American Dietetic Association

RESEARCH

Review

Green Tea Catechins Decrease Total and Low-Density Lipoprotein Cholesterol: A Systematic Review and Meta-Analysis

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ABSTRACT

Green tea catechins (GTCs) have been studied in randomized control trials for their lipid-lowering effects. Studies, however, have been small and demonstrated conflicting results. The objective of this study was to perform a systematic review and meta-analysis of randomized controlled trials evaluating the relationship between GTCs and serum lipid levels, including total, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglycerides. A systematic literature search of MEDLINE, EMBASE, Cochrane CENTRAL, and the Natural Medicines Comprehensive Database was conducted through March 2010. Randomized controlled trials evaluating GTCs vs control in human beings and reporting efficacy data on at least one of the aforementioned serum lipid endpoints were included. Weighted mean differences for changes from baseline (with 95% confidence intervals [CIs]) for lipid endpoints were calculated using random-effects models. Twenty trials (N=1,415) met all inclusion criteria. Upon meta-analysis, GTCs at doses ranging from 145 to 3,000 mg/day taken for 3 to 24 weeks reduced total (−5.46 mg/dL [−0.14 mmol/L]; 95% CI −9.59 to −1.32) and LDL cholesterol (−5.30 mg/dL [−0.14 mmol/L]; 95% CI −9.99 to −0.62) compared to control. GTCs did not significantly alter HDL cholesterol (−0.27 mg/dL [−0.007 mmol/L]; 95% CI −1.62 to 1.09) or triglyceride (3.00 mg/dL [−0.034 mmol/L]; 95% CI −2.73 to 8.73) levels. The consumption of GTCs is associated with a statistically significant reduction in total and LDL cholesterol levels; however, there was no significant effect on HDL cholesterol or triglyceride levels.

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Lipid level modification remains an important target for cardiovascular disease prevention. Both the American Heart Association (1) and the National Cholesterol Education Program (2) acknowledge the association between high levels total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, and low levels of high-density lipoprotein (HDL) cholesterol and cardiovascular morbidity and mortality. Strategies to modify lipid parameters may include medication, lifestyle modification, or the use of herbal supplements.

Green tea has sparked growing interest in its potential health benefits, such as the ability to modify serum lipid parameters. It has been suggested that the effects of green tea can be attributed to polyphenols; high levels of these antioxidants can be found in green tea (3). Catechins comprise 80% to 90% of the polyphenols found in green tea, most abundantly including epigallocatechin, believed to be the most potent (3). The remaining catechins include epicatechin, epicatechin gallate, epigallocatechin, gallocatechin, catechin gallate, gallocatechin gallate, and catechin (3). Animal studies have suggested that green tea catechins (GTCs) reduce lipid absorption in the intestines (4), promote fecal excretion of cholesterols (5), and inhibit enzymes involved in hepatic cholesterol synthesis (6).

In human beings, large epidemiologic studies suggest efficacy of GTCs in reducing lipid levels (7,8). Several randomized controlled trials (RCTs) also exist to answer the clinical question of GTCs' efficacy; however, there are conflicting results among them and modest sample sizes (9-28). To summarize the available evidence and to increase statistical ability to detect effects, a systematic review and meta-analysis of RCTs to determine the effect of GTCs on serum lipid parameters was conducted.

METHODS

Study Selection

A systematic literature search was conducted through March 2010 in the following databases: MEDLINE (beginning 1950), EMBASE (beginning 1990), Cochrane Central Register of Controlled Trials (Indexed January 2010), and the Natural Medicines Comprehensive Data-

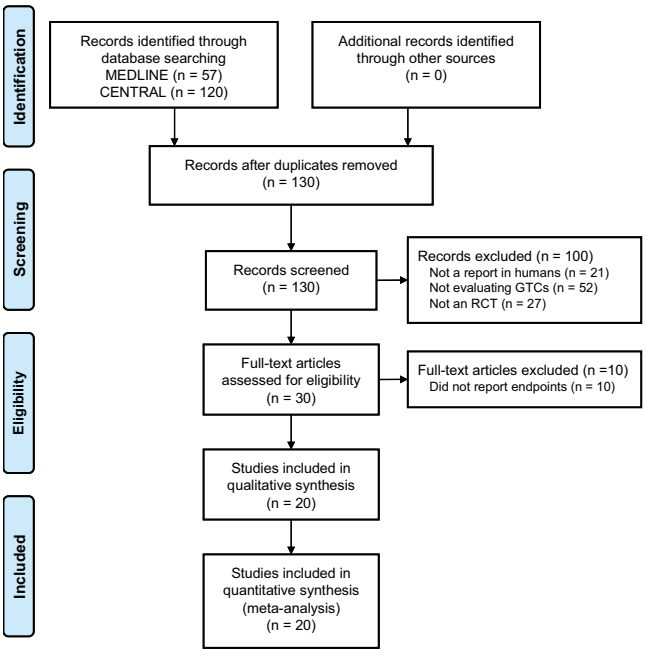

Figure 1. Preferred reporting items in systematic reviews and meta-analyses flow diagram of study selection, inclusion, and exclusion of randomized controlled trials (RCTs) evaluating green tea catechins on serum lipid levels.

base. A search strategy was performed combining the Medical Subject Headings and text keywords "tea," "green tea," "green tea extract," "catechin," "EGCG," "tea polyphenols," "theaflavin," or "*Camelia sinesis*," with "total cholesterol," "LDL cholesterol," "HDL cholesterol," "triglycerides," or "metabolic syndrome." No language restrictions were imposed and duplicate citations were removed. In addition, a manual search of references from primary or review articles was performed to identify additional relevant trials.

Trials were included in the analysis if they were randomized trials evaluating the use of GTCs (in any dose or form, including extract tablets/capsules, powders, or beverages) and reported data on at least one of the following endpoints: total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides. Both parallel and crossover trials were eligible for inclusion. Crossover trials that reported data separately among different treatment periods were analyzed and recorded as a parallel trial using data from the first period. Two investigators reviewed potentially relevant articles independently with differences resolved through discussion (O.J.P., C.I.C.). Institutional review board approval was not necessary for this systematic review.

Data Abstraction and Validity Assessment

Through the use of a standardized data abstraction tool, two reviewers of the research team independently abstracted data from each trial (A.K., A.C., M.K.B.), with disagreement resolved through discussion or by a third investigator (O.J.P.). The following information was obtained from each trial: author identification, year of publication, study design, source of study funding, study population (including study inclusion and exclusion criteria and baseline lipid values), sample size, duration of participant follow-up, catechin dose and formulation used, caffeine use, concurrent diet, and effect on lipid parameters (ie, total, LDL, and HDL cholesterol and triglyceride). In cases where data insufficient for meta-analysis were provided, authors were contacted with requests to provide additional data.

Validity assessment was performed by two investigators (A.C., M.K.B.) using the American Dietetic Association Research Design and Implementation Checklist for primary research (29). This checklist includes 10 validity questions covering the following domains: a clear statement of research question, bias-free subject selection, comparable groups, description of withdrawal handling, blinding, detailed description of protocol, clear definition of outcomes, appropriate statistical analysis, conclusions supported by data, and unlikely bias due to sponsorship or funding. Each of the 10 questions has a series of subquestions that aid in answering the overall question as either yes, no, or unclear. The four questions pertaining to bias-free subject selection, comparable groups, detailed description of protocol, and clear definition of outcomes received the most consideration, whereas evaluating the overall study quality. The study was rated as positive if the four major criteria were met along with at least one other "yes," neutral if the four major criteria were not all "yes," and minus if most ($\geq$6) questions were answered as "no."

Statistical Analysis

The mean changes in total, LDL, and HDL cholesterol and triglyceride levels from baseline were treated as continuous variables, and the weighted mean differences were calculated as the differences between the mean change from baseline in the GTCs and control groups. A DerSimonian and Laird random-effects model (a variation on the inverse variance method that incorporated an assumption that the different studies were estimating different, yet related, treatment effects) was used in calculating the weighted mean differences with accompanying 95% confidence intervals (CIs) (30). Changes from baseline in outcomes were extracted from trials; in instances where changes were not reported directly, they were calculated from end-of-study and baseline results. When necessary, variances for the changes from baseline were calculated using a correlation coefficient of .5, as suggested by Follman and colleagues (31).

The statistical analysis was performed by using StatsDirect software (version 2.4.6, 2008, StatsDirect Ltd, Cheshire, UK). A P value <0.05 was considered statistically significant for all analyses. Statistical heterogeneity was be assessed using the I^2 statistic, where values of 25%, 50%, and 75% represent low, medium, and high degrees of heterogeneity, respectively, where low levels of heterogeneity are desired. To assess for the presence of publication bias, visual inspection of funnel plots were used to investigate the relationship between effect size and sample size, and Egger's weight regression statistics tested for asymmetry.

Subgroup and sensitivity analyses were performed in an attempt to assess the effect of potential clinical or methodologic heterogeneity on our meta-analysis' results.

Table 1. Characteristics of randomized controlled trials evaluating the effect of green tea catechins on serum lipid levels

Study, year, sample size	Study design	ADA[a] quality rating	Population	Baseline characteristics (I,C)
Batista and colleagues, 2009, n=33 (9)	Double-blinded, crossover	+	Men and woman >20 y, no history of CAD[b], TC[c] >200 mg/dL[d], LDL[e] >130 mg/dL[d]	TC: 246.5, 245.6; LDL: 155.0, 151.2; HDL[f]: 57.6, 59.1; TG[g]:165.8, 172.4
Brown and colleagues, 2009, n=88 (10)	Double-blinded, parallel	+	Male, nonsmokers, 40-65 y, BMI[j] >28 and <38, fasting plasma glucose <7, no history of disease or on medication	TC: 218.2, 208.5; LDL: 141.2, 135.8; HDL: 46.4, 45.2; TG: 149.7, 155
Dipierro and colleagues, 2009, n=100 (11)	Open-label, parallel	−	Ages 25-60 y, overweight (20%-40% over ideal weight)	LDL: 132, 130; HDL: 42, 40
Eichenberger and colleagues, 2009, n=10 (12)	Double-blinded, crossover	Ø[i]	Healthy, male endurance-trained cyclists	TC: 153.6 LDL: 75.8 HDL: 55.3 TG: 116.9
Frank and colleagues., 2009, n= 33 (13)	Double-blinded, parallel	+	Healthy men, age 18-55 y, BMI 22-32	TC: 158.2, 146.6 HDL: 34.0, 38.3
Maki and colleagues, 2009, n=128 (14)	Double-blinded, parallel	+	Age 21-65 y, WC ≥90, 87 (men/women), total cholesterol ≥201.2	TC: 220.5, 224.4; LDL: 139.3, 139.3; HDL: 49.9, 52.2; TG: 150.6, 177.2
Bertipaglia de Santana and colleagues, 2008, n=50 (15)	Single-blinded, parallel	Ø	>18 y, total cholesterol ≥220 mg/dL[d]	TC: 240, 257; LDL: 163, 178; HDL: 44, 44; TG: 132, 147
Fukino and colleagues, 2008, n= 60 (16)	Open-label, crossover	Ø	FBG[q] >6.1 or non-FBG >7.8	TC: 224.8, 220.1; LDL: 136.7, 135.6; HDL: 57.3, 54.3; TG: 154.2, 151.3
Hsu and colleagues, 2008, n= 78 (17)	Double-blinded, parallel	+	Females age 16-60 y, BMI > 27	TC: 211.3, 202.7; LDL: 150.6, 135.5; HDL: 42.5, 45.1; TG: 141.4, 138.1
Matsuyama and colleagues, 2008, n=40 (18)	Double-blinded, parallel	+	Children aged 6-16 y, BMI ≥28 or diagnosis of obesity	TC: 185.3, 200.8; LDL: 121.9, 136.2; HDL: 48.7, 50.3; TG: 104.5, 110.7
Nagao and colleagues, 2008, n= 43 (19)	Double-blinded, parallel	+	Japanese persons with type 2 diabetes (no insulin therapy, stable medication and diet)	TC: 215.0, 204.9; TG: 128.1, 137.6
Takeshita and colleagues, 2008, n=81 (20)	Double-blinded, parallel	Ø	Healthy males, BMI ≥25	TC: 196, 202 LDL: 126, 131 HDL: 51, 50 TG: 115, 130
Inami and colleagues, 2007, n=40 (21)	Parallel	−	Healthy adults	TC: 183.5, 200.7; LDL: 102.3, 113.7; HDL: 65.9, 69.3; TG: 67.4, 89.8

(continued)

Table 1. Characteristics of randomized controlled trials evaluating the effect of green tea catechins on serum lipid levels (continued)

Follow-up (wk)	Tea group (dose/d)	Control group (dose/d)	Catechin components (mg)	Concurrent lifestyle modifications
8	250 mg GTE[n] capsules	Placebo (not specified)	NR[i]	<35% total energy from total fat, <7% saturated fat, ≤10% polyunsaturated fat, ≤20% monounsaturated fat, <200 mg/d cholesterol recommended
8	800 mg EGCG[k] capsule	800 mg lactose	EGCG: 800	Strenuous exercise and alcohol prohibited 24 h before each visit, no green tea or diet supplements affecting glucose and lipid metabolism during intervention phase; other flavonoid-food products were not restricted
12.86	300 mg Monoselect Camellia capsules	Diet only	NR	Hypocaloric diet (males ~1,850 kcal/d, females ~1,350 kcal/d)
3	500 mg GTE (160 mg catechins)	Placebo 400 mg capsule (0 mg catechins), 0 mg caffeine	ECG: 22 EGCG: 68 EGC: 58 EC[m]: 12	Maintain habitual level of physical activity
3	Aqueous GTE capsule (714 mg catechins)	Placebo (maltodextrin) capsules with 114 mg caffeine	EGC: 282; EGCG: 150; ECG: 84; GC[n]: 54; GCG: 48; EC: 30; CG: 18; C[o]:6	Limit daily tea and coffee consumption to ≤3 c (711 mL) but maintain normal diet and exercise
12	500 mL green tea beverage (625 mg catechins)	Placebo beverage (0 mg catechins), 39 mg caffeine, same number of calories	GC: 51.8; EGC: 207.5; C: 19.2; EC: 53.9; EGCG: 214.4; GCG: 15.4; ECG: 56.5; CG[p]: 6	Normal diet; ≥180 min exercise weekly, including 3 supervised exercise sessions/wk
12.86	500 mL green tea beverage (145 mg EGCG)	Hypocholesterolemic diet low in saturated fat and cholesterol and high in polyunsaturated fatty acids	EGCG: 145	Maintain sedentary habitual lifestyle
8	GTE powder packet (456 mg catechins)	No intervention	NR	Both groups allowed to drink green tea as normal; no changes in diet/exercise
12	1,200 mg GTE capsules (491 mg catechins)	Placebo (cellulose) capsules	GC: 61.6; EGC: 36.9; C: 8.3: EC: 70.3; EGCG: 377.1; GCG: 27.5; ECG: 31.8	Maintain normal diet, no other antiobesity treatment
24	340 mL green tea beverage (576 mg catechins)	340 mL green tea beverage (75 mg catechins)	Enriched tea: C: 39.8; CG: 36.7; GC: 128.9; GCG: 135.7; EC: 29.2; ECG: 32; EGC: 71.4; EGCG: 102.3 Control tea: C: 5.8; CG: 3.7; GC: 20.4; GCG: 17.3; EC: 4.4; ECG: 3.7; EGC: 7.8; EGCG: 11.6	No excess lipids, sugars or caffeine; no catechin-rich foods: no "foods that reduce excess adiposity;" maintain usual exercise
12	340 mL green tea beverage (583 mg catechins)	340 mL green tea beverage (96 mg catechins)	Enriched tea: C: 42.8; CG: 40.1; GC: 127.5; GCG: 139.7; EC: 32.3; ECG: 30.9; EGC: 69.4; EGCG: 100.3 Control Tea: C: 6.1; CG: 4.4; GC: 23.8; GCG: 24.1; EC: 4.8; ECG: 5.1; EGC: 11.2; EGCG: 16.7	Normal diet; no catechin-rich foods that might change carbohydrate or lipid metabolism
12	"Sports drink" containing GTE (548 mg catechins)	"Sports drink" with no catechins	C: 17.5; EC: 50.5; CG: 0; EGC: 18.5; GC: 39.5; EGCG: 282; GCG: 132.5	Maintain habitual lifestyle; no additional tea; limited to 200 mL/day
4	1 capsule daily (500 mg catechin)	NR	NR	No lifestyle modification

(continued)

Table 1. Characteristics of randomized controlled trials evaluating the effect of green tea catechins on serum lipid levels (continued)

Study, year, sample size	Study design	ADA[a] quality rating	Population	Baseline characteristics (I,C)
Nagao and colleagues, 2007, n=240 (22)	Double-blinded, parallel	+	Japanese, age 25-55 y, BMI 24-30, and/or WC[r] 80-94	TC: 215.9, 210.5; LDL: 131.9, 129.2; HDL: 54.9, 53.7; TG: 171.8, 161.2;
Chan and colleagues, 2006, n= 34 (23)	Single-blinded, parallel	+	Women ages 25-40 y with PCOS[s], BMI ≥28	TC:181.9, 201.2; LDL: 110.3, 135.5; HDL: 37.9, 40.2; TG: 106.3, 119.6
Ryu and colleagues, 2006, n=55 (24)	Crossover	Ø	Type 2 diabetes	TC: 178 LDL: 108.3 HDL: 46.4 TG: 132.9
Erba and colleagues, 2005, n= 24 (25)	Open-label, parallel	−	Healthy female subjects	TC: 174.6, 170.9; LDL: 119.9, 115.5; HDL: 55.8, 56.8; TG: 84.9, 66.1
Maron and colleagues, 2003, n=240 (26)	Double-blinded, parallel	+	Mild to moderate hypercholesterolemia, age >18y, LDL 130-190 mg/dL[d] on a low fat	TC: 244, 239 LDL: 159, 155 HDL: 55, 55 TG: 189, 175
Princen and colleagues, 1998, n=28 (27)	Single-blinded, parallel	+	Healthy, normal weight, ≥10 cigarettes/d	(I1, I2, C) TC: 207, 195.8, 209.7 LDL: 135, 127.7, 138.9 HDL: 48.7, 42.9, 41 TG: 116, 129.3, 150.6
Van het Hof and colleagues, 1997, n=30 (28)	Open-label, parallel	Ø	Healthy, non-smoking, age 18-65 y	TC: 212.5, 208.6; LDL: 104.5, 95.2; HDL: 63.1, 57.7; TG: 77.1, 85.1

[a]ADA=American Dietetic Association.
[b]CD=coronary artery disease.
[c]TC=total cholesterol.
[d]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.6. Cholesterol of 130 mg/dL=3.38 mmol/L.
[e]LDL=low-density lipoprotein.
[f]HDL=high-density lipoprotein.
[g]TG=triglyceride.
[h]GTE=green tea extract.
[i]NR=not reported.
[j]BMI=body mass index.
[k]EGCG=epigallocatechin gallate.
[l]ø=neutral.
[m]EC=epicatechin.
[n]GC=gallocatechin.
[o]C=catechin.
[p]CG=catechin gallate.
[q]FBG=fasting blood glucose.
[r]WC=waist circumference.
[s]PCOS=polycystic ovarian syndrome.

(continued)

This included running analyses that included positively rated trials only, included both positive and neutral rated trials (excluding negatively rated trials), evaluated parallel and crossover trials separately, evaluated trials separately based on their GTC dosage form, evaluated trials separately based on their catechin dose (using a cutoff of 200 mg/day), evaluated trials separately based on baseline lipid parameters, with mean/median total cholesterol >200 mg/dL (5.1 mmol/L) and/or LDL cholesterol >130 mg/dL (3.4 mmol/L) representing hyperlipidemia, and anything less to represent normolipidemia, and included trials not utilizing lifestyle modification. A post hoc sensitivity analysis excluding the trial conducted by Maron and colleagues (26) was conducted because this trial was the only one to independently show statistically significant reductions in total and LDL cholesterol.

RESULTS

Study Characteristics

Of the 130 nonduplicate citations retrieved, 30 full-text articles underwent detailed evaluation (Figure 1). Ten

Table 1. Characteristics of randomized controlled trials evaluating the effect of green tea catechins on serum lipid levels (continued)

Follow-up (wk)	Tea group (dose/d)	Control group (dose/d)	Catechin components (mg)	Concurrent lifestyle modifications
12	340 mL green tea beverage (583 mg catechins)	340 mL green tea beverage (96 mg catechins)	Enriched tea: C: 42.8; CG: 40.1; GC: 127.5; GCG: 139.7; EC: 32.3; ECG: 30.9; EGC: 69.4; EGCG: 100.3 Control tea: C: 6.1; CG: 434; GC: 23.8; GCG: 24.1; EC: 4.8; ECG: 5.1 EGC: 11.2; EGCG: 16.7	Normal diet; no medications or supplements that change carbohydrate or lipid metabolism; no restrictions on tea or coffee intake
12	Green tea capsules (661 mg catechins)	Placebo (not specified)	EGCG: 538.4: EGC: 50.6; ECG: 38.3; EC: 32	No additional caffeine; nutritional consults; diet monitored but no interventions
4	900 mL water containing 9 g green tea daily	900 ml water	NR	NR
6	160 mg GTE in 200 mL warm water (250 mg catechins)	Diet only	EGCG: 167.5; ECG: 18; EGC: 2.75; EC: 4.75; C: 1.5	Diet with controlled amount of polyphenols
12	Theaflavin-rich GTE (150 mg catechins)	Placebo (inert ingredients)	NR	Habitual, traditional Chinese diet including customary intake of tea
4	(I1, I2) 900 mL green tea beverage (852 mg catechins/d) Or 3,600 mg capsules of green tea polyphenol isolate with control beverage (2,489 mg catechins/d)	900 ml water	C: 10.8; GC: 58.5; GCG: 78; EC: 85.2; ECG: 73.2; EGC: 237; EGCG: 309 Or C: 57.24; GC: 110.1; GCG: 136; EC: 285.1; ECG: 412.2; EGC: 448.9; EGCG: 1,037.8	Maintain normal eating habit; Not allowed: red wine, >2 oranges or >2 glasses of fruit juice, outside tea, milk in tea
4	900 mL green tea beverage/day (3 g GTE)	900 mL mineral water	C:642; EC:10.5; ECG: 51.3; EGC: 234.6; ECGC: 271.8	Normal diet; no green tea allowed outside experiment

full-text articles were excluded because relevant endpoints were not reported. Ultimately, 20 trials (N=1,415) (9-28) were included in the systematic review (Table 1) with 19 trials reporting results on total cholesterol (9,10,12-28), 19 reporting LDL cholesterol (9-12,14-28), 19 reporting HDL cholesterol (9-18,20-28), and 19 reporting triglycerides (9,10,12-28).

Mean ages of patients evaluated in the RCTs ranged from 11 to 65 years (Table 1). Four trials enrolled only male patients (10,12,13,20), three enrolled only female patients (17,23,25), and the remaining trials enrolled both male and female patients (9,11,14-16,18,19,21,22,24,26-28). The duration of study ranged from 3 to 24 weeks and doses of GTCs ranged from 145 to 3,000 mg/day. Various forms of GTCs were evaluated, including green tea extract capsules (9-13,17,21,23,26,27), extract powders (16), or green tea beverages (14,15,18-20,22,24,25,27,28).

Of the 20 trials included, four were crossover trials (9,12,16,24). Due to the reporting of data as separate time periods, data from two of the crossover trials were analyzed as parallel data (9,16). The remaining trials had parallel study design (10-15,17-28).

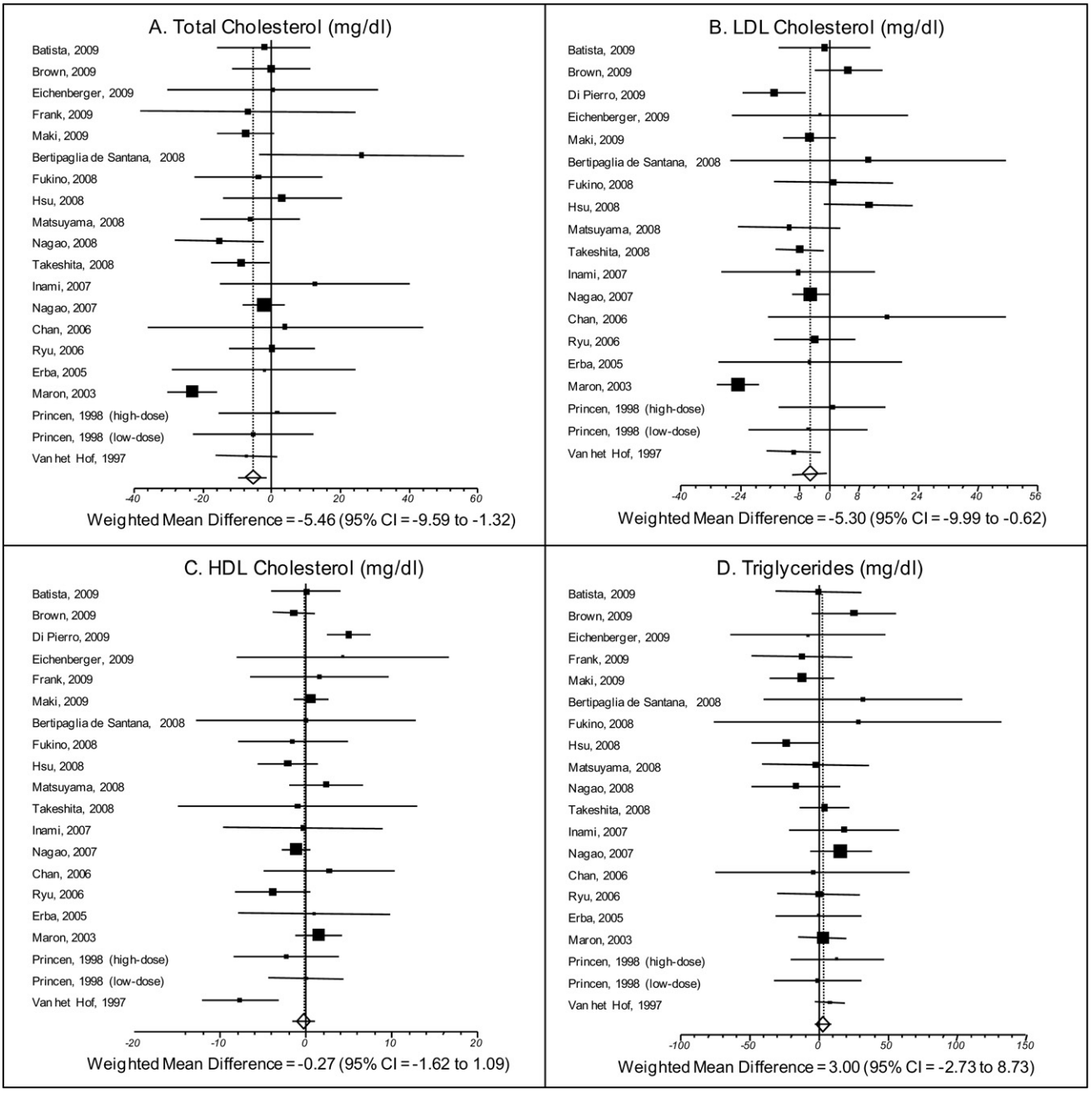

Figure 2. Forest plot depicting the results of meta-analyzing randomized controlled trials evaluating green tea catechins on serum levels of (A) total cholesterol, (B) low-density lipoprotein (LDL) cholesterol, (C) high-density lipoprotein (HDL) cholesterol, and (D) triglycerides. The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals (CIs). The diamonds represent the pooled results. The solid vertical line extending upward from zero is the null value. To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.6. Cholesterol of 130 mg/dL=3.38 mmol/L.

Quantitative Data Synthesis

Upon meta-analysis, GTCs were associated with statistically significant reductions in total cholesterol (weighted mean differences −5.46 mg/dL [−0.14 mmol/L]; 95% CI −9.59 to −1.32 mg/dL [−0.25 to −0.03 mmol/L]) and LDL cholesterol (weighted mean differences −5.30 mg/dL [−0.138 mmol/L]; 95% CI −9.99 to −0.62 mg/dL [−0.26 to −0.02 mmol/L]) compared to control (Figure 2). There was no significant effect of GTCs on HDL cholesterol (weighted mean differences −0.27 mg/dL [−0.007 mmol/L]; 95% CI

Table 2. Results of subgroup and sensitivity analyses from a meta-analysis of randomized controlled trials evaluating the effect of green tea catechins on serum lipid levels

	Total cholesterol	Low-density lipoprotein cholesterol	High-density lipoprotein cholesterol	Triglyceride
	← *weighted mean difference (95% confidence interval)* →			
Base-case (all trials)	−5.45 (−9.59 to −1.32) n=1,326	−5.30 (−9.99 to −0.62) n=1,350	−0.27 (−1.62 to 1.09) n=1,343	3.00 (−2.73 to 8.73) n=1,326
Sensitivity analyses				
Positive ratings	−6.44 (−12.12 to −0.76) n=980	−4.33 (−11.02 to 2.34) n=985	−0.30 (−1.22 to 0.61) n=937	−0.62 (−8.84 to 7.60) n=980
Positive or neutral ratings	−5.68 (−9.96 to −1.40) n=1,266	−4.33 (−9.54 to 0.83) n=1,190	−0.77 (−1.88 to 0.33) n=1,183	2.75 (−3.15 to 8.65) n=1,266
Parallel design	−5.99 (−10.64 to −1.34) n=1,228	−5.63 (−10.92 to −0.34) n=1,252	−0.12 (−1.61 to 1.36) n=1,245	3.37 (−2.60 to 9.35) n=1,228
Crossover design	−0.87 (−9.65 to 7.90) n=98	−2.79 (−10.54 to 4.96) n=98	−1.40 (−4.83 to 2.02) n=98	−1.27 (−21.44 to 18.91) n=98
Excluding trial by Maron and colleagues	−4.25 (−7.16 to −1.34) n=1,106	−4.47 (−7.56 to −1.38) n=1,130	−0.43 (−1.88 to 1.02) n=1,123	3.04 (−3.03 to 9.11) n=1,106
Subgroup analyses				
Beverages only	−5.62 (−9.46 to −1.79) n=687	−6.51 (−9.42 to −3.60) n=644	−1.36 (−3.55 to 0.82) n=604	4.12 (−3.01 to 11.25) n=687
Capsules only	−4.37 (−13.25 to 4.51) n=776	−4.07 (−15.67 to 7.54) n=603	0.96 (−1.16 to 3.07) n=636	−0.36 (−11.61 to 10.88) n=536
High catechin dose[a]	−5.36 (−9.41 to −1.32) n=482	−2.26 (−7.57 to 3.05) n=482	−1.47 (−3.38 to 0.45) n=442	1.93 (−7.74 to 11.61) n=480
Low catechin dose[b]	−1.45 (−32.77 to 29.87) n=280	−10.80 (−32.29 to 10.69) n=280	1.54 (−1.10 to 4.17) n=280	3.26 (−12.89 to 19.41) n=280
Enrolled patients with hyperlipidemia[c]	−6.04 (−10.75 to −1.33) n=1,168	−4.35 (−10.02 to 1.32) n=1,125	−0.69 (−1.86 to 0.48) n=1,085	3.44 (−2.70 to 9.58) n=1,168
Enrolled patients with normolipidemia[d]	0.17 (−9.19 to 9.54) n=192	−3.07 (−11.40 to 5.25) n=159	−0.82 (−3.75 to 2.12) n=192	−0.18 (−15.78 to 15.42) n=192
Without lifestyle modification	−5.20 (−9.97 to −0.42) n=1,165	−4.52 (−10.17 to 1.14) n=1,089	−1.02 (−2.20 to 0.15) n=1,082	4.14 (−1.89 to 10.16) n=1,165

[a]A high catechin dose for the purpose of subgroup analysis was defined as catechin ingestion (of any type) ≥200 mg/d.

[b]A low catechin dose for the purpose of subgroup analysis was defined as catechin ingestion (of any type) <200 mg/d.

[c]Trials were categorized as enrolling patients with hyperlipidemia if the mean baseline total cholesterol was ≥200 mg/dL (5.2 mmol/L) and/or LDL cholesterol was ≥130 mg/dL (3.38 mmol/L).

[d]Trials were categorized as enrolling patients with normolipidemia if the mean baseline total cholesterol was <200 mg/dL (5.2 mmol/L) and/or LDL cholesterol was <130 mg/dL (3.38 mmol/L).

−1.62 to 1.09 mg/dL [−0.042 to 0.03 mmol/L]) or triglycerides (weighted mean differences 3.00 mg/dL [0.034 mmol/L]; 95% CI −2.73 to 8.73 mg/dL [−0.031 to 0.10 mmol/L]) vs control. Statistical heterogeneity was not detected in the analysis on triglycerides (I^2=0%), but moderate to high degrees of heterogeneity were present for total, LDL, and HDL cholesterol (I^2=45%, 71%, and 51%, respectively). Review of funnel plots (not shown) and Egger's weighted regression P values suggested potential publication bias for total and LDL cholesterol analyses (P<0.08 for both), but low likelihood for publication bias for HDL cholesterol and triglyceride analyses (P>0.6 for both). No appreciable alterations in the effect of GTCs were noted upon most subgroup and sensitivity analyses (Table 2). However, there appeared to be no effect of GTCs on total or LDL cholesterol when evaluating GTC capsules alone, low doses of catechins or patients with normolipidemia.

DISCUSSION

Observational data shows conflicting results of the effect of green tea on lipid parameters. Consumption of up to 4 cups green tea per day was not associated with changes in lipid parameters (7), but >10 c/day was associated with reductions in total and LDL cholesterol levels and increases in HDL cholesterol level (32). Interest in health benefits of green tea prompted proposed health claims on labels of green tea products. However, in 2005, the Food and Drug Administration concluded that there was inconclusive evidence to support health claims of green tea products (33). Since then, there have been RCTs evaluating the effect of GTCs. Statistical pooling of 20 trials found that GTCs were associated with reductions in total and LDL cholesterol values compared to control (5.46 mg/dL [0.14 mmol/L] and 5.30 mg/dL [0.138 mmol/L] reductions, respectively). No effect was seen with HDL cholesterol or triglycerides.

Study characteristics of the trials included in the analysis may have contributed to clinical and statistical heterogeneity and is a limitation of this meta-analysis. The populations studied varied among children; healthy adults; and adults with comorbidities such as hyperlipidemia, overweight, or obesity, or diabetes mellitus. Although the wide range of populations may make results difficult to apply, subgroup analysis suggests that no effect of GTCs was seen on lipid parameters in patients with normolipidemia. The range of GTC dose and dosage form may also contribute to heterogeneous results. Subgroup analysis based on dosage form showed significant effect in green tea beverages but not GTC capsules; a potential reasoning for this may be due to higher degrees of heterogeneity among trials evaluating GTC capsules. Subgroup analysis of catechin dose suggests that effects are seen with higher doses and not lower doses, but a true dose–response relationship could not be assessed. In future investigations, a multivariate analysis controlling for multiple influential factors, such as dosage form, dose, and baseline lipid levels may be necessary to identify the ideal product and population to exert benefit.

When evaluating each study independently, only one trial conducted by Maron and colleagues (26) showed statistically significant reductions in total and LDL cholesterol levels, which may have strongly contributed to the meta-analysis' results showing significant reductions in these lipid parameters. Upon sensitivity analysis that excludes the trial by Maron and colleagues (26), results for total and LDL cholesterol remained statistically significant, suggesting that this single trial did not heavily skew the overall analysis. It is important to note that the green tea product evaluated by Maron and colleagues (26) was enriched with theaflavin, a black tea polyphenol, which may have contributed to the magnitude of total and LDL cholesterol level reductions observed. This trial also included patients with one of the highest baseline levels among the included trials of the meta-analysis, potentially contributing to the improvements seen.

This meta-analysis did not pool safety data because the reporting of adverse events and tolerability were not consistent among the RCTs. However, several included trials stated no significant differences between groups or no side effects at all (13,17,19,23,26). Concerns of possible hepatotoxicity involving green tea products from case reports have led the US Pharmacopeia Dietary Supplement Information Expert Committee to propose a cautionary statement in the labeling of green tea extract products (34). Experts suggest taking green tea extract products with food, and patients with liver disorders should discontinue use and consult a health care practitioner (34). It is necessary to conduct trials in a long-term extension of GTC supplementation to better understand and investigate long-term safety and tolerability of GTCs.

With all meta-analyses, there is risk of publication bias. Our results suggested low likelihood for publication bias on HDL cholesterol and triglyceride outcomes, but potential for publication bias on total and LDL cholesterol outcomes. The extensive search strategy and inclusion of non-English language publications strengthens this meta-analysis and reduces the effect of publication bias on the overall results. The majority of studies identified showed no significant effect of GTCs on total and LDL cholesterol, suggesting that results would remain significant if additional studies were included.

CONCLUSIONS

Based on currently available literature, GTCs may have a beneficial effect on total and LDL cholesterol levels in human beings. However, there is no statistically significant effect on HDL cholesterol or triglyceride levels. Future studies should be conducted to determine the ideal dose and duration of GTCs. The effect of specific catechins components should also be further investigated because there may be an additive or synergistic effect on lipid values. Further investigations should be conducted to determine if certain target populations have an additional benefit with GTCs.

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