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Review

Effectiveness of black tea versus placebo in subjects with hypercholesterolemia: A PRISMA systematic review and meta-analysis

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ABSTRACT

Aim: To determine if the black tea is more effective in serum lipid profile that placebo in subjects with hypercholesterolemia.
Design: Systematic review with meta-analysis of randomized clinical trials (RCTs).
Data sources: The databases Medline, Central, Embase, Lilacs, Cinahl, SPORTDiscus, and Web of Science were searched from inception up to January 2019.
Eligibility criteria for selecting studies: RCTs that compared black tea versus placebo, that included serum lipid profile outcomes in subjects older than 18 years of age with hypercholesterolemia.
Results: Seven RCTs met the eligibility criteria, and for the quantitative synthesis, six studies were included. Mean difference for total cholesterol was 1.67 mg/dl 95% CI = −5.47 to 8.80 (p = 0.65), mean difference 0.28 mg/dl, 95% CI = −3.89 to 4.45 (p = 0.90) for triglycerides, mean difference 3.21 mg/dl, 95% CI = −11.02 to 4.60 (p = 0.42) for low density lipoprotein-cholesterol, mean difference 0.38 mg/dl, 95% CI = −1.12 to 1.87 (p = 0.62) for high density lipoprotein-cholesterol.
Conclusion: In the short term, no significant differences were found in lipid serum profile comparing black tea consumption with placebo.

1. Introduction

Hypercholesterolemia (HC) is a common metabolic condition and is characterized by a high level of plasma cholesterol, being a risk factor of development for cardiovascular diseases [1–3]. Currently, cardiovascular diseases is responsible for 17.3 million death every year and remains the primary global death cause [4,5]. Low high-density lipoprotein-cholesterol (HDL-C) concentrations, high total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) concentrations are the major risk factors of cardiovascular diseases [5–7]. Also, the combination of risk factors like genetics, age, sedentary lifestyle, and unhealthy diet contribute to elevated levels of TC and LDL-C [1,8]. For prevention of cardiovascular diseases, the modification of serum cholesterol profile remains the most important method, and it was estimated that for every 1% reduction in total cholesterol concentration, decreased an average of 2% of cardiovascular diseases, and 1 mg/dl reduction of LDL-C concentration can reduce coronary artery disease risk by 1% [9].

Current approaches treatments in reducing blood LDL-C and TC, espouse inhibiting cholesterol synthesis and blocking the absorption of dietary cholesterol [10–12]. The first step towards reducing LDL-C concentrations in subjects with HC is lifestyle modification, including physical activity and healthy diet [13–15]. However, when lifestyle changes are not effective, drug therapy with statins is recommended first-line [12,16].

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The flavonoids are natural polyphenolic compounds extracted from plants like green tea or black tea (BTE) and have antioxidant properties that inhibit the intestinal absorption of cholesterol [1,17–20], likewise BTE is a rich source of polyphenols, and can be a major contributor to total polyphenol intake in the human diet [21,22].

Some previous studies in animals models showed the antioxidant effectiveness of flavonoids in cholesterol [23–25]. Based on these findings, some experimental studies have supported the use of flavonoids like BTE in subjects with HC [1,19,26–29]. However, despite the results of previous studies, systematic review have not been consistent in the results on the effectiveness of BTE in cholesterol [30–32]. Hartley et al. [30] showed limited evidence of effectiveness of tea on cardiovascular diseases risk factors. However, the small number of clinical trials included in their systematic review, makes that the analysis of the results should be interpreted with caution. Zhao et al. [31] showed that the consumption of BTE significantly decreased only the serum concentrations in LDL-C, without significant effects in the other serum concentrations, only including three RCTs. Wang et al. [32] showed that the consumption of BTE might not have beneficial effects on serum concentrations of TC, HDL-C, LDL-C, however, the low quality and small number of studies in subjects with hypercholesterolemia make it difficult to extrapolate the results. Therefore, we performed this meta-analysis to further assess the effectiveness of BTE on serum concentrations in specific population with hypercholesterolemia based on the PRISMA guidelines. The objective of this systematic review with meta-analysis was to determine if the BTE is more effective that placebo for lipid serum profile in subjects with hypercholesterolemia.

2. Methods

2.1. Protocol and registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and followed the recommendations of the Cochrane Colaboration Handbook [33–35]. The register number in the International Prospective Register of Systematic Review (PROSPERO) CRD42018107160.

2.2. Eligibility criteria

Studies were regarded eligible for inclusion if the following criteria were fulfilled. (1) Population: subjects older than 18 years of age with medical diagnosis of hypercholesterolemia (HC) or high cholesterol; (2) Type of intervention: BTE consumption can include types such as, beverage, capsules and extract or infusions BTE. (3) Type of comparison: placebo (4) Types of outcomes: assessment of lipid profile with parameters such as total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and High density lipoprotein (HDL) (5) Types of studies: randomized clinical trials (RCTs), controlled clinical trials (CCTs) or Cross over trials, published in English and Spanish. Exclusion criteria were as follows: (1) studies that involving subjects with other pathologies conditions such as metabolic syndrome, diabetes mellitus, hypertension non controlled, etc. (2) Subjects female with pregnant and (3) smokers or alcohol drinkers were not considered. (4) Subjects with cancer and not taking prescription medication that could interfere with lipid metabolism.

2.3. Electronic search

We carried out a search of six electronic databases for studies published from inception until the search date (last search January 2019): MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, the Latin American and the Caribbean Literature in Health Sciences (LILACS), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science.

The search strategy used included a combination of the following Medical Subjects Headings (MeSH) terms: “Hypercholesterolemia”; “Hyperlipidemia”; “Tea”; “*Camellia sinensis*”. With the free-text terms: “High cholesterol”; “elevated cholesterol”; black tea”; “black tea extracts”; “infusions black tea”. For the search in the Medline, Central, and Embase databases, the Cochrane Highly Sensitive Search Strategies for identifying randomized trials was used [22]. We also manually searched the references of selective articles to identify additional potentially relevant studies. The literature search was independently conducted by three reviewers (FA-Q, HG-E, and VM-G), and disagreements were solved by consensus or involving a four research (MJ-M).

2.4. Study selection

Three authors (FA-Q, HG-E and VM-G) independently screened the titles and abstracts of references retrieved from searches. We obtained the full text for references that either author considered potentially relevant. Disagreements were resolved by consensus or by consultation with a fourth author (MJ-M).

2.5. Data collection process

Three authors (FA-Q, HG-E, and VM-G) used a standardized form to independently extract data on outcomes for each trial. The following data were extracted from the original reports: i) author's and year of publication; ii) country; iii) sample characteristics (sample size, age distribution, and sex); iv) characteristics of black tea; v) characteristics of placebo; vi) length of follow-up and mail outcomes, and vii) main results.

2.6. Risk of bias of individual studies

Assessment of risk of bias of individual studies was performed as recommended by the Cochrane Collaboration Handbook [35]. This tool evaluates the risk of bias according to seven domains: Generation of the random sequence; concealment of the randomization sequence; blinding of participants and treatments; blinding of the evaluation of the results; incomplete results data; selective reporting of results and other biases. Each domain could be considered as low risk of bias, unclear risk of bias) or high risk of bias. Data extraction and quality assessment were independently performed by three reviewers (FA-Q, HG-E, and VM-G), and inconsistencies were solved by consensus or involving a four researcher (MJ-M). The agreement rate between reviewers was calculated using kappa statistics.

2.7. Statistical methods

The DerSimonian and Laird random effects of Mantel-Haenszel fixed effects methods were used [36], depending on the heterogeneity, to compute a pooled estimate of mean difference (MD) or standardized mean difference (SMD), and respective 95% confidence intervals (CI) for TC, HDL, LDL and TG. The heterogeneity of results across studies was evaluated using the I2 statistic, which are considered as: might not be important (0%–40%), may represent moderate (30%–60%), may represent substantial (50%–90%) and considerable (75%–100%) heterogeneity [35]. Also, the corresponding p-values were considered. Meta-analysis were performed in RevMan 5.3 program.

3. Results

3.1. Study selection

A total of 128 studies were found through the electronic searching. Finally, seven studies met our eligibility criteria, and were included in the systematic review [1,22,26,28,29,37,38]. The detailed steps of the articles selection process for the systematic review are described as a flow diagram in Fig. 1.

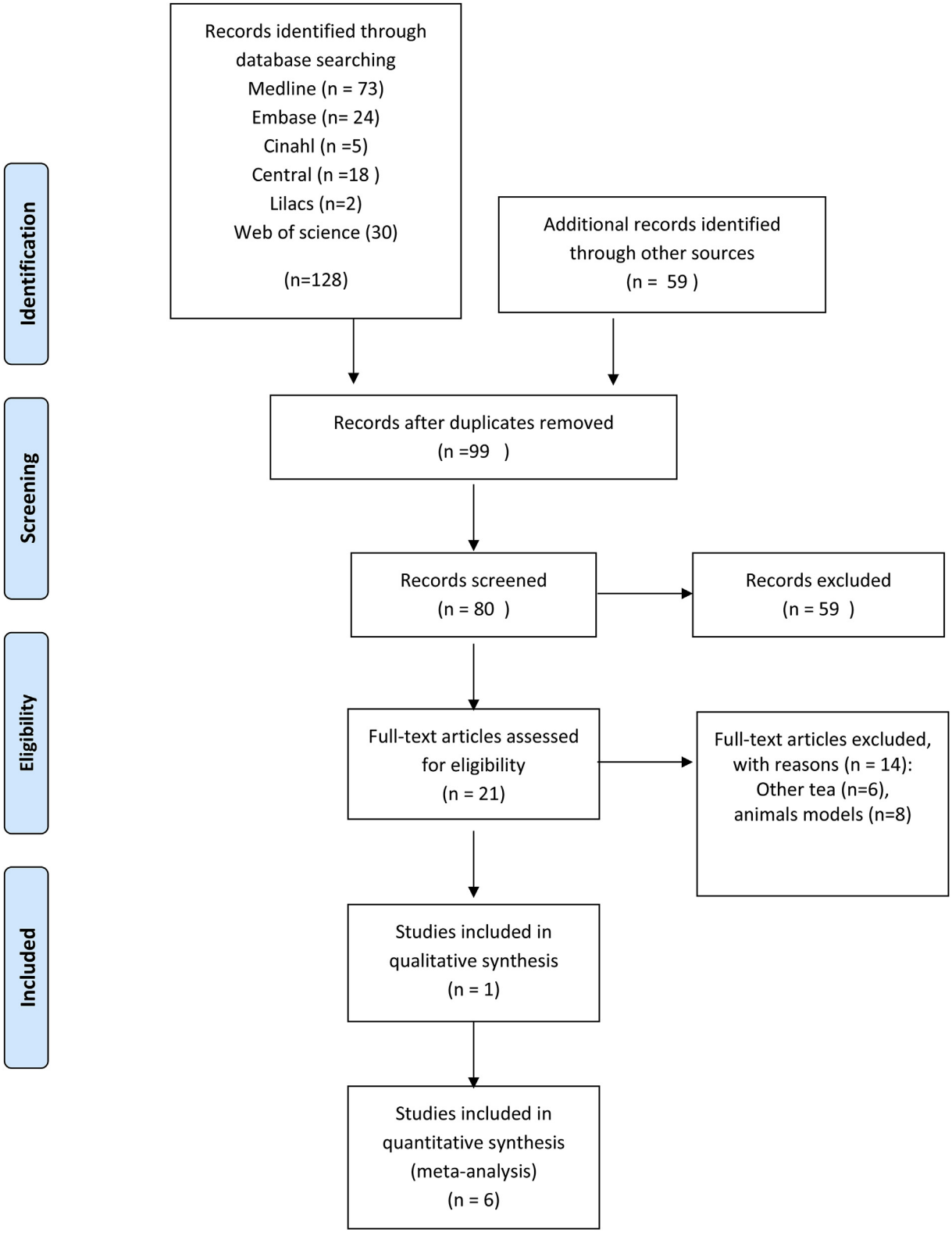

Fig. 1. Flow chart diagram.

Table 1
Characteristics of the studies included in the systematic review and meta-analyses of the effects of Black tea versus placebo in patients with hypercholesterolemia.

First author/year	Country	Population/Age Mean (SD)	Gender (%)	Black Tea (BT)	Dose	Placebo(P)	Dose	Follow-up/Outcomes	Results between groups
Troup 2015 (26)	USA	n = 57 patients BT: 51.7 years (5.1) TP: 53.2 years (4.9)	BT: 14 females (46.7) 16 males (53.5) TP: 40.7 females (11) 59.3 males (16)	n = 30 patients The intake of cups of black tea from the Lipton Tea Company, plus a provided, low-flavonoid diet (15% protein, 51% carbohydrate and 34% fat)	Two periods of 4 weeks taking 5 cups of BT per day, and a wash-out period between the treatment periods	n = 27 patients The intake of cups of tea-like placebo from the Lipton Tea Company, plus a provided, low-flavonoid diet	Two periods of 4 weeks taking 5 cups per day of tea-like placebo, and a wash-out period between the treatment periods	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p = 0.20 - LDL: p = 0.70 - HDL: p = 0.30 - TG: p = 0.10
Trautwein 2010 (29)	China	n = 102 patients TFs: 47.54 years (6.70) TFs/C : 50.07 years (3.58) P: 46.85 years 7.07)	TFs: 13 females (36.1) 23 males (63.9) TFs/C: 11 females (35.5) 20 males (64.5) P: 11 females (31.4) 24 males (68.6)	TFs n = 36 patients The intake of capsules with TFs prepared at GMP-certificaded ISP Laboratory TFs/C n = 31 patients The intake of capsules with TFs/C prepared at GMP-certificaded ISP Laboratory	9-day run-in period and 11-week intervention period taking one capsule daily directly after the dinner meal (TFs capsules contained 77.5 mg of this component, and TFs/C contained 75 mg of TFs and 149.4 mg of catechins)	n = 35 patients The intake of capsules with Placebo prepared at GMP-certificaded ISP Laboratory	9-day run-in period and 11-week intervention period taking one capsule daily directly after the dinner meal (capsules contained 320 mg of only cellulose)	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p = 0.11 - LDL: p = 0.17 - HDL: p = 0.88 - TG: p = 0.79
Fujita 2008 (38)	Japan	n = 47 patients BTE: 62.7 years (1.4) P: 62.9 years (2.1)	BTE: 44 males (11) 56 females (14) P: 10 males (45.45) 12 females (54.54)	n = 25 patients The intake of BTE tablets as a dietary suplement	2 tablets (with 166.5 mg of BTE) 3 times daily before meals for 3 months	n = 22 patients The intake of P tablets as a dietary suplement	2 tablets (with 66.6% of dextrin) 3 times daily before meals for 3 months	1 month follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p = 0.05* - LDL: p = 0.05* - HDL: p > 0.05 - TG: p = 0.05*
Davies 2003 (22)	USA	n = 15 patients BT: 53.9 years (2.4) P: 53.9 years (2.4)	BT: 7 males (46.7) 8 females (53.3) P: 7 males (46.7) 8 females (53.3)	n = 15 patiens The intake of servings per day of black tea from Unilever Bestfoods NA, plus a NCEP Step I-type diet (58% carbohydrates, 26% fat and 16% protein)	2 weeks run-in period taking 5 servings of BT per day in 180 ml of water, followed of three periods of treatment of 1 week. Between each treatment period, there was a wash-out period of 4 weeks	n = 15 patients The intake of servings per day of Placebo from Unilever Bestfoods NA, plus a NCEP Step I-type diet	2 weeks run-in period 5 servings of P per day in 180 ml of water, followed of three periods of treatment of 1 week. Between each treatment period, there was a wash-out period of 4 weeks	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p = 0.05* - LDL: p = 0.01* - HDL: p > 0.05 - TG: p > 0.05
Hodgson 2002 (37)	Australia	n = 21 patients BT: 60.9 years (1.7) HW: 57.5 years (2.8)	BT: 7 males (70) 3 females (30) HW: 9 males (81.82) 2 females (18.18)	n = 10 patiens The intake of cups of black tea from Tea Trade Health Research Association of Canada	4-week intervention period taking 5 cups per day of 2 g of black tea with 250 ml of hot water proceeded by a 4-week baseline period (taking 5 cups per day of 250 ml of hot water)	n = 11 patiens The intake of cups of hot water	4-week intervention period taking 5 cups per day of 250 ml of hot water proceeded by a 4-week baseline period (taking 5 cups per day of 250 ml of hot water)	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p > 0.05 - LDL: p > 0.05 - HDL: p > 0.05 - TG: p > 0.05

(*continued on next page*)

Table 1 (*continued*)

First author/year	Country	Population/Age Mean (SD)	Gender (%)	Black Tea (BT)	Dose	Placebo(P)	Dose	Follow-up/Outcomes	Results between groups
Orem 2017 (1)	Turquía	n = 99 patients P: 41 years (11) IBT: 41 years (10) FBT: 42 years (12)	P: 23 males (69.7) 10 females (30.3) IBT: 25 males (73.5) 9 females (26.5) FBT: 24 males (75) 8 females (25)	IBT = 34 patients The intake of samples of IBT in powder form prepared by the food institute of TUBITAK Marmara Research Center FBT = 32 patients The intake of two samples of FBT in powder form prepared by the food institute of TUBITAK Marmara Research Center	A washout period from tea for 2 weeks followed by 4 weeks intervention period taking two samples per day of IBT/FBT in 250 ml of hot water (FBT contained 2.5 g of black tea and 1 g of phytosterol mixture)	n = 33 patients The intake of samples of P in powder form prepared by the food institute of TUBITAK Marmara Research Center	A washout period from tea for 2 weeks followed by 4 weeks intervention period taking two samples per day of P in 250 ml of hot water	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p = 0.03* - LDL: p = 0.007* - HDL: p = 0.83 - TG: p = 0.43
Jensen 2016 (28)	USA	n = 59 patients PTE: 52 years (8) males, 57 years (9) females P: 55 (11) years males, 55 (10) years females	PTE: 10 males (33.3) 20 females (66.7) P: 10 males (34.5) 19 females (65.5)	n = 30 patients The intake of samples of PTE in powder form prepared by Tasly Pharmaceuticals Inc	20 weeks intervention period taking two samples per day of 1.5 g of PTE in 250 ml of hot water, with visits every 4 weeks	n = 29 patients The intake of samples of P in powder form prepared by Tasly Pharmaceuticals Inc	20 weeks intervention period taking two samples per day of P in 250 ml of hot water, with visits every 4 weeks	Not follow-up Outcomes: - TC - LDL - HDL - TG	At end of treatment: - TC: p > 0.05 - LDL: p > 0.05 - HDL: p > 0.05 - TG: p > 0.05

BTE: Black tea; **TP:** Tea-like placebo; **TFs:** Tea theaflavins; **TFs/C:** Tea theaflavins with catechins; **P:** Placebo; **NCEP:** National Cholesterol Education Program; **HW:** Hot water; **IBT:** Instant black tea; **FBT:** Functional black tea; **TC:** Total cholesterol; **LDL:** Low-density lipoprotein; **HDL:** High-density lipoprotein; **TG:** Triglycerides; **PTE:** Puer tea extract. * = Statistically significant differences.

3.2. Study characteristics

Table 1 summarizes the characteristics of the included studies. The overall population included 415 patients (243 and 172 in BTE and placebo, respectively), with 242 males and 173 females. The mean age was 53.22 years, and mean follow-up was 4 weeks.

In the included studies, the diagnosis of HC was based on hematological values. In six studies, these was confirmed with a fasting blood sample in a mildly range [1,26,28,29,37,38] One study did not indicate specifically how was the inclusion procedure of the subjects [22].

Regarding to the interventions, three studies [22,26,37] used five servings per day of BTE, and in two of these studies added a type of diet [22,26]. One study [26] included low flavonoid diet, and the other study [22] included a diet based in the National Cholesterol Education Program [39]. Two studies used two samples per day of tea in powder form [1,28]. Two studies used tablets of BTE, one using two tablets three times daily [38], and the other using one tablet per day [29].

Regarding to the placebo intervention, two studies used five servings per day of a tea-like placebo plus a specific diet [22,26]. Two studies used two samples per day of placebo in powder form [1,28]. Two studies used placebo capsules, one using two tablets three times daily [38], and the other using one capsule per day [29]. One study used five cups of hot water as placebo [37].

The evaluation of the results was done using two different units of measurement; mmol/L or mg/dl. Three studies used mmol/L [29,37,38]. One of these studies indicated that ranged from 4.65 to 6.72 mmol/L for TC and 2.59–4.14 mmol/L for LDL indicated borderline hypercholesterolemia [38]. The second study, indicates a ranged of 4.80–7.00 mmol/lL for TC, 2.50–4.90 mmol/L to LDL and <4.50 mmol/L for TG [29]. The third study, indicates a range of > or equal to 5.0 mmol/L for TC and > or equal to 1.8 mmol/L for TG [37]. The other four studies used the unit of measure mg/dl [1,22,26,28]. One study indicates a range of TC between 200 and 239 mg/dl [1]. Other study indicates a range of 190–260 mg/dl for TC, 35–65 mg/dl for HDL, and <600 mg/dl for TG [26]. Other study, indicates a range of > or equal to 220 mg/dl for TC [28] and other study just mention they used mildly elevated TC but without indicating the exact value [22]. Howewer, to perform the statistical analysis, values are standardized to international measures of mg/dl [39].

3.3. Risk of bias within studies

As evaluated by the Cochrane Collaboration's tool for assessing risk of bias for all clinical trials, 35.6% of the studies showed a high risk of bias [1,28], 21.6% a medium risk of bias [22,37,38], and 42.8% a low risk of bias [26,29]. When studies were analysed by individual domains, in 25,7% of trials the random sequence generation was unclear. Adequate allocation concealment was observed as unclear risk of bias in 100% of the included trials. Outcome assessors were blinded in 26%, while incomplete outcome data in 40% was observed as low risk of bias in the included trials, and selective reported were reported in 100% was observed as low risk of bias in all trials. (Fig. 2 and Fig. 3).

3.4. Publication bias

Publication bias was not performed due to only seven articles were included in this systematic review and meta-analysis [40].

3.5. Synthesis of results

3.5.1. Total cholesterol (TC)

Six trials reported the details of TC [1,22,26,29,37,38]. The

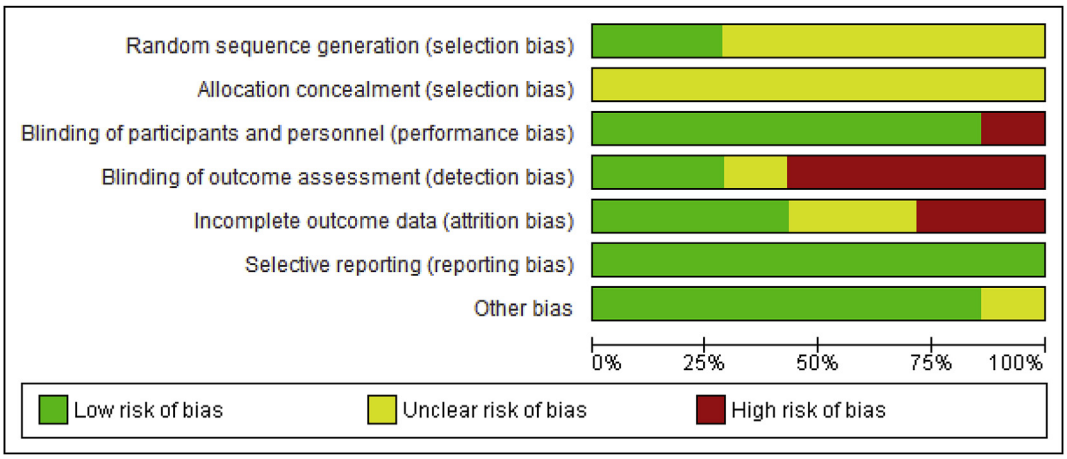

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

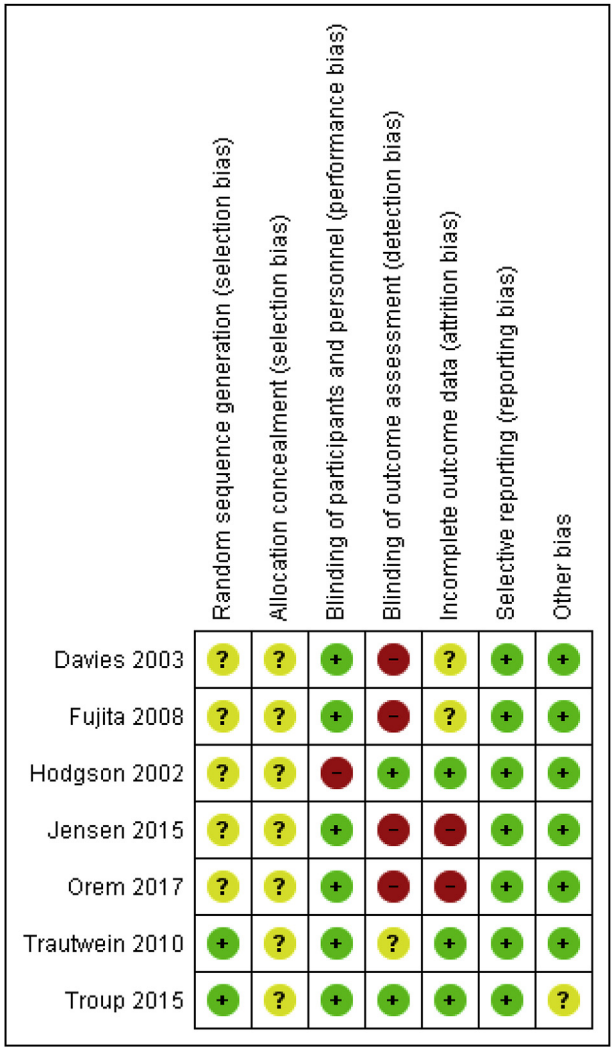

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

pooled results from the meta-analysis showed that no significant difference was found in the level of TC in the BTE group compared with Placebo at the four weeks of treatment, (MD = −1.67 mg/dl, 95% CI = −5.47 to 8.80, P = 0.65 Fig. 4) with a significant heterogeneity (x [2] 74.17, df = 5, I^2 = 100%, p < 0.00001); therefore a random model was performed.

3.5.2. Triglycerides (TG)

Six trials reported the details of TG [1,22,26,29,37,38]. The pooled results from the meta-analysis showed that no significant difference was found in the level of TG in the BTE group compared with Placebo at the four weeks of treatment (MD = 0.28 mg/dl, 95% CI = −3.89 to 4.45, P = 0.90 Fig. 5), with a significant heterogeneity (x [2] 19.60, df = 5, I^2 = 100%, p < 0.0001); therefore a random model was performed.

3.5.3. Low density lipoprotein cholesterol (LDL-C)

Six trials reported the details of LDL-C [1,22,26,29,37,38]. The pooled results from the meta-analysis showed that no significant difference was found in the level of LDL-C in the BTE group compared with Placebo at the four weeks of treatment, (MD = −3.21 mg/dl, 95% CI = −11.02 to 4.60, P = 0.42 Fig. 6) with a significant heterogeneity (x [2] 90.53, df = 5, I^2 = 100%, p < 0.0001); therefore a random model was performed.

3.5.4. High density lipoprotein cholesterol (HDL-C)

Six trials reported the details of HDL-C [1,22,26,29,37,38]. The pooled results from the meta-analysis showed that no significant difference was found in the level of HDL-C in the BTE group compared with Placebo at the four weeks of treatment (MD = 0.38 mg/dl, 95% CI = −1.12 to 1.87, P = 0.62 Fig. 7), with a significant heterogeneity (x [2] 3.07, df = 5, I^2 = 100%, p < 0.0001); therefore a random model was performed.

4. Discussion

The aim of this systematic review was to determine if the BTE is more effective in serum lipid profile that placebo in subjects with hypercholesterolemia. It was found no significant differences in favor of the BTE group, for the lipid serum profile. Our hypothesis that RCTs could show clinically significant effects with BTE has not been confirmed yet and the effectiveness remains unclear.

Three systematic review have studied the effectiveness of BTE for the management of CVD [30–32]. One systematic review concluded that the evidence was limited for cardiovascular diseases [30], other systematic review concluded that black tea has effect in LDL-C [31]. However, the overall meta-analysis of the study were based on the combined populations with different health status,

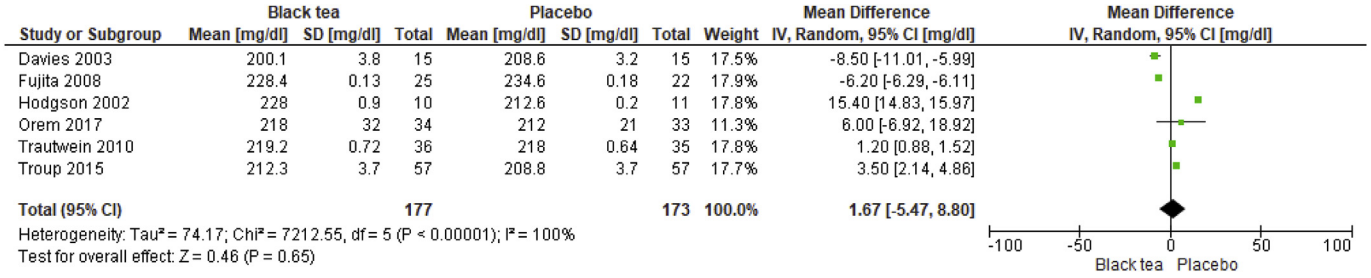

Fig. 4. Comparison black tea versus placebo for total cholesterol (TC) at the four weeks.

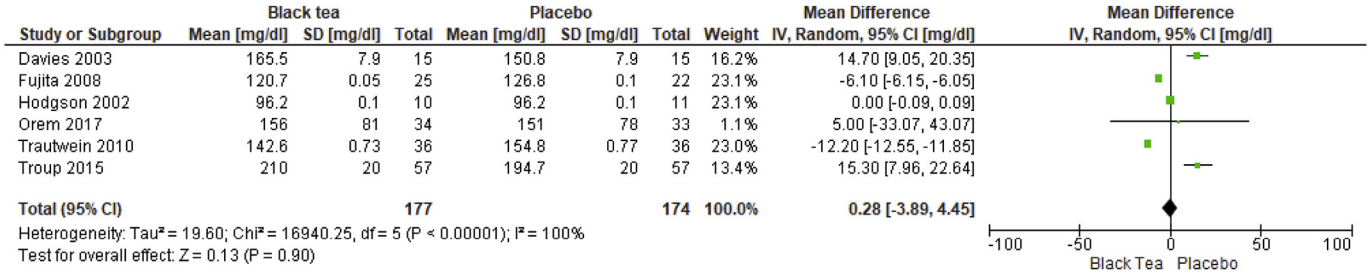

Fig. 5. Comparison Black tea versus placebo for TG at the four weeks.

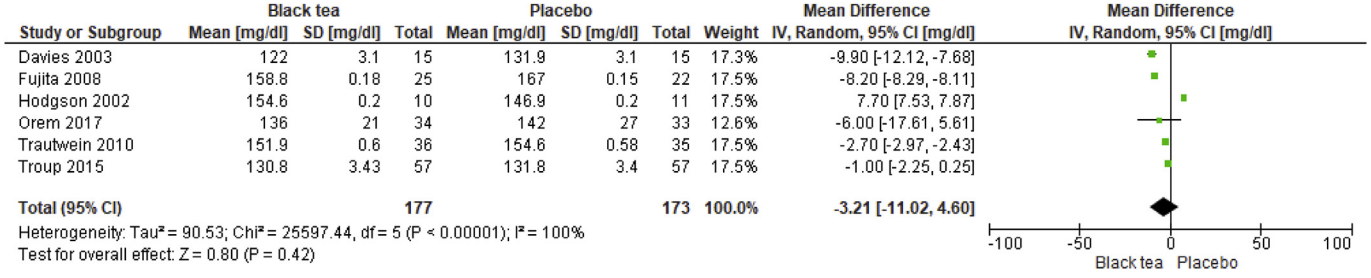

Fig. 6. Comparison black tea versus placebo for LDL-C at the four weeks.

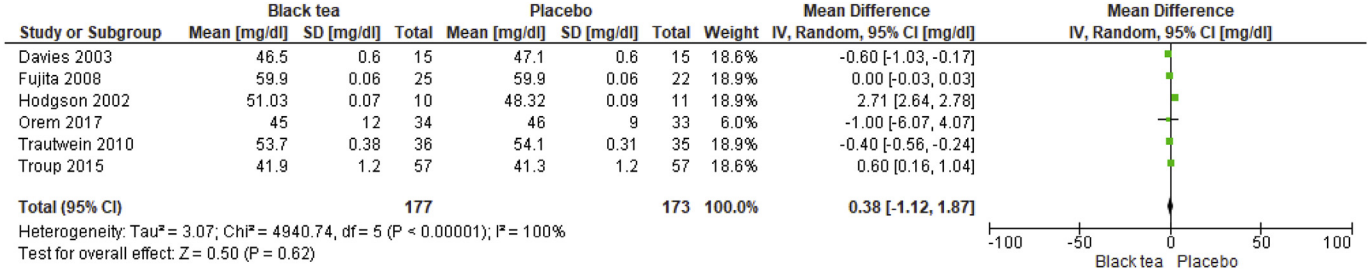

Fig. 7. Comparison Black tea versus placebo for HDL-C at the four weeks.

which might limit the drawing of conclusion about the specific populations, and other systematic review concluded that BTE consumption might not have beneficial effects on concentrations of TC, LDL-C and HDL-C in different health states without subgroup analysis for hypercholesterolemia [32]. Despite this, a previous meta-analysis of observational studies also reported that black tea had substantial protective effect on cardiovascular disease [41], It has been reported that 1 mg/dL reduction of LDL cholesterol concentration can reduce coronary artery disease risk by 1%, therefore a 4.64 mg/dL reduction of serum LDL cholesterol concentration is of both statistical significance and clinical importance [31,42].

Our results can be partly explained because that BTE contains less antioxidant and compounds that green tea [43,44] Additionally, the amount and composition of catechins are substantially various between BTE and green tea due to the different degrees of fermentation. It has been reported that catechins constitute 80%–90% of total green tea flavonoids, whereas they only constitute 20%–30% of black tea flavonoids [45,46]. This is mainly due to the fact that black tea catechins are usually converted to some complex varieties, such as the arubigins and theaflavins during the oxidation process in the manufacture of black tea [46,47]. Some studies suggested that catechins can directly inhibit the biosynthesis of cholesterol by selectively inhibiting the activity of squalene epoxidase and reduce plasma and liver cholesterol concentration

[48–50] Therefore, if catechins represent the greatest beneficial effect of tea, the missing effect of black tea is reasonable. Other reason can be explain our results, is the method of administration of BTE in the RCTs. A previous study has reported that when matched for similar contents of total flavonoids, polyphenols administered in the form of green tea extract showed enhanced bioavailability compared with that of green tea beverage, which led to a small but significant increase in antioxidant capacity [50]. In our systematic review, four RCTs [1,26,28,37] administered the black tea in the form of beverage. Furthermore, tea consumption may be a surrogate marker for lifestyle factors that could be served as confounders, exercise habits, smoking patterns, lower coffee consumption or dietary differences may explain the inconsistent results. In addition, all of the included studies selected participants with TC concentrations lower 240 ml/dl, and included subjects with high concentrations of HDL - C (Higher than 40 mg/dl) [1,22,26,28,29,37,38]. This may also partially explain the null effects of BTE on TC and HDL-C concentrations, because TC and HDL-C concentrations may fluctuate in a certain range in the subjects with normal cholesterol conditions [44].

Regarding to adverse effects of BTE, are primarily due to three main factors: its caffeine content, presence of aluminum, and the effects of tea polyphenols on iron bioavailability[51]. The reported negative effects produced by caffeine present in many tea products are nervousness, restlessness, tremors, palpitations, sleep disorders, vomiting, diarrhea, headaches, epigastric pain and tachycardia. However, the RCTs included in our systematic review, there are no reports of adverse effects in patients with hypercholesterolemia.

4.1. Limitations

The limitations of our study are as follows: (1) in a meta-analysis of published studies, publication bias is an inevitable problem; (2) although we searched six databases and included manual references search, we might have missed articles relevant to our search; (3) a high degree of clinical and statistical heterogeneity existed among the included studies. Potential sources of heterogeneity include variations in the type and dose of the interventions occupied, and the outcomes measured; and (4) In the planning stages, we intend conducted subgroup analyses based on age, type of BTE, gender, and level cholesterol, whereas the results of stratified analysis in the individual trials were not available.

5. Conclusion

In summary, this systematic review and meta-analysis demonstrates that black tea consumption compared with placebo has not significant difference in lipid serum profile in subjects with hypercholesterolemia. Thus, our study is unable to demonstrate the clinical benefits of black tea consumption in these subjects.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.019.

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