP, Otto AD, Kuller L, Vockley J, South-Paul JE, et al. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. JAMA. 2010;304(16):1795–802.
6. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130(8):2073S–85S.
7. Menezes R, Rodriguez-Mateos A, Kaltsatou A, González-Sarrías A, Greyling A, Giannaki C, et al. Impact of flavonols on cardiometabolic biomarkers: a meta-analysis of randomized controlled human trials to explore the role of inter-individual variability. Nutrients. 2017;9(2):117.
8. Gardiner P, Phillips RS, Shaughnessy AF. Herbal and dietary supplement-drug interactions in patients with chronic illnesses. Am Fam Physician. 2008;77(1):73–8.
9. Cornelis MC. Toward systems epidemiology of coffee and health. Curr Opin Lipidol. 2015;26(1):20–9.
10. Li Q, Liu Y, Sun X, Yin Z, Li H, Cheng C, et al. Caffeinated and decaffeinated coffee consumption and risk of all-cause mortality: a dose–response meta-analysis of cohort studies. J Acad Nutr Diet. 2019;32(3):279–87.
11. Gaafar A, El-Ghamery H, Mahmuod S. Effect of green and degree of roasted Arabic coffee on hyperlipidemia and antioxidant status in diabetic rats. Adv J Food Sci Technol. 2013;5(5):619–26.
12. Farrell TL, Dew TP, Poquet L, Hanson P, Williamson G. Absorption and metabolism of chlorogenic acids in cultured gastric epithelial monolayers. Drug Metab Dispos. 2011;39(12):2338–46.
13. Tajik N, Tajik M, Mack I, Enck P. The potential effects of chlorogenic acid, the main phenolic components in coffee, on health: a comprehensive review of the literature. Eur J Nutr. 2017;56(7):2215–44.
14. Loader TB, Taylor CG, Zahradka P, Jones PJ. Chlorogenic acid from coffee beans: evaluating the evidence for a blood pressure-regulating health claim. Nutr Rev. 2017;75(2):114–33.
15. Yamagata K, Izawa Y, Onodera D, Tagami M. Chlorogenic acid regulates apoptosis and stem cell marker-related gene expression in A549 human lung cancer cells. Mol Cell Biochem. 2018;441(1–2):9–19.
16. Santana-Galvez J, Cisneros-Zevallos L, Jacobo-Velazquez DA. Chlorogenic Acid: Recent Advances on Its Dual Role as a Food Additive and a Nutraceutical against Metabolic Syndrome. Molecules. 2017;22(3).
17. Meng S, Cao J, Feng Q, Peng J, Hu Y. Roles of chlorogenic acid on regulating glucose and lipids metabolism: a review. Evid.-Based Complementary Altern. Med. 2013;2013.
18. Ong KW, Hsu A, Tan BKH. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. Biochem Pharmacol. 2013;85(9):1341–51.
19. Cho AS, Jeon SM, Kim MJ, Yeo J, Seo KI, Choi MS, et al. Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice. Food Chem Toxicol. 2010;48(3):937–43.
20. Ma Y, Gao M, Liu D. Chlorogenic acid improves high fat diet-induced hepatic steatosis and insulin resistance in mice. Pharm Res. 2015;32(4):1200–9.
21. Han B, Nazary-Vannani A, Talaei S, Clark CCT, Rahmani J, Rasekhmagham R, et al. The effect of green coffee extract supplementation on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Phytother Res. 2019;33(11):2918–26.
22. Haidari F, Samadi M, Mohammadshahi M, Jalali MT, Engali KA. Energy restriction combined with green coffee bean extract affects serum adipocytokines and the body composition in obese women. Asia Pac J Clin Nutr. 2017;26(6):1048–54.
23. Roshan H, Nikpayam O, Sedaghat M, Sohrab G. Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance and appetite in patients with the metabolic syndrome: a randomised clinical trial. Br J Nutr. 2018;119(3):250–8.

24. Ochiai R, Jokura H, Suzuki A, Tokimitsu I, Ohishi M, Komai N, et al. Green coffee bean extract improves human vasoreactivity. Hypertens Res. 2004;27(10):731–7.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
26. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Banitalebi E, Rahimi A, Faramarzi M, Ghahfarrokhi MM. The effects of elastic resistance band training and green coffee bean extract supplement on novel combined indices of cardiometabolic risk in obese women. Res Pharm Sci. 2019;14(5):414–23.
28. Fasihi M, Yousefi M. Safaiyan A. Rostami M, Barzegar A. Effects of green coffee extract supplementation on level of chemerin, malondialdehyde, nutritional and metabolic status in patients with metabolic syndrome. Nutrition & Food Science: Mele MM; 2019.
29. Mansour A, Mohajeri-Tehrani MR, Samadi M, Qorbani M, Merat S, Adibi H, et al. Effects of supplementation with Main coffee components on hepatic, metabolic, and inflammatory indices in patients with non-alcoholic fatty liver disease and type 2 diabetes: a randomized, double-blind, placebo-controlled. Clinical Trial J Diabetes Endocrinol. 2019;2.
30. Sarriá B, Martínez-López S, Mateos R, Bravo-Clemente L. Long-term consumption of a green/roasted coffee blend positively affects glucose metabolism and insulin resistance in humans. Food Res Int. 2016;89:1023–8.
31. Suzuki A, Nomura T, Jokura H, Kitamura N, Saiki A, Fujii A. Chlorogenic acid-enriched green coffee bean extract affects arterial stiffness assessed by the cardio-ankle vascular index in healthy men: a pilot study. Int J Food Sci Nutr. 2019:1–8.
32. Alhamhany NN, Alassady EH. Does green coffee has a positive effect on body mass index and lipid profile in a sample of obese people. J Chem Pharm Res. 2018;10(3):627–30.
33. Aljamal A. Effect of Xenical and green coffee on BMI and lipid profiles among Jordanian people. J Chem Pharm Res. 2018;10(10):80–3.
34. Hosseinabadi S. Effect of green coffee extract supplementation on metabolic status, serum leptin level and anthropometric measurements in patients with non-alcoholic fatty liver disease (NAFLD): Tabriz University of Medical Sciences, Faculty of Nutrition and Food Sciences; 2018.
35. Katada S, Watanabe T, Mizuno T, Kobayashi S, Takeshita M, Osaki N, et al. Effects of Chlorogenic acid-enriched and Hydroxyhydroquinone-reduced coffee on postprandial fat oxidation and Antioxidative capacity in healthy men: a randomized, double-blind, placebo-controlled. Crossover Trial Nutrients. 2018;10(4):525.
36. Martinez-Lopez S, Sarria B, Mateos R, Bravo-Clemente L. Moderate consumption of a soluble green/roasted coffee rich in caffeoylquinic acids reduces cardiovascular risk markers: results from a randomized, cross-over, controlled trial in healthy and hypercholesterolemic subjects. Eur J Nutr. 2019;58(2):865–78.
37. Salamat S, Mohammadshahi FHM, Haghighizadeh M, Heli B, Mohammadshahi M. The effect of green coffee bean extract supplementation on anthropometric indices, lipid profile and high-sensitivity C-reactive protein in adult men with dyslipidemia. J Biochem Tech. 2018;2:75–81.
38. Zuniga LY, Aceves-de la Mora MCA, Gonzalez-Ortiz M, Ramos-Nunez JL, Martinez-Abundis E. effect of Chlorogenic acid administration on glycemic control, insulin secretion, and insulin sensitivity in patients with impaired glucose tolerance. J Med Food 2018;21(5):469–473.
39. Fukagawa S, Haramizu S, Sasaoka S, Yasuda Y, Tsujimura H, Murase T. Coffee polyphenols extracted from green coffee beans improve skin properties and microcirculatory function. Biosci Biotechnol Biochem. 2017;81(9):1814–22.
40. Shahmohammadi HA, Hosseini SA, Hajiani E, Malehi AS, Alipour M. Effects of green coffee bean extract supplementation on patients with non-alcoholic fatty liver disease: a randomized clinical trial. Hepat Mon. 2017;17(4).
41. Naderi L, Sharifi G. Comparison of the effect of 8 weeks concurrent training and green coffee supplementation on serum adipsin and insulin resistance in obese women. Armaghane danesh. 2017;22(5):623–36.
42. Nikpayam O, Roshan H, Sohrab G, Sedaghat M. Effects of Green Coffee Extract Supplementation on Oxidative Stress, Systemic and Vascular Inflammation in Patients with Metabolic Syndrome: A Randomized Clinical Trial. Iran Red Crescent Med J. 2018;20(6).
43. Agudelo-Ochoa GM, Pulgarin-Zapata IC, Velasquez-Rodriguez CM, Duque-Ramirez M, Naranjo-Cano M, Quintero-Ortiz MM, et al. Coffee consumption increases the antioxidant capacity of plasma and has no effect on the lipid profile or vascular function in healthy adults in a randomized controlled trial. J Nutr. 2016;146(3):524–31.
44. Kim T-S, Yang W-S, Park S-I, Lee S-P, Kang M-H, Lee J-H, et al. Effect of green coffee bean extract supplementation on body fat reduction in mildly obese women. J Korean Soc Food Cult. 2012;27(4):407–13.
45. van Rooij J, Van der Stegen G, Schoemaker RC, Kroon C, Burggraaf J, Hollaar L, et al. A placebo-controlled parallel study of the effect of two types of coffee oil on serum lipids and transaminases: identification of chemical substances involved in the cholesterol-raising effect of coffee. Am J Clin Nutr. 1995;61(6):1277–83.
46. Kozuma K, Tsuchiya S, Kohori J, Hase T, Tokimitsu I. Antihypertensive effect of green coffee bean extract on mildly hypertensive subjects. Hypertens Res. 2005;28(9):711–8.
47. Blum J, Lemaire B, Lafay S. Effect of a green decaffeinated coffee extract on glycaemia. NutraFoods Res. 2007;6:13–7.
48. Watanabe T, Arai Y, Mitsui Y, Kusaura T, Okawa W, Kajihara Y, et al. The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. Clin Exp Hypertens. 2006;28(5):439–49.
49. Sarria B, Martinez-Lopez S, Sierra-Cinos JL, Garcia-Diz L, Mateos R, Bravo-Clemente L. Regularly consuming a green/roasted coffee blend reduces the risk of metabolic syndrome. Eur J Nutr. 2018;57(1):269–78.
50. Park JY, Kim JY, Lee SP, Lee JH. The effect of green coffee bean extract supplementation on body fat reduction in overweight/obese women. Korean J Nutr. 2010;43(4):374–81.
51. Jin S, Chang C, Zhang L, Liu Y, Huang X, Chen Z. Chlorogenic acid improves late diabetes through adiponectin receptor signaling pathways in db/db mice. PLoS One. 2015;10(4):e0120842.
52. Nikpayam O, Najafi M, Ghaffari S, Jafarabadi MA, Sohrab G, Roshanravan N. Effects of green coffee extract on fasting blood glucose, insulin concentration and homeostatic model assessment of insulin resistance (HOMA-IR): a systematic review and meta-analysis of interventional studies. Diabetol Metab Syndr. 2019;11:91.
53. van Dijk AE, Olthof MR, Meeuse JC, Seebus E, Heine RJ, van Dam RM. Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. Diabetes Care. 2009;32(6):1023–5.
54. Song SJ, Choi S, Park T. Decaffeinated green coffee bean extract attenuates diet-induced obesity and insulin resistance in mice. Evid Based Complement Alternat Med. 2014;718379.
55. Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. Am J Clin Nutr. 2003;78(4):728–33.

56. Tunnicliffe JM, Eller LK, Reimer RA, Hittel DS, Shearer J. Chlorogenic acid differentially affects postprandial glucose and glucose-dependent insulinotropic polypeptide response in rats. Appl Physiol Nutr Metab. 2011;36(5):650–9.
57. Ong KW, Hsu A, Tan BKH. Chlorogenic acid stimulates glucose transport in skeletal muscle via AMPK activation: a contributor to the beneficial effects of coffee on diabetes. PloS one. 2012;7(3): e32718-e.
58. Narita Y, Inouye K. Kinetic analysis and mechanism on the inhibition of chlorogenic acid and its components against porcine pancreas alpha-amylase isozymes I and II. J Agric Food Chem. 2009;57(19):9218–25.
59. Oboh G, Agunloye OM, Adefegha SA, Akinyemi AJ, Ademiluyi AO. Caffeic and chlorogenic acids inhibit key enzymes linked to type 2 diabetes (in vitro): a comparative study. J Basic Clin Physiol Pharmacol. 2015;26(2):165–70.
60. Li SY, Chang CQ, Ma FY, Yu CL. Modulating effects of chlorogenic acid on lipids and glucose metabolism and expression of hepatic peroxisome proliferator-activated receptor-alpha in golden hamsters fed on high fat diet. Biomed Environ Sci. 2009;22(2): 122–9.
61. Henry-Vitrac C, Ibarra A, Roller M, Merillon JM, Vitrac X. Contribution of chlorogenic acids to the inhibition of human hepatic glucose-6-phosphatase activity in vitro by Svetol, a standardized decaffeinated green coffee extract. J Agric Food Chem. 2010;58(7): 4141–4.
62. Welsch CA, Lachance PA, Wasserman BP. Dietary phenolic compounds: inhibition of Na+−dependent D-glucose uptake in rat intestinal brush border membrane vesicles. J Nutr. 1989;119(11): 1698–704.
63. Kempf K, Herder C, Erlund I, Kolb H, Martin S, Carstensen M, et al. Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial. Am J Clin Nutr. 2010;91(4):950–7.
64. Kondo Y, Goto A, Noma H, Iso H, Hayashi K, Noda M. Effects of Coffee and Tea Consumption on Glucose Metabolism: A Systematic Review and Network Meta-Analysis. Nutrients. 2018 ;11(1).
65. Rodriguez de Sotillo DV, Hadley M. Chlorogenic acid modifies plasma and liver concentrations of: cholesterol, triacylglycerol, and minerals in (fa/fa) Zucker rats. J Nutr Biochem. 2002;13(12): 717–26.
66. Ding F, Ma B, Nazary-Vannani A, Kord-Varkaneh H, Fatahi S, Papageorgiou M, et al. The effects of green coffee bean extract supplementation on lipid profile in humans: a systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2020;30(1):1–10.
67. Choi BK, Park SB, Lee DR, Lee HJ, Jin YY, Yang SH, et al. Green coffee bean extract improves obesity by decreasing body fat in high-fat diet-induced obese mice. Asian Pac J Trop Med. 2016;9(7):635–43.
68. Yukawa GS, Mune M, Otani H, Tone Y, Liang XM, Iwahashi H, et al. Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. Biochemistry (Mosc). 2004;69(1):70–4.
69. Oboh G, Agunloye OM, Akinyemi AJ, Ademiluyi AO, Adefegha SA. Comparative study on the inhibitory effect of caffeic and chlorogenic acids on key enzymes linked to Alzheimer's disease and some pro-oxidant induced oxidative stress in rats' brain-in vitro. Neurochem Res. 2013;38(2):413–9.
70. Aro A, Tuomilehto J, Kostiainen E, Uusitalo U, Pietinen P. Boiled coffee increases serum low density lipoprotein concentration. Metabolism. 1987;36(11):1027–30.
71. Cai L, Ma D, Zhang Y, Liu Z, Wang P. The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2012;66(8):872–7.
72. Silverio Ados S, Pereira RG, Lima AR, Paula FB, Rodrigues MR, Baldissera L Jr, et al. The effects of the decaffeination of coffee samples on platelet aggregation in hyperlipidemic rats. Plant Foods Hum Nutr. 2013;68(3):268–73.
73. Lopez-Garcia E, van Dam RM, Qi L, Hu FB. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. Am J Clin Nutr. 2006;84(4):888–93.
74. Arsenault BJ, Earnest CP, Despres JP, Blair SN, Church TS. Obesity, coffee consumption and CRP levels in postmenopausal overweight/obese women: importance of hormone replacement therapy use. Eur J Clin Nutr. 2009;63(12):1419–24.
75. Maki T, Pham NM, Yoshida D, Yin G, Ohnaka K, Takayanagi R, et al. The relationship of coffee and green tea consumption with high-sensitivity C-reactive protein in Japanese men and women. Clin Chem Lab Med. 2010;48(6):849–54.
76. Suzuki A, Nomura T, Jokura H, Kitamura N, Saiki A, Fujii A. Chlorogenic acid-enriched green coffee bean extract affects arterial stiffness assessed by the cardio-ankle vascular index in healthy men: a pilot study. Int J Food Sci Nutr. 2019;70(7):901–8.
77. Li Kwok Cheong JD, Croft KD, Henry PD, Matthews V, Hodgson JM, Ward NC. Green coffee polyphenols do not attenuate features of the metabolic syndrome and improve endothelial function in mice fed a high fat diet. Arch Biochem Biophys. 2014;559:46–52.
78. Priftis A, Panagiotou E-M, Lakis K, Plika C, Halabalaki M, Ntasi G, et al. Roasted and green coffee extracts show antioxidant and cytotoxic activity in myoblast and endothelial cell lines in a cell specific manner. Food Chem Toxicol. 2018;114:119–27.
79. Kajikawa M, Maruhashi T, Hidaka T, Nakano Y, Kurisu S, Matsumoto T, et al. Coffee with a high content of chlorogenic acids and low content of hydroxyhydroquinone improves postprandial endothelial dysfunction in patients with borderline and stage 1 hypertension. Eur J Nutr. 2019;58(3):989–96.
80. Higashi Y. Coffee and Endothelial Function: A Coffee Paradox? Nutrients. 2019;11(9).