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SYSTEMATIC REVIEW

The effect of green tea on blood pressure and lipid profile: A systematic review and meta-analysis of randomized clinical trials

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KEYWORDS
Green tea;
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Abstract *Introduction:* Many different dietary supplements are currently marketed for the management of hypertension, but the evidence for effectiveness is mixed. The aim of this systematic review was to evaluate the evidence for or against the effectiveness of green tea (*Camellia sinensis*) on blood pressure and lipid parameters.
Methods and results: Electronic searches were conducted in Medline, Embase, Amed, Cinahl and the Cochrane Library to identify relevant human randomized clinical trials (RCTs). Hand searches of bibliographies were also conducted. The reporting quality of included studies was assessed using a checklist adapted from the CONSORT Statement. Two reviewers independently determined eligibility, assessed the reporting quality of the included studies, and extracted the data. As many as 474 citations were identified and 20 RCTs comprising 1536 participants were included. There were variations in the designs of the RCTs. A meta-analysis revealed a significant reduction in systolic blood pressure favouring green tea (MD: −1.94 mmHg; 95% CI: −2.95 to −0.93; $I^2 = 8\%$; $p = 0.0002$). Similar results were also observed for total cholesterol (MD: −0.13 mmol/l; 95% CI: −0.2 to −0.07; $I^2 = 8\%$; $p < 0.0001$) and LDL cholesterol (MD: −0.19 mmol/l; 95% CI: −0.3 to −0.09; $I^2 = 70\%$; $p = 0.0004$). Adverse events included rash, elevated blood pressure, and abdominal discomfort.
Conclusion: Green tea intake results in significant reductions in systolic blood pressure, total cholesterol, and LDL cholesterol. The effect size on systolic blood pressure is small, but the effects on total and LDL cholesterol appear moderate. Longer-term independent clinical trials evaluating the effects of green tea are warranted.

Introduction

Hypertension is a leading cause of death, and a major risk factor for cardiovascular disease [1]. Its global prevalence varies worldwide from as low as 3.4% to as high as 72.5% [2]. Although over 90% of hypertensive cases are idiopathic [3], dietary and lifestyle factors are major risk factors associated with its increasing incidence [4,5]. Many different dietary supplements are currently marketed for the management of hypertension, but the evidence for effectiveness is mixed [6]. One such supplement thought to have an antihypertensive effect is the extract of *Camellia sinensis*, green tea.

Green tea is one of the most commonly consumed beverages worldwide [7]. The leaves of the plant contain a variety of phytochemicals including phenols and catechins [8]. The polyphenolic compounds in green tea are thought to possess antioxidant properties by virtue of their ability to scavenge for free oxygen and nitrogen radicals [9]. The

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catechins in green tea comprise epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin-3-gallate, and epicatechin. EGCG is reported as the most abundant catechin in green tea, comprising over half of the total catechin content, as well as being the most bioactive component [10,11].

Green tea catechins have been postulated to stimulate thermogenesis, modify appetite and downregulate the enzymes involved in lipid metabolism [12]; consequently this group of flavonoids are commonly marketed as slimming aids. *Invitro* studies have shown that the epigallocatechins in green tea have angiotensin converting enzyme inhibitor properties [13,14], and findings from several animal studies have suggested that green tea lowers blood pressure by suppressing the NADPH oxidase activity and reducing the numbers of reactive oxygen species in the vascular system [15,16]. Molecular studies have demonstrated that green tea catechins enhance cholesterol 7alpha-hydroxylase gene expression in HepG2 cells [17,18], a process which is thought to stimulate bile acid production and decrease cholesterol concentration in the hepatocytes. Animal studies have also shown that green tea extracts inhibit intestinal absorption of lipids and also upregulate low-density lipoprotein receptors in the liver [19–21]; mechanisms which lead to improvements in the blood lipid profile.

Case-control and epidemiologic studies have suggested that green tea intake has a cardioprotective effect [22,23], but a previous meta-analysis of five studies concluded that green tea had no beneficial effect on blood pressure [24]. However, a recent meta-analysis reported beneficial effects of green tea on blood vessel dilatation [25], and two meta-analyses (both including open-label and blinded trials) reported beneficial effects on lipid profile [26,27]. Therefore, the purpose of this systematic review was to evaluate the evidence for or against the efficacy of green tea extracts on blood pressure and lipid profile, using published data from blinded-only clinical trials.

Methods

We conducted electronic searches in the following databases: Medline, Embase, Amed, Cinahl, and The Cochrane Library. Each database was searched from inception to May, 2013. The search terms used included green tea, *Camellia sinensis*, catechins, blood pressure, hypertension, lipids, and derivatives of these (comprehensive search strategy included as a Supplement Fig. 1S). We also searched the internet for relevant conference proceedings and hand searched relevant medical journals. The bibliographies of all located articles were also searched. No age, gender, or language restrictions were imposed.

Only double-blinded, randomized clinical trials (RCTs) were included in this review. To be considered for inclusion, RCTs had to test the effectiveness of orally administered green tea supplement against placebos or identical controls for blood pressure reduction in normotensive or hypertensive human volunteers. Studies had to report blood pressure and lipid profile as outcome measures, and must have had at least two weeks of intervention. Studies were included irrespective of lifestyle modification.

Two reviewers [IO and ES] independently assessed the eligibility of studies. Data extracted by two reviewers [IO and ES] included patient characteristics, interventions and results. The reporting quality of all included studies was assessed by the use of a quality assessment checklist adapted from the Consolidated Standard of Reporting Trials (CONSORT) Statement [28]. Disagreements were resolved through discussion.

The data were presented as means with standard deviations. Mean changes in systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were used as primary endpoints to assess the differences between the intervention (green tea) and comparison (placebo or identical control) groups. Using standard meta-analysis software (RevMan 5.0) [29], we computed mean differences (MD) and 95% confidence intervals (CI) for studies with sufficient data for statistical pooling. The random-effects model was used for meta-analyses [30]. Sensitivity analyses (by analyzing trials based on reporting quality, duration of intervention, green tea formulation or lifestyle modification) were used to test the robustness of overall analyses. Subgroup analyses (by assessing the difference between groups in trials with similar participant characteristics, and by funding source) were used to investigate heterogeneity, using the I^2 statistic; values of 25%, 50%, and 75% indicated low, medium, and high statistical heterogeneity respectively. Heterogeneity was further explored by using dose-effect correlations (scatter plots of mean differences against daily dose) to examine the relationship between the dosage of EGCG and changes in blood pressure and lipid profile for studies $\geq$12 weeks in duration. Funnel plots with cumulative forest plots were used to test for publication bias.

Results

Our electronic searches returned 474 non-duplicate citations (Fig. 1), out of which 34 eligible trials were identified. Five RCTs were excluded because they did not report blood pressure as an outcome measure [31–35], and four because they were not double-blinded [36–39]. Two RCTs were excluded because they lasted less than two weeks in duration [40,41], and another two because green tea was combined with other supplements [42,43]. A total of 21 articles comprising 20 RCTs [44–64], and including a total of 1536 participants were included in the review. Key details of the RCTs are summarized in Tables 1 and 2.

All the RCTs were parallel design except three which were cross-over (Table 1). Nine RCTs reported adequate randomization techniques, four reported adequate allocation concealment, and three did not report adequate blinding procedures. Nine RCTs reported performing sample size calculations, and three reported intention-to-treat analyses. Participants in all RCTs had similar baseline demographics, except in one RCT where the green tea group had higher systolic and diastolic blood pressures compared with controls [64]. Only in one RCT were all participants described as hypertensive [45].

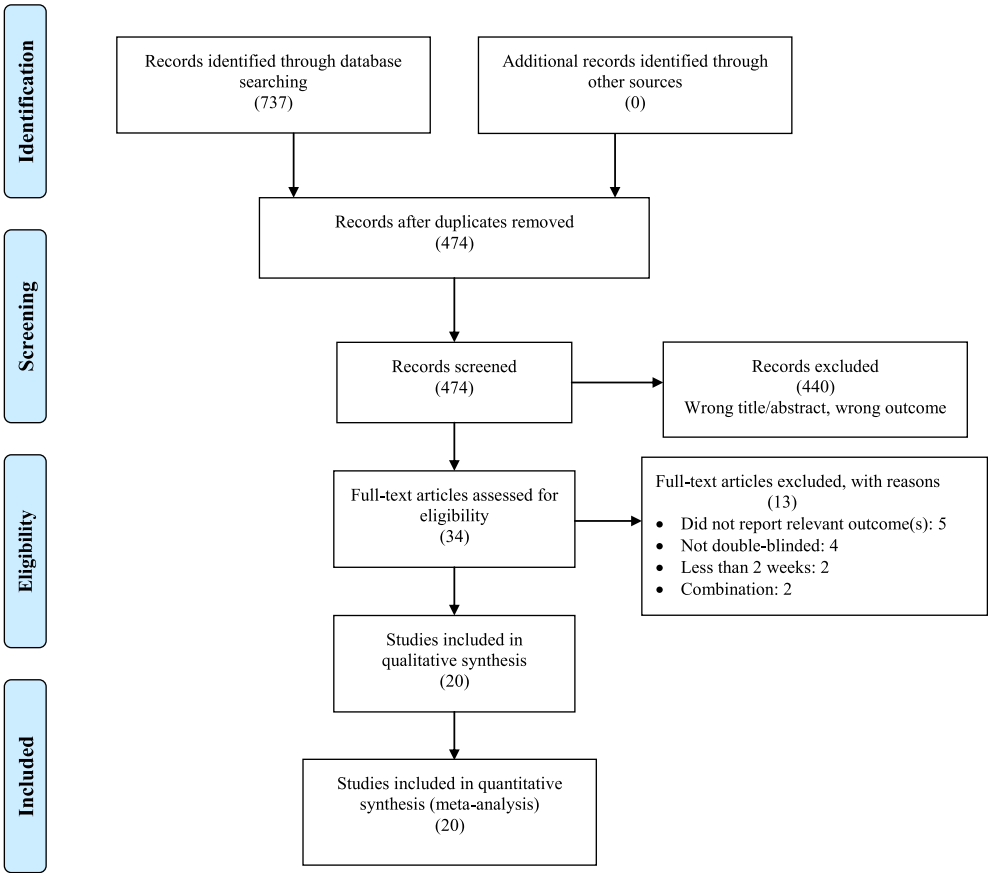

Figure 1 Flow diagram showing process for inclusion and analysis of green tea RCTs[a,b]. [a]The flow diagram has been adapted from the online version of the PRISMA statement, 2009. Available from: http://www.prisma-statement.org/statement.htm, [b]21 articles were included; these contained 20 RCTs, as the results of one RCT were reported as two separate articles.

Eight RCTs (40%) were exclusively funded by green tea manufacturers, five (25%) were funded by government or public institutions, and one was jointly funded by both government and a green tea manufacturer (Table 2). Six RCTs did not receive any study funding, however authors in five of these RCTs [56–58,62,63] were affiliated with green tea manufacturing industries, while those in one [61] were affiliated to a public institution.

There were some variations in the lifestyle modifications instituted in the included RCTs (Table 2). While the amount of daily tea and/or coffee intake was restricted in 14 RCTs, subjects in one RCT did not have restrictions to the amount of tea or caffeine [57]. The control for habitual tea or coffee intake was not specified in five RCTs [44,45,52,53,61].

Effect on systolic blood pressure

Two RCTs [44,55] reported no significant changes in systolic pressure between green tea and controls (p values not specified), and did not report data for statistical pooling. A meta-analysis of 18 RCTs (Fig. 2) revealed a significant reduction in systolic blood pressure favouring green tea over placebo (MD: -1.94 mmHg; 95% CI: -2.95 to −0.93; $I^2 = 8\%$; $p = 0.0002$). A funnel plot of these studies (Appendix 1a) suggests symmetrical distribution around the mean difference for all the trials, indicating a low risk of publication bias. A cumulative forest plot revealed that the point estimate stabilized after the inclusion of the nine larger studies which were symmetrically distributed around the mean (MD = −1.53 mmHg; Appendix 1b), and the addition of each subsequent smaller study to this plot did not result in a shift of this estimate. A dose-effect plot (Fig. 3) indicates a significant correlation between EGCG dosage and reduction in systolic blood pressure in RCTs lasting at least 12 weeks ($r = 0.75$; $p = 0.003$), and also suggests that EGCG doses above 200 mg (about 5–6 cups of tea) do not offer additional reductions on systolic blood pressure. A meta-analysis of 15 RCTs which reported adequate blinding of care providers and participants showed a significant reduction in systolic blood pressure in favour of green tea (MD: −1.46 mmHg; 95% CI: −2.5 to −0.43; $I^2 = 0\%$; $p = 0.006$). Sensitivity analysis of 13 RCTs lasting ≥12 weeks revealed a significant reduction in systolic blood pressure in favour of green tea (MD: −2.68 mmHg; 95% CI: −3.81 to −1.54; $I^2 = 0\%$; $p = <0.00001$).

Meta-analysis of 12 RCTs ($n = 1010$) funded by manufacturers or with manufacturer-affiliated authors showed a significant reduction in systolic blood pressure in favour of green tea (MD: −1.65 mmHg; 95% CI: −2.72 to −0.57; $I^2 = 0\%$; $p = 0.003$). In contrast, the six RCTs ($n = 332$) funded by public institutions or with authors affiliated with public organizations revealed a non-significant

Table 1 Reporting quality of RCTs of green tea supplements.

Study Year Country	Study design	Randomization appropriate?	Allocation concealed?	Sample size determined?	Groups similar at baseline?	Care provider blinded?	Patients blinded?	Attrition bias?	ITT analysis?	Instrument used for measuring blood pressure	Instrument used for measuring blood lipids
Batista et al. 2009 [44] Brazil	Cross-over	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Mercury sphygmomanometer	Calorimetry; Friedewald formula
Bogdanski et al. 2012 [45] Poland	Parallel	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Not specified	Integrated Chemistry System Analyzer
Brown et al. 2009 [46] UK	Parallel	Yes	Yes	Unclear	Yes	Yes	Yes	No	No	Mercury sphygmomanometer	ABX Pentra 400
Brown et al. 2011 [47] UK	Cross-over	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Non-invasive oscillometry	MIRA Plus
Diepvens et al. 2005/6 [48/9][a] Netherlands	Parallel	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Automatic blood pressure monitor	Cholesterol 100 kit; the GPO-trinder kit
Frank et al. 2009 [50] UK	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Not specified	Calorimetry
Hill et al. 2007 [51] Australia	Parallel	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Pulsewave Cardiovascular Profiler	Not specified
Hsu et al. 2008 [52] Taiwan	Parallel	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not specified	Not specified
Hsu et al. 2011 [53] Taiwan	Parallel	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not specified	Not specified
Kajimoto et al. 2003 [54] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Not specified	Friedewald formula
Maki et al. 2009 [55] USA	Parallel	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes	Mercury sphygmomanometer; automatic blood pressure device	Friedewald formula
Matsuyama et al. 2008 [56] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Automated sphygmomanometer	Enzymatic and selective inhibition methods
Nagao et al. 2007 [57] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Mercury manometer	Not specified
Nagao et al. 2009 [58] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Automatic sphygmomanometer	Not specified
Nantz et al. 2009 [59] USA	Parallel	Yes	Unclear	Yes	Yes	Yes	Yes	No	No	Automatic blood pressure monitor	Enzymatic method

Sone et al. 2010 [60] Japan	Parallel	Yes	Unclear	Yes	Yes	Yes	Yes	No	No	Not specified	Enzymatic and selective detergent methods
Saliburska et al. 2010 [61] Poland	Parallel	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Not specified	Enzymatic method, Friedewald's formula
Takase et al. 2008 [62] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	Automated sphygmomanometer	Not specified
Takeshita et al., 2008 [63] Japan	Parallel	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Automated sphygmomanometer	Not specified
Widlansky et al., 2007 [64] USA	Cross-over	Yes	Unclear	Yes	No	Yes	Yes	No	No	Automatic haemodynamic monitor	Friedewald's formula

Abbreviation: M/F: males/females; ITT: intention-to-treat analysis.
[a] This was an RCT with outcomes reported as two separate articles [48 & 49].

difference (MD: −1.69 mmHg; 95% CI: −4.26 to 0.88; $I^2 = 30\%$; $p = 0.2$).

Effect on diastolic blood pressure

Two RCTs [44,55] reported no significant changes in systolic pressure between green tea and controls (p values not specified). A meta-analysis of 18 RCTs ($n = 1342$) failed to reveal a significant reduction with green tea compared with controls (MD: −0.98 mmHg; 95% CI: −2.14 to 0.18; $I^2 = 62\%$; $p = 0.1$). Similar relationships were observed for sensitivity and subgroup analyses (Table 3). A cumulative forest plot revealed that the point estimate stabilized after the inclusion of the nine larger studies which were symmetrically distributed around the mean (data not shown), but the addition of each subsequent smaller study to this plot resulted in a shift of this estimate, suggesting that small sample sizes could have biased study results. A dose-effect plot showed no association between EGCG dosage and diastolic blood pressure reduction for RCTs lasting ≥12 weeks ($r = 0.22$; $p = 0.5$).

Meta-analysis of 12 RCTs ($n = 1010$) funded by manufacturers or with manufacturer-affiliated authors showed a non-significant difference in systolic blood pressure (MD: −0.93 mmHg; 95% CI: −2.21 to 0.36; $I^2 = 64\%$; $p = 0.16$). Similar findings were observed in the six RCTs ($n = 332$) funded by public institutions or with authors affiliated to public organizations (MD: −0.90 mmHg; 95% CI: −2.88 to 1.09; $I^2 = 42\%$; $p = 0.38$).

Effect on blood lipid profile

A meta-analysis of 19 RCTs (Fig. 4) revealed a significant reduction in total cholesterol in subjects receiving green tea group compared with controls (MD: −0.13 mmol/l; 95% CI: −0.2 to −0.07; $I^2 = 8\%$; $p < 0.0001$). Similar relationships were observed for sensitivity and subgroup analyses (Table 3). A cumulative forest plot revealed that the point estimate stabilized after the inclusion of the 11 larger studies which were symmetrically distributed around the mean (data not shown), and the addition of each subsequent smaller study to this plot did not result in a shift of this estimate. A dose-effect plot revealed a moderate, non-significant correlation between EGCG dosage and total cholesterol reduction for RCTs lasting ≥12 weeks ($r = 0.47$; $p = 0.1$). Meta-analyses of manufacturer-funded RCTs showed similar results (MD = −0.12 mmol/l; 95% CI: −0.19 to −0.06; $I^2 = 0\%$; $p = 0.0001$), but analysis of government-funded studies did not show a significant difference (MD = −0.2 mmol/l; 95% CI: −0.47 to 0.08; $I^2 = 55\%$; $p = 0.16$).

A meta-analysis of 17 RCTs (Fig. 5) showed a significant reduction in LDL cholesterol in the green tea group compared with control (MD: −0.19 mmol/l; 95% CI: −0.3 to −0.09; $I^2 = 70\%$; $p = 0.0004$). Similar reductions were observed for sensitivity and subgroup analyses (Table 3). A cumulative forest plot revealed that the point estimate stabilized after the inclusion of the 11 larger studies which were symmetrically distributed around the mean (MD: −0.15 mmol/l); the addition of each subsequent smaller

Table 2 Study characteristics of RCTs of green tea supplements.[a]

Study Year	Relevant outcome	Type of subjects and sample size	Age (years)	Study duration	Green tea extracts (daily dose)	Controls	Baseline BP (mmHg): Green tea/control	Adverse events (*n*)	Lifestyle modification	Funding source
Batista 2009 [44]	Blood pressure, lipid profile	Dyslipidemia (33)	21–71	16 weeks	250 mg dry GTE as capsules	Placebo (NS)	SBP = 135.7(23.9) DBP = 85.2(13.6)	Not reported	Low-fat diet; caffeine control unspecified	Public Institution & Manufacturer
Bogdanski 2012 [45]	Blood pressure, lipid profile	Obese hypertensive (56)	30–60	13 weeks	379 mg GTE; 208 mg EGCG as capsules	Cellulose	SBP = 145(10)/146(10) DBP = 88.2(4)/89(3)	Not reported	Isocaloric diet; caffeine control unspecified	Government
Brown 2009 [46]	Blood pressure, lipid profile	Overweight &obese males (100)	40–65	8 weeks	800 mg EGCG as capsules	Lactose	SBP = 136·2(13)/138.2(18.2) DBP = 86.7(7.3)/87.2(9.2)	Not reported	Normal lifestyle; caffeine intake restricted	Manufacturer
Brown 2011 [47]	Blood pressure, lipid profile	Overweight &obese males (83)	40–69	6 weeks	1060 mg GTE; 430 mg EGCG as capsules	Lactose	SBP = 127·1(8.7)/127.7(8.3) DBP = 79.1(6.1)/79.5(5.9)	GIT symptoms (18)	Normal lifestyle; caffeine intake restricted	Manufacturer
Diepvens 2005/6 [48/9]	Blood pressure, lipid profile	Overweight females (46)	19–57	12 weeks	1206·9 mg GTC; 596 mg EGCG as capsules	Maltodextrin	SBP = 127·4(11.8)/122·5(13) DBP = 80(12)/78·6(8.9)	None	Low-energy diet; caffeine intake restricted	Manufacturer
Frank 2009 [50]	Blood pressure, lipid profile	Healthy males (35)	30–50	3 weeks	2304 mg GTE; 150 mg EGCG as capsules	Maltodextrin	SBP = 125(10)/126(16) DBP = 78(8)/79(11)	None	Normal lifestyle; caffeine intake restricted	Public Institution
Hill 2007 [51]	Blood pressure, lipid profile	Overweight postmenopausal (42)	45–70	12 weeks	336 mg GTE; 300 mg EGCG as capsules	Lactose	SBP = 125.2(12.9)/122.6(14) DBP = 70.9(5.9)/69.5(7.5)	None	Normal lifestyle; caffeine control unspecified	Manufacturer
Hsu 2008 [52]	Blood pressure, lipid profile	Obese women (100)	16–60	12 weeks	1200 mg GTE; 377.15 mg EGCG as capsules	Cellulose	SBP = 134.9(16.2)/135.4(20) DBP = 82.9(9.3)/81.6(11.5)	Constipation (3), abd discomfort (2)	Normal diet; caffeine control unspecified	Government
Hsu 2011 [53]	Blood pressure, lipid profile	Obese type 2 diabetics (80)	20–65	16 weeks	1500 mg GTE; 856.8 mg EGCG as capsules	Cellulose	SBP = 147(20.6)/150(17.6) DBP = 88.6(12.7)/87.6(2.7)	Constipation, (2) abd discomfort (2) Hypoglycemia (1)	Isocaloric diet; caffeine intake restricted	Government
Kajimoto 2003 [54]	Blood pressure, lipid profile	Volunteers with ↑d cholesterol (60)	20–60	13 weeks	394.8 mg GTC; 135 mg EGCG as beverage	Cyclodextrin,	SBP = 137.5(20.9)/132.3(17.8) DBP = 81.9(11.8)/79.4(14.9)	None	Normal lifestyle; caffeine intake restricted	Manufacturer
Maki 2009 [55]	Blood pressure, lipid profile	Obese with ↑d cholesterol (132)	21–65	12 weeks	625 mg GTC; 214.4 mg EGCG as beverage	Identical beverage	Not reported	Elevated BP (3), dyspepsia (1) ↑d LFT (1)	Normal lifestyle; caffeine intake restricted	Manufacturer
Matsuyama 2008 [56]	Blood pressure, lipid profile	Overweight and obese children (42)	6–16	24 weeks	600 mg GTC; 172 mg EGCG as beverage	96.3 mg GTC; as beverage	SBP = 124.3(13.3)/120.5(15.7) DBP = 63.2(11)/64.8(11.3)	None-related	Normal lifestyle; caffeine intake restricted	None
Nagao 2007 [57]	Blood pressure, lipid profile	Visceral fat-type obesity (270)	25–55	12 weeks	600 mg GTC; 172 mg EGCG as beverage	96.3 mg GTC; as beverage	SBP = 127(14.8)/128.8(14.3) DBP = 76.9(10.4)/77.9(9.2)	None	Normal lifestyle; no caffeine restriction	None
Nagao 2009 [58]	Blood pressure, lipid profile	Type 2 DM not on insulin (50)	61–67	12 weeks	600 mg GTC; 172 mg EGCG as beverage	96.3 mg GTC; as beverage	SBP = 138(12.5)/135(13.9) DBP = 78.2(8.6)/76.9(11.2)	None	Normal lifestyle; caffeine intake restricted	None
Nantz 2009 [59]	Blood pressure, lipid profile	Healthy males and females (124)	21–70	13 weeks	400 mg GTE; 180 mg EGCG as capsules	Cellulose	SBP = 130(6.9)/129.7(6.2) DBP = 80.2(4.2)/78.3(3.8)	Mild skin rash (2)	Normal lifestyle; caffeine intake restricted	Manufacturer

Sone 2011 [60]	Blood pressure, lipid profile	Healthy males and females (51)	20–70	9 weeks	400 mg GTC with 105 mg caffeine in beverage	100 mg GTC; as beverage	SBP = 123(15)/123(16) DBP = 75(10)/76(10)	Not reported	No consumption of other catechin beverage	Public Institution
Saliburska 2010 [61]	Blood pressure, lipid profile	Obese males and females (46)	30–60	13 weeks	379 mg GTE; 208 mg EGCG as capsule	Cellulose	SBP = 130.7(7)/129.6(7.9) DBP = 85.1(12.5)/84.2(3.3)	None	Isocaloric diet, caffeine control unspecified	Public Institution
Takase 2008 [62]	Blood pressure, lipid profile	Obese females (101)	42–54	12 weeks	540 mg GTC; 201.4 mg EGCG as beverage	Beverage	SBP = 125.2(16)/128(15) DBP = 79(12)/79(11)	None	Normal lifestyle; caffeine intake restricted	None
Takeshita 2008 [63]	Blood pressure, lipid profile	Overweight and obese males (81)	20–65	12 weeks	548 mg GTC in sports drink	GTC-free sport drink	SBP = 130(11)/132(12) DBP = 80(9)/82(9)	None	Normal lifestyle; caffeine intake restricted	None
Widlansky 2007 [64]	Blood pressure, lipid profile	CAD patients (54)	50–68	2 weeks	336 mg GTE; EGCG 300 mg as capsules	Gelatin capsules	SBP = 144(18)/124(31) DBP = 80(9)/72(8)	Mild rash (1)	Caffeine intake restricted	Manufacturer

Abbreviations: CAD: coronary artery disease; GTE: green tea extract; GTC: green tea catechins; EGCG: epigallocatechin-3-gallate; SBP: systolic blood pressure; DBP: diastolic blood pressure.
[a] Unless otherwise stated, blood pressure values have been reported as means with standard deviations (SD). Two studies [48,49] have been reported as one RCT.

study to this plot did not result in a shift of this estimate. A dose-effect plot showed no association between daily EGCG dose and LDL cholesterol reduction ($r = 0.1$; $p = 0.76$); removal of an RCT with the largest dose resulted in a strong correlation being observed ($r = 0.74$; $p < 0.01$). Meta-analyses of manufacturer-funded RCTs and government sponsored trials revealed similar results, MD = −0.2 mmol/l (95% CI: −0.34 to −0.07; $I^2 = 80\%$; $p = 0.003$) and MD = −0.17 mmol/l (95% CI: −0.34 to 0.01; $I^2 = 9\%$; $p = 0.04$) respectively.

Meta-analyses of 17 RCTs (Table 3) failed to show significant differences for HDL cholesterol (MD: −0.01 mmol/l; 95% CI: −0.08 to 0.06; $I^2 = 90\%$; $p = 0.79$) and triglycerides (MD: −0.02 mmol/l; 95% CI: −0.16 to 0.12; $I^2 = 53\%$; $p = 0.79$). Cumulative forest plots showed that the point estimates for these analyses were stabilized after the inclusion of the 10 larger studies, and addition of smaller studies was accompanied with increases in heterogeneity without a shift in the point estimate. Dose-effect plots did not reveal any significant associations between EGCG dosage and changes in HDL cholesterol and triglycerides (data not shown). Meta-analysis of manufacturer-funded RCTs did not reveal any significant difference in HDL cholesterol between groups (MD: −0.04 mmol/l; 95%CI: −0.13 to 0.05; $I^2 = 93\%$; $p = 0.37$); but a significant increase in favour of controls was observed for government sponsored trials (MD: 0.06 mmol/l; 95%CI: 0.01 to 0.11; $I^2 = 0\%$; $p = 0.03$. Meta-analyses of manufacturer- and government-funded RCTs revealed no significant differences in triglyceride between groups: MD: 0.01 mmol/l; 95%CI: −0.10 to 0.13; $I^2 = 18\%$; $p = 0.82$; and MD: −0.04 mmol/l; 95%CI: −0.39 to 0.30; $I^2 = 68\%$; $p = 0.8$ respectively.

Adverse events and attrition

Adverse events were reported in seven RCTs (Table 2), including constipation, elevated blood pressure, and rash. No adverse events were reported in nine RCTs, and four RCTs did not provide information on adverse events. In general, the RCTs reported no significant differences in the frequency of adverse events, but the frequency and severity of events were greater in RCTs where the daily dosages of EGCG exceeded 200 mg (Table 2). In total, 148 drop-outs from 14 RCTs were reported; there were no significant differences in the number of drop-outs between the green tea and control groups. Nine (45%) of the RCTs reported compliance monitoring – this included pill count [46,47,50,59,64] and unused servings or bottles [55–57,60]; the remaining 55% did either nor report compliance, or did not report the method by which such compliance was monitored.

Discussion

Main findings

Based on the results of our meta-analyses which included 20 RCTs and 1536 participants, green tea intake results in significant reductions in systolic blood pressure, total

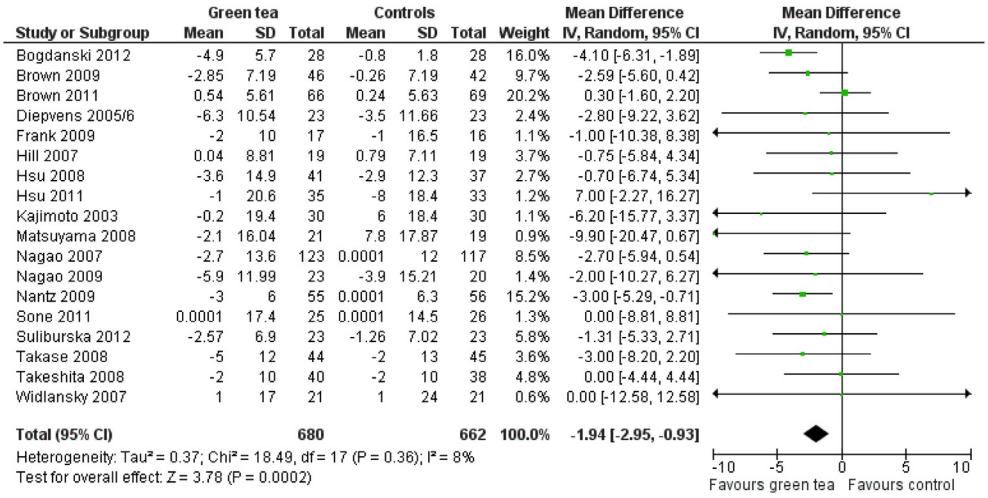

Figure 2 Effect of green tea supplementation on systolic blood pressure (mmHg).

cholesterol, and LDL cholesterol; and effects appear greater with longer duration of intervention. Our results also show that green tea fails to generate significant changes in diastolic blood pressure, HDL cholesterol, and triglycerides. Between-group comparisons by gender revealed that the effect of green tea was significantly greater in males for total cholesterol reduction, and in females for LDL cholesterol reduction; our results also showed that there was a greater effect of green tea on normolipidemics for systolic blood pressure and LDL cholesterol reduction, but greater in dyslipidemics for total cholesterol reduction. The meta-analyses results should be interpreted with caution because of some variation in their designs, and the short durations of interventions. The meta-analytic results contradict those of an earlier systematic review which reported no beneficial effects of green tea on blood pressure [24]. Contrary to that report, our review included at least 15 more studies which were not available in that review. Our results corroborate the results of two previous meta-analyses which reported beneficial effects of green tea on blood lipid profile [26,27]. In contrast to those studies, our review included only double-blinded studies. Our meta-analysis also corroborates the findings of a recent review of studies lasting $\geq$3 months which showed that green tea has beneficial effects on blood pressure and lipid profile [65]. In contrast to that review, our review included an additional seven RCTs, and we also used dose-effect plots to explore the relationship between daily EGCG dose and changes in blood pressure and lipid profile. The observed maximum effect of EGCG on blood pressure at daily dosages of 200 mg support previous research reports indicating that consumption

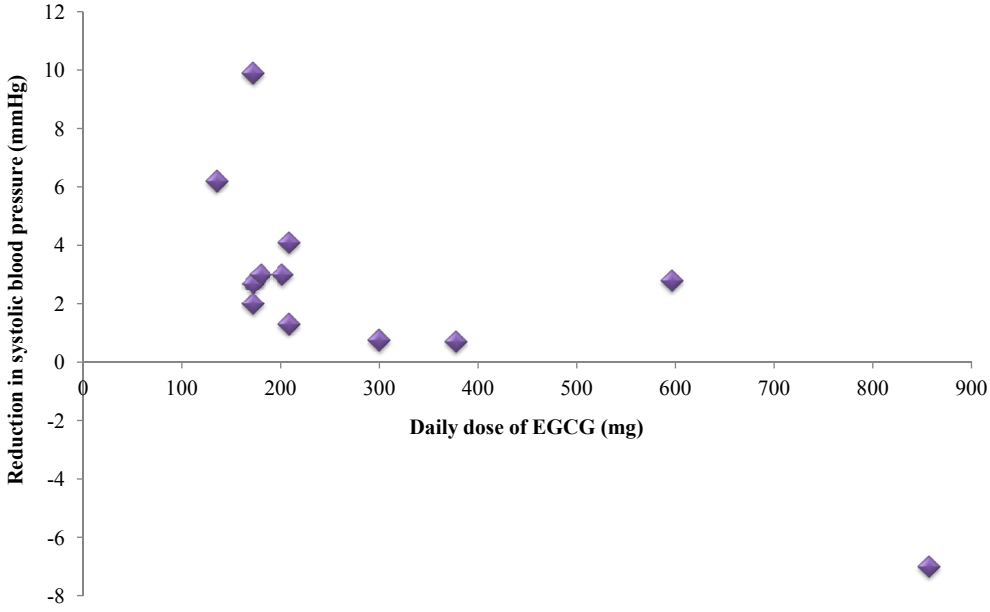

Figure 3 Reduction in systolic blood pressure with different dosages of epigallocatechin-3-gallate (EGCG). The co-efficient of correlation, r was 0.75 ($p = 0.003$). Negative values on the y axis indicate an increase in systolic blood pressure.

Table 3 Results of Meta-analyses of RCTs evaluating the effects of green tea.[a]

Outcome	Overall analyses	Sensitivity analyses	Subgroup analyses
Systolic blood pressure	18 RCTs, $n = 1342$ MD: −1.94 mmHg; 95% CI: −2.95, −0.93; $I^2 = 8\%$; $p = 0.0002$	15 RCTs with adequate blinding ($n = 1202$): MD: −1.46 mmHg; 95% CI: −2.5, −0.43; $I^2 = 0\%$; $p = 0.006$ 13 RCTs lasting ≥12 weeks ($n = 993$): MD: −2.68 mmHg; 95% CI: −3.81, −1.54; $I^2 = 0\%$; $p = <0.00001$ 8 RCTs with green tea as beverage ($n = 647$): MD: −2.17 mmHg; 95% CI: −4.02, −0.32; $I^2 = 0\%$; $p = 0.02$ 10 RCTs with green tea as capsules ($n = 695$): MD: −1.78 mmHg; 95% CI: −3.32, −0.23; $I^2 = 36\%$; $p = 0.02$ 14 RCTs without caloric restriction ($n = 1126$): −1.55 mmHg; 95% CI: −2.61, −0.5; $I^2 = 0\%$; $p = 0.004$ 4 RCTs with caloric restriction ($n = 216$): MD: −1.91 mmHg; 95% CI: −5.22, −1.4; $I^2 = 51\%$; $p = 0.26$	4 RCTs [46,47,50,53] including only men ($n = 334$): MD: −0.48 mmHg; 95% CI: −1.97, 1.01; $I^2 = 0\%$; $p = 0.53$ 4 RCTs [48/9,51,52,62] including only women ($n = 251$): MD: −1.78 mmHg; 95% CI: −4.59, 1.02; $I^2 = 0\%$; $p = 0.21$ Men vs women (8 RCTs [46–53,62]; $n = 585$): MD: −0.76 mmHg; 95% CI: −2.08, 0.55; $I^2 = 0\%$; $p = 0.42$ 14 RCTs [45–52,56,57,59–63] including participants without dyslipidemia ($n = 1129$): MD: −2.01 mmHg; 95% CI: −3.01, −1.00; $I^2 = 8\%$; $p < 0.0001$ 4 RCTs [53,54,58,64] including participants with dyslipidemia ($n = 213$): MD: −0.34 mmHg; 95% CI: −5.94, 5.26; $I^2 = 25\%$; $p = 0.91$ Normolipidemic vs dyslipidemic (18 RCTs [45–54,56–64]; $n = 1342$): −1.94 mmHg; 95% CI: −2.94, −0.95 $I^2 = 0\%$; $p = 0.58$
Diastolic blood pressure	18 RCTs, $n = 1342$ MD: −0.98 mmHg; 95% CI: −2.14, 0.18; $I^2 = 62\%$; $p = 0.1$	15 RCTs with adequate blinding ($n = 1202$): MD: −0.59 mmHg; 95% CI: −1.78, 0.6; $I^2 = 56\%$; $p = 0.33$ 13 RCTs lasting ≥12 weeks ($n = 993$): MD: −1.11 mmHg; 95% CI: −2.61, 0.38; $I^2 = 68\%$; $p = 0.14$ 14 RCTs without caloric restriction ($n = 1126$): −0.62 mmHg; 95% CI: −1.83, 0.58; $I^2 = 59\%$; $p = 0.31$ 4 RCTs with caloric restriction ($n = 216$): MD: −2.85 mmHg; 95% CI: −5.04, −0.66; $I^2 = 22\%$; $p = 0.01$	4 RCTs [46,47,50,53] including only men ($n = 334$): MD: −0.44 mmHg; 95% CI: −2.43, 1.55; $I^2 = 57\%$; $p = 0.66$ 4 RCTs [48/9,51,52,62] including only women ($n = 251$): MD: −0.79 mmHg; 95% CI: −2.73, 1.16; $I^2 = 0\%$; $p = 0.43$ Men vs women (8 RCTs [46–53,62]; $n = 585$): −0.59 mmHg; 95%CI: −1.73, 0.56; $I^2 = 0\%$; $p = 0.81$ 14 RCTs [45–52,56,57,59–63] including participants without dyslipidemia ($n = 1129$): MD: −0.9 mmHg; 95% CI: −2.2, 0.41; $I^2 = 70\%$; $p = 0.18$ 4 RCTs [53,54,58,64] including participants with dyslipidemia ($n = 213$): MD: −1.42 mmHg; 95% CI: −4.08, 1.24; $I^2 = 0\%$; $p = 0.3$ Normolipidemic vs dyslipidemic (18 RCTs [45–54,56–64]; $n = 1342$): −0.98 mmHg; 95% CI: −2.14, 0.18; $I^2 = 0\%$; $p = 0.73$
Total cholesterol	19 RCTs, $n = 1487$ MD: −0.13 mmol/l; 95% CI: −0.2, −0.07; $I^2 = 8\%$; $p < 0.0001$	17 RCTs with adequate blinding ($n = 1385$): MD: −0.12 mmol/l; 95% CI: −0.18, −0.06; $I^2 = 2\%$; $p = 0.0001$ 14 RCTs lasting ≥ 12 weeks ($n = 1149$): MD: −0.16 mmol/l; 95% CI: −0.24, −0.09; $I^2 = 21\%$; $p < 0.0001$ 14 RCTs without caloric restriction ($n = 1205$): MD: −0.12 mmol/l; 95% CI: −0.18, −0.05; $I^2 = 0\%$; $p = 0.0002$ 5 RCTs with caloric restriction ($n = 282$): MD: −0.25 mmol/l; 95% CI: −0.52, 0.02; $I^2 = 54\%$; $p = 0.07$	4 RCTs [46,47,50,53] including only men ($n = 323$): MD: −0.13 mmol/l; 95% CI: −0.25, −0.00; $I^2 = 0\%$; $p = 0.04$ 3 RCTs [48,49,52,62] including only women ($n = 213$): MD: −0.12 mmol/l; 95% CI: −0.29, −0.05; $I^2 = 0\%$; $p = 0.16$ Men vs women (7 RCTs [46–50,52,53,63]; $n = 536$): −0.13 mmol/l; 95% CI: −0.23, −0.03; $I^2 = 0\%$; $p = 0.94$ 13 RCTs [45–50,52,56,57,59–63] including participants without dyslipidemia ($n = 1080$): MD: −0.12 mmol/l; 95% CI: −0.19, −0.05; $I^2 = 9\%$; $p = 0.0008$ 6 RCTs [44,53–55,58,64] with dyslipidemia or type 2 DM ($n = 407$): MD: −0.17 mmol/l; 95% CI: −0.31, −0.03; $I^2 = 16\%$; $p = 0.02$ Normolipidemic vs dyslipidemic (19 RCTs [45–64]; $n = 1487$): −0.13 mmol/l; 95% CI: −0.20, −0.07; $I^2 = 0\%$; $p = 0.57$
LDL cholesterol	17 RCTs, $n = 1422$ MD: −0.19 mmol/l; 95% CI: −0.3, −0.09; $I^2 = 70\%$; $p = 0.0004$	15 RCTs with adequate blinding ($n = 1320$): MD: −0.14 mmol/l; 95% CI: −0.23, −0.05; $I^2 = 2\%$; $p = 0.002$ 13 RCTs lasting ≥ 12 weeks ($n = 1106$): MD: −0.25 mmol/l; 95% CI: −0.37, −0.12; $I^2 = 73\%$; $p < 0.0001$ 12 RCTs without caloric restriction ($n = 1140$): MD: −0.15 mmol/l; 95% CI: −0.25, −0.04; $I^2 = 66\%$; $p = 0.005$ 5 RCTs with caloric restriction ($n = 282$): MD: −0.36 mmol/l; 95% CI: −0.7, 0.01; $I^2 = 78\%$; $p = 0.04$	3 RCTs [46,47,63] including only men ($n = 301$): MD: −0.19 mmol/l; 95% CI: −0.51, 0.14; $I^2 = 89\%$; $p = 0.26$ 3 RCTs [48/9,52,62] including only women ($n = 213$): MD: −0.40 mmol/l; 95% CI: −0.96, −0.16; $I^2 = 91\%$; $p = 0.16$ Men vs women (6 RCTs [46–49,52,62,63]; $n = 514$): −0.28 mmol/l; 95% CI: −0.53, −0.02; $I^2 = 0\%$; $p = 0.52$ 11 RCTs [45–49,52,56,59–63] including participants without dyslipidemia ($n = 818$): MD: −0.24 mmol/l; 95% CI: −0.39, −0.08; $I^2 = 78\%$; $p < 0.00001$

(*continued on next page*)

Table 3 (*continued*)

Outcome	Overall analyses	Sensitivity analyses	Subgroup analyses
			6 RCTs [44,53–55,58,64] with dyslipidemia or type 2 DM (n = 475): MD: −0.12 mmol/l; 95% CI: −0.23, −0.01; I^2 = 25%; p = 0.03 Normolipidemic vs dyslipidemic (17 RCTs [44–49,52–56,58–64]; n = 1422): MD: −0.19 mmol/l; 95% CI: −0.30, −0.09 I^2 = 5.4%; p = 0.3
HDL cholesterol	17 RCTs, n = 1344 MD: −0.01 mmol/l; 95% CI: −0.08, 0.06; I^2 = 90%; p = 0.79	15 RCTs with adequate blinding (n = 1320): MD: −0.01 mmol/l; 95% CI: −0.09, 0.06; I^2 = 91%; p = 0.73 13 RCTs lasting ≥12 weeks (n = 1017): MD: −0.01 mmol/l; 95% CI: −0.11, 0.08; I^2 = 92%; p = 0.77 12 RCTs without caloric restriction (n = 1051): MD: −0.03 mmol/l; 95% CI: −0.11, 0.06; I^2 = 92%; p = 0.56 5 RCTs with caloric restriction (n = 282): MD: 0.04 mmol/l; 95% CI: −0.03, 0.11; I^2 = 37%; p = 0.26	4 RCTs [46,47,50,53] including only men (n = 323): MD: −0.02 mmol/l; 95% CI: −0.05, 0.02; I^2 = 0%; p = 0.34 3 RCTs [48,49,52,62] including only women (n = 213): MD: 0.01 mmol/l; 95% CI: −0.05, 0.07; I^2 = 9%; p = 0.71 Men vs women (7 RCTs [46–50,52,53,63]; n = 536): −0.01 mmol/l; 95% CI: −0.04, 0.02; I^2 = 0%; p = 0.41 12 RCTs [45–50,52,56,57,60–63] including participants without dyslipidemia (n = 969): MD: 0.0 mmol/l; 95% CI: −0.2, 0.3; I^2 = 23%; p = 0.77 5 RCTs [44,53–55,64] with dyslipidemia or type 2 DM (n = 364): MD: −0.07 mmol/l; 95% CI: −0.29, −0.15; I^2 = 95%; p = 0.56 Normolipidemic vs dyslipidemic (17 RCTs [44–50,52–57,60–64]; n = 1344): MD: −0.01 mmol/l; 95% CI: −0.08, 0.06; I^2 = 0%; p = 0.54
Triglycerides	17 RCTs, n = 1354 MD: −0.02 mmol/l; 95% CI: −0.16, 0.12; I^2 = 53%; p = 0.79	15 RCTs with adequate blinding (n = 1252): MD: 0.03 mmol/l; 95% CI: −0.11, 0.17; I^2 = 39%; p = 0.65 13 RCTs lasting ≥12 weeks (n = 1038): MD: −0.08 mmol/l; 95% CI: −0.24, 0.07; I^2 = 49%; p = 0.31 12 RCTs without caloric restriction (n = 1072): MD: 0.07 mmol/l; 95% CI: −0.08, 0.22; I^2 = 35%; p = 0.33 5 RCTs with caloric restriction (n = 282): MD: 0.27 mmol/l; 95% CI: −0.41, −0.14; I^2 = 0%; p < 0.0001	3 RCTs [46,47,63] including only men (n = 301): MD: 0.14 mmol/l; 95% CI: −0.03, 0.30; I^2 = 0%; p = 0.1 3 RCTs [48,49,52,62] including only women (n = 213): MD: 0.09 mmol/l; 95% CI: −0.34, 0.52; I^2 = 55%; p = 0.68 Men vs women (6 RCTs [46–49,52,62,63]; n = 514): MD: 0.10 mmol/l; 95% CI: −0.07, 0.27; I^2 = 0%; p = 0.84 11 RCTs [45–50,56,57,60–63] including participants without dyslipidemia (n = 947): MD: 0.1 mmol/l; 95% CI: −0.16, 0.18; I^2 = 65%; p = 0.87 6 RCTs [44,53–55,58,64] with dyslipidemia or type 2 DM (n = 407): MD: −0.19 mmol/l; 95% CI: −0.38, −0.00; I^2 = 0%; p = 0.05 Normolipidemic vs dyslipidemic (17 RCTs [44–50,52–57,60–64]; n = 1354): MD: −0.02 mmol/l; 95% CI: −0.16, 0.12; I^2 = 0%; p = 0.73

[a] Participants were included in the analyses irrespective of cardiovascular status; the mean differences represent the difference in treatment effect between the green tea and control groups. Two studies [48,49] have been reported as one RCT.

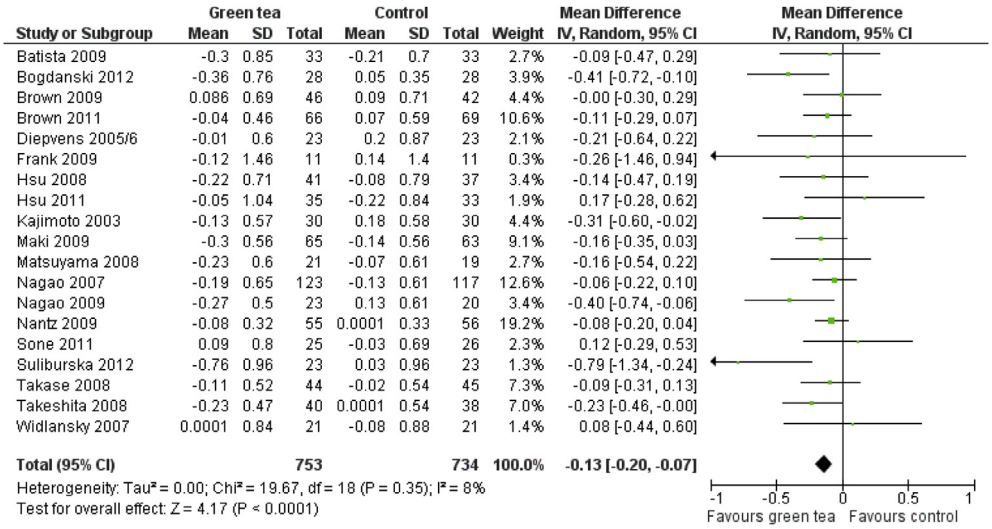

Figure 4 Effect of green tea supplementation of total cholesterol (mmol/l).

5–6 cups of green tea daily may be beneficial for blood pressure and lipid profile [23].

The effect of green tea on blood pressure could occur through several different possible mechanisms. Besides decreasing the actions of ACE and NADPH oxidase, animal and human studies have shown that EGCG decreases the concentrations of kallikrein and prostaglandin E_2 [66,67]; actions which can lead to reductions in blood pressure [68,69]. Green tea also contains gamma-aminobutyric acid (GABA) which may decrease blood pressure by modulating neurotransmitter release [70,71]. Indeed, consumption of food enriched with GABA resulted in significant reductions in blood pressure in mildly hypertensive patients [72]. Aside the free radical scavenging properties of green tea polyphenols, animal studies have shown that flavan-3-ols which are abundant in green tea modulate endothelial function by reducing monocyte adhesion [73], and dietary intake of flavan-3-ols in humans has been reported to be inversely associated with the risk of high blood pressure [74]. Our meta-analyses results suggested significant reductions in systolic blood pressure. Though the effect size was small, statistical heterogeneity amongst the RCTs was low, and thus, such reductions could be clinically relevant particularly for longer term management of hypertension. However, the discrepancies in the direction of study results when manufacturer-funded trials were compared with government-sponsored studies requires further investigation. A significant reduction in diastolic blood pressure with low heterogeneity was also observed in subgroup analysis of RCTs in which caloric intake was restricted (as opposed to a non-significant difference with high heterogeneity in the overall meta-analysis), indicating that lifestyle modification may play in role in blood pressure control in addition to green tea consumption.

The effects of green tea on the blood lipid profile were consistent with those of previous reports [26,27,65]. The

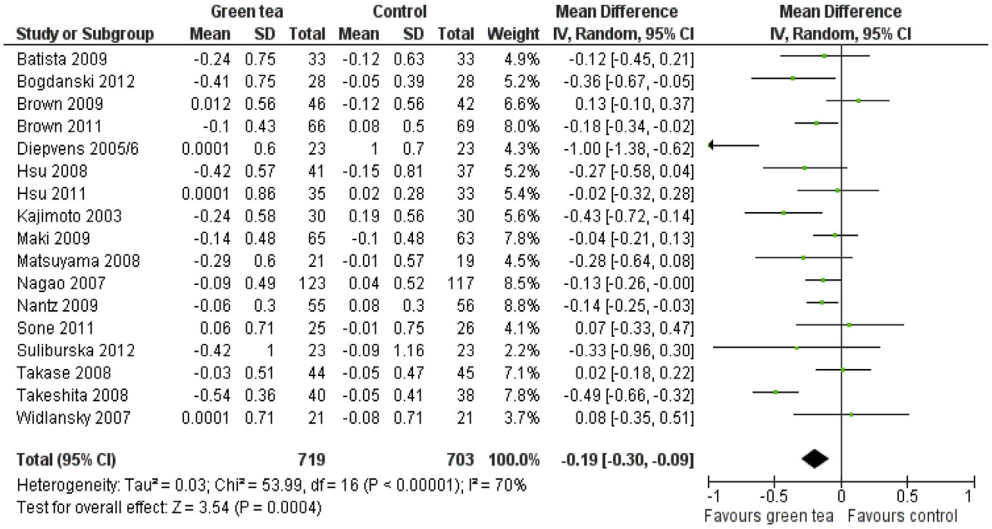

Figure 5 Effect of green tea supplementation on LDL cholesterol (mmol/l).

high statistical heterogeneity observed in the analyses for LDL and HDL cholesterol may have been due to variations in the types of participants in the individual RCTs. The reduction in heterogeneity observed with HDL cholesterol and triglycerides when studies were analyzed based on caloric restrictions suggests that differences in lifestyle adjustments across the RCTs may have contributed to the heterogeneity observed in some of the analyses; small sample sizes in some of the studies could also have caused high heterogeneity observed in some of the meta-analytic results. However, the sensitivity and subgroup analyses revealed a similar trend in the direction of the results. Though the effect sizes for total and LDL cholesterol are moderate and are of limited clinical significance, they suggest that green tea extracts could be of some benefit in the control of cholesterol levels; this is especially so considering the fact that the reductions achieved were generally observed within 12 weeks.

Adverse events were observed in some participants who received green tea extracts. Of particular note was an elevation in blood pressure which was observed in three patients consuming green tea in one RCT [55]. The investigators in this RCT concluded that the increased blood pressure was probably related to the green tea. Whether this was associated with additional caffeine in the green tea extract in a susceptible group of participants is unclear, and requires further research. Severe adverse events were observed in RCTs included in our review where the daily intake of EGCG exceeded 200 mg; this suggests that long term consumption of green tea above this limit may be associated with risks. Concerns have been raised about possible hepatotoxic effects of green tea extracts [75]. Animal and *in vitro* studies have shown that there could be an increased risk of adverse events when concentrated green tea is consumed on an empty stomach [76–78], and a systematic review of 34 case reports also suggested a possible link between green tea consumption and risk of liver damage [79]. Contrary to this, however, *in vivo* studies have shown that green tea consumption could be hepatoprotective [80,81], and results of pharmacokinetic studies in humans have demonstrated that green tea consumption is quite safe [82].

Strengths and limitations

The results of our meta-analyses showed low overall statistical heterogeneity across the included RCTs, and most of our sensitivity and subgroup analyses were also consistent with our overall analyses for the outcome variables. However, we recognize several limitations. Though we employed a robust search strategy, we may not have identified all RCTs evaluating the effects of green tea on blood pressure and lipid profile. We could not perform a subgroup analysis of hypertensive patients due to paucity of RCTs. The variations between trials in whether concurrent tea and caffeine ingestion was controlled for, and the differences in additional lifestyle adjustments between RCTs could have blunted the true effect of green tea consumption. Furthermore, the variations in the study designs could have influenced the direction of study results, and the median study duration of 12 weeks prevents us from making from conclusions about the effectiveness and safety of green tea extracts on the long-term.

Implications for research

Well conducted clinical trials with longer durations of intervention evaluating the effects of green tea supplements on blood pressure and lipid profile are warranted. Because of subtle differences in the effects seen on blood pressure and lipid profile between manufacturer- and government-funded studies, more independent clinical trials which are adequately powered to detect such effects are required. Longer-term surveillance for adverse events is also advocated to allow for a more robust evaluation of its safety.

Implications for practice

There is some evidence that daily consumption of 5–6 cups of green tea could result in reductions in systolic blood pressure, total cholesterol, and LDL cholesterol. However, at this time green tea should not be recommended as a substitute for current management of patients with established hypertension or dyslipidaemia. Green tea appears to be well tolerated, but consumption in high doses may be associated with adverse events. Therefore, excessive consumption of green tea products should be discouraged.

Conclusion

The available evidence from RCTs suggests that dietary supplementation with green tea generates significant reductions on systolic blood pressure, total and LDL cholesterol. The effect size on systolic blood pressure is small, but the sizes of the effects on total and LDL cholesterol appear moderate. Longer-term independent clinical trials evaluating the effects of green tea are warranted.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.numecd.2014.01.016.

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