

A META-ANÁLISE DOS EFEITOS DO CHÁ VERDE COMBINADO COM ATIVIDADE FÍSICA SOBRE LÍPIDES SANGUÍNEOS EM SERES HUMANOS



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METAANÁLISIS DE LOS EFECTOS DEL TÉ VERDE COMBINADO CON ACTIVIDAD FÍSICA SOBRE LÍPIDOS SANGUÍNEOS EN SERES HUMANOS

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ABSTRACT

Introduction: Most studies of green tea extract (GTE) combined with physical activity have reported a preventative effect for cardiovascular disease; however, the findings regarding the effects on serum lipids are controversial. **Objective:** This meta-analysis aimed to examine the evidence of the effects of GTE combined with physical activity on the serum lipid content in humans. **Methods:** In June 2017, we conducted electronic searches of PubMed, Web of Science, and Cochrane Library to identify pertinent studies: those with an experiment period exceeding two weeks, human randomized controlled trials (RCTs), and those that only assessed GTE with physical activity were included. A random effects model meta-analysis was used in this review. **Results:** A total of 271 citations were retrieved in our search of the electronic literature, and 7 RCTs, which included 608 individuals, were identified. Overall, there was no significant decrease in low-density lipoprotein cholesterol (LDL-C) (SMD: -0.169; 95% confidence interval [CI]: -0.414 to 0.076; $I^2=22.7\%$; $p=0.177$) or total cholesterol (TC) levels between the GTE and placebo combined with the physical activity group. Similar results were also observed for high density-lipoprotein cholesterol (HDL-C) and triglycerides (TG). In the subgroup and sensitivity analyses of the five studies, the TC levels of the subjects who received a lower dose of epigallocatechin gallate (EGCG) together with performing physical activity were significantly decreased. **Conclusion:** Current evidence suggests that green tea combined with physical activity does not improve the lipid and lipoprotein levels in humans. **Level of evidence I; Systematic review.**

Keywords: Green tea; Physical activity; Humans.

RESUMO

Introdução: A maioria dos estudos sobre extrato de chá verde (ECV) em combinação com atividade física relata efeito preventivo em doenças cardiovasculares; entretanto, os achados sobre os efeitos sobre lipídeos séricos são controversos. **Objetivo:** Esta metanálise tem como objetivo examinar as evidências dos efeitos do ECV em combinação com atividade física sobre o teor de lipídeos séricos no ser humano. **Métodos:** Em junho de 2017, realizamos pesquisas eletrônicas nos bancos de dados PubMed, Web of Science e Cochrane Library para identificar estudos pertinentes; foram incluídos os que tinham período experimental superior a duas semanas, estudos clínicos randomizados (ECRs) e que avaliaram apenas ECV com atividade física. Neste trabalho, empregamos o modelo de metanálise de efeitos aleatórios. **Resultados:** Um total de 271 citações foi recuperado em nossa busca, e sete ECRs foram identificados, totalizando 608 indivíduos incluídos. No geral, não houve redução significativa nos níveis da lipoproteína de baixa densidade do colesterol (LDL-C) (DMP: -0,169; 95% de intervalo de confiança [IC]: -0,414 a 0,076; $I^2 = 22,7\%$; $p = 0,177$) ou no colesterol total (CT) entre o ECV e placebo combinados com o Grupo atividade física. Resultados semelhantes foram observados também para a lipoproteína de alta densidade do colesterol (HDL-C) e para os triglicérides (TG). No subgrupo e nas análises de sensibilidade de cinco estudos, os níveis de CT dos indivíduos que receberam dose mais baixa de epigallocatequina-3-galato (EGCG) em combinação com atividade física foram significativamente reduzidos. **Conclusão:** A evidência atual sugere que o chá verde em combinação com atividade física não melhora os níveis de lipídeos e lipoproteínas no ser humano. **Nível de Evidência I; Revisão sistemática.**

Descritores: Chá verde; Exercício físico; Humanos.

RESUMEN

Introducción: La mayoría de los estudios sobre extracto de té verde (ETV) en combinación con actividad física relata efecto preventivo en enfermedades cardiovasculares; entretanto, los hallazgos sobre los efectos sobre lípidos séricos son controvertidos. **Objetivo:** Este metaanálisis tiene como objetivo examinar las evidencias de los efectos del ETV en combinación con actividad física sobre el tenor de lípidos séricos en el ser humano. **Métodos:** En junio de 2017, realizamos búsquedas electrónicas en los bancos de datos PubMed, Web of Science y Cochrane Library para identificar estudios pertinentes; fueron incluídos los que tenían período experimental superior a dos semanas, estudios clínicos aleatorizados (ECAs) y que evaluaron sólo ETV con actividad física. En este trabajo, empleamos el modelo de metaanálisis de efectos aleatorios. **Resultados:** Un total de 271 citas fue recuperado en nuestra búsqueda, y siete ECAs fueron identificados, totalizando 608 individuos incluídos. En general, no hubo reducción significativa en los niveles de la lipoproteína de baja densidad del colesterol (LDL-C) (DPE: -0,169; 95% de intervalo de confianza [IC]: -0,414 a 0,076;



12 = 22,7%; $p = 0,177$) o en el colesterol total (CT) entre el ETV y placebo combinados con el Grupo actividad física. Fueron observados resultados semejantes también para la lipoproteína de alta densidad del colesterol (HDL-C) y para los triglicéridos (TG). En el subgrupo y en los análisis de sensibilidad de cinco estudios, los niveles de CT de los individuos que recibieron dosis más baja de epigallocatequina-3-galato (EGCG) en combinación con actividad física fueron significativamente reducidos. Conclusión: La evidencia actual sugiere que el té verde en combinación con actividad física no mejora los niveles de lípidos y lipoproteínas en el ser humano. **Nivel de Evidencia I; Revisión sistemática.**

Descriptor: Té verde; Ejercicio físico; Humanos.

DOI: <http://dx.doi.org/10.1590/1517-869220202605212295>

Article received on 01/31/2019 accepted on 11/27/2019

INTRODUCTION

Green tea (*Camellia sinensis*), which contains several kinds of polyphenol, is one of the most popular beverages in the world. These polyphenols are classified into pyrogallol-type and non-pyrogallol-type catechins. Previous studies have reported four major catechins in green tea, (both pyrogallol and non-pyrogallol-type catechins): epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechingallate (ECG), and epicatechin (EC).¹⁻³ EGCG is the most pharmacologically active of these catechins.⁴ Study have shown that tea catechins can be used to help prevent various types of disease, describing their anti-bacterial, anti-obesity, anti-diabetic, and anti-cancer effects.⁵ The preventing of CVD is a major, important effect of GTE and can be largely attributed to EGCG, the major the most pharmacologically active component of tea catechins.⁶ Several mechanisms through which green tea extract can reduce the risk of CVD have been suggested. One of the main mechanisms is the antioxidant effects, which prevent oxidative modification to LDL-C, which is an important step in the progression of atherosclerosis.⁷ A meta-analysis reported that the intake of GTE improved the lipid profile in humans, especially for LDL-C and TC.⁸ Cardiovascular disease (CVD) alone accounts for 48% of Non-communicable diseases, which leading cause of death worldwide, and is expected to affect more than 23.6 million people by 2030.⁹ CVD not only harms individuals but also places a heavy economic burden on governments around the world.¹⁰ The major risk factors for CVD include smoking, overall alcohol consumption, dietary cholesterol, hypertension, and diabetes mellitus.¹¹ Thus, controlling the risk factors for CVD is important for reducing its incidence. As a well-established risk factor of CVD, LDL-C has been key target in the treatment, control and prevention of CVD. In addition, lower levels of HDL-C, and higher levels of TC and TG have been associated with an increased risk of CVD.¹²

The European guidelines for the prevention of CVD suggest that nutrition supplementation and physical activity might be useful for preventing CVD and modifying an unhealthy lifestyle.¹² It is widely accepted that physical activity not only helps maintain or promote one's physical fitness but also reduces weight¹³ and improves type 2 diabetes mellitus,¹⁴ and cognition and health defects due to an unhealthy lifestyle across age groups.¹⁵ Physical activity also improves the serum lipid profile through mechanisms that increase the lipoprotein lipase activity in skeletal muscle, elevate HDL-C levels, and enhance the transport of plasma lipids and lipoproteins from the peripheral circulation and tissues to the liver.¹⁶ Numerous studies have shown that physical activity increases HDL-C levels and reduces the TG levels in adults, and the risk of CVD is reduced linearly with increased activity.^{17,18} In addition, aerobic exercise increases the HDL-C content, while exercise reduces the LDL-C and postprandial TG levels, with a particularly significant effect on the HDL-C content.¹⁹ However, exercise in combination with green tea has shown a controversial result on the lipid and lipoprotein content. Although many systematic reviews and/or meta-analyses have summarized the effects of the consumption green tea on CVD and the total mortality, blood pressure, and lipid profile, there have no meta-analyses to assess the effects of GTE combined with physical

activity on the serum lipid content. Thus, the aim of this meta-analysis was to compile evidence on the effects of physical activity combined with GTE on the serum lipids and lipoprotein content in humans.

METHODS

Search strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, 2009. Three electronic databases (PubMed, Web of Science, and the Cochrane Library) were searched for articles written in English and published before June 2017, using the following combinations of text and medical subjects heading [MeSH] terms: "green tea extract" or "catechin" or "tea polyphenols" or "EGCG" or "*Camellia sinensis*" and "physical activity" or "exercise" or "walking" or "training" or "strength training" or "aerobic exercise" or "isometric exercises"; and "serum lipids" ("lipoproteins" or "high density lipoprotein cholesterol" or "HDL-C" or "low density lipoprotein cholesterol" or "LDL-C" or "total cholesterol" or "TC" or "triglyceride" or "TG"). Two reviewers independently searched the studies.

Eligibility criteria

We included randomized controlled trials (RCTs) investigating the effect of physical activity combined with GTE on the lipid profiles parameters (HDL-C, LDL-C, TG, and TC) in participants of both sexes. The inclusion criteria were as follows: studies should involve (1) physical activity combined with GTE ingestion; (2) randomized control trials; and (3) human research. The exclusion criteria were as follows: the trial (1) involved transient testing; (2) did not report at least one of HDL, LDL, TG, or TC; (3) had a study period of less than two weeks; (4) included other nutritional supplements combined with GTE.

Data extraction

Two researchers extracted all relevant data independently. One author extracted the following data from the eligible articles: first author and publication year, study design, intervention duration, participant (men and women), dose of GTE, intervention characteristics, control group characteristics, exercise (volume and intensity), and outcomes of HDL-C, LDL-C, TG and TC (mean standard deviation).

Quality assessment

The quality of the studies was assessed using the Cochrane Risk of Bias Tool. The criteria included random allocation, blinding of supplement, outcome assessors and individuals, allocation concealment, use of an intention-to-treat analysis, and other biases. Two researchers assessed the studies, separately. If any differences in their findings were noted, conflict was resolved by discussion.

Statistical analyses

We estimated the relationship between the GTE combined with physical activity group and the control group based on the data presented as the standardized mean difference (SMD). Mean changes in the LDL-C, TC, HDL-C and TG were used to first assess the differences between the trial

and control groups. Due to the different units of measurement used in study, we converted all measures of mg/dl to mmol/L. We therefore used a random-effects model meta-analysis. Subgroup analyses (based the daily dosages of EGCG [≤ 150 mg or >150 mg] in trials, and based on the exercise intensity in studies)²⁰ were performed. I^2 was used to assess heterogeneity between studies, and I^2 values of $<25\%$, $25\%-75\%$, and $>75\%$ were considered to indicate low moderate, and high heterogeneity, respectively. Egger's test was used to assess the publication bias ($P<0.1$ was considered to indicate significant publication bias). Statistical analyses were performed using the STATA version 15.0 software program (Stata Corporation, College Station, TX, USA). P values of <0.05 were considered to indicate statistical significance.

RESULTS

The results of our electronic literature search and the study selection process are shown in Figure 1. We searched 271 articles and

identified 31 potentially eligible trials. We included 7 of the RTC trials²¹⁻²⁷ that enrolled a total of 608 participants in the meta-analysis. All of the studies had a randomized design: four had a double-blind randomized design, one had a single-blind design, and two simply had a randomized design. Physical activity included aerobic exercise, and resistance training combined with aerobic exercise. Two studies used an activity level assessment. One study did not report the main component of GTE, and one used decaffeinated GTE. The participants in all of the RCTs were different, they included healthy subjects (two studies), obese subjects (two studies), overweight breast cancer survivors (one studies), subjects with metabolic syndrome (one studies), and subjects with hypercholesterolemia (one studies). The characteristics of the patients that were evaluated in the meta-analysis are listed in Table 1. The risk of bias in the included studies is summarized in appendix figures.

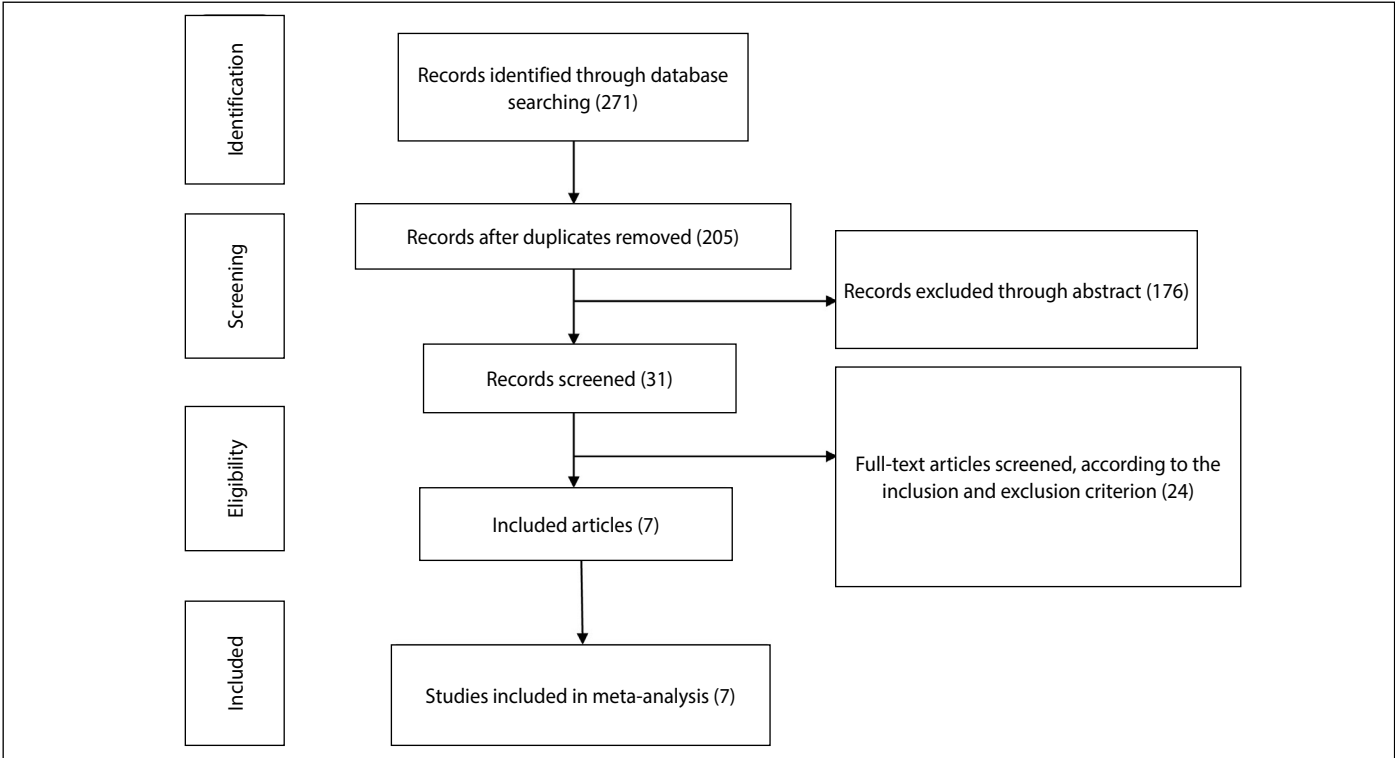


Figure 1. Flow diagram showing the literature search and selection process.

Table 1. Basic characteristic of included 7 trials.

| Reference | Year | study design | Duration | P (N) | age(year) | GTE(mg) | Placebo (mg) | Density- exercise | health condition | Lipids |
|---|------|------------------------------------|----------|-----------------------|------------------------|---|-----------------------------|---|------------------------------------|--------------------------------|
| Belcaro G et al. ²⁷ | 2013 | randomized, single-blinded | 24 W | male and female; 100N | 47.6±5.5 C:45.3±3.5 | 300mg/d EGCG≥13% Ps:19%-25%; | Cellulose | 70% moderate aerobic; 30% muscular strength | borderline metabolic syndrome | TG ↓ HDL ↑ |
| Rostamian M et al. ²¹ | 2017 | Randomized | 2 W | female; 24N | 50-58 | GTE: 1200 | Cellulose | aerobic exercise 4 times/week; 40-50min/session | sedentary postmenopausal women | TG ↓ LDL ↓ HDL ↑ |
| Nagao T et al. ²⁶ | 2007 | randomized, double-blind, parallel | 12 W | male and female; 270N | 25-55 | TCs: 583 Cs: 42.8 CG: 40.1 GC: 127.5 GCG: 139.7 EG: 69.4 EGCG: 100.3 | Cs: 100 Caffeine: 75 | daily activityassessment | visceral fat-type obesity | LDL ↓ |
| Miyazaki R et al. ²² | 2013 | double-blind, placebo | 14 W | male and female; 52N | 69.1±5.9 | TCs: 630.9 Cs: 30 CG: 24.8 GC:125.7 GCG:112.6 EG:45.8 EGCG: 143.2 | TCs: 88.7 Caffeine: 82.4 | walking | older people | TC ↓ LDL ↓ |
| Gahreman D et al. ²⁵ | 2016 | Randomized | 12 W | male 48N | 26.1±0.7 | GTE: 750 Ps: 562.5 EGCG: 375 | None | Interval spring exercise 3times/week | overweight men | none |
| Stendell-Hollis NR et al. ²⁴ | 2010 | randomized, double-blind | 24 W | female; 54N | 56.6±8.1 C:57.8±8.5 | Cs: 235.64 EGCG: 128.84 | herbal tea | activity level assessment | overweight breast cancer survivors | HDL ↑ |
| KajimotoOet al. ²³ | 2003 | double-blind | 12 W | male and female;60N | 47.4±10 | TCs:197.4 EGCG: 67.5 ECG: 25 GCG:82.5 | Cyclodextrin | walking | hypercholesterolemia patients | TG ↓ LDL ↓ HDL ↑ TC ↓ |

TCs =total catechins; Cs =catechin; Ps = polyphenols; C =control; W =weeks; P =participants; N =numbers; GCG=Gallocatechin-3-O-Gallate; CG =Catechin-3-O-Gallate; GC = Gallocatechin.

Effects of GTE on LDL-C and TC

Three RCT studies reported that GTE combined with physical activity increased the level of LDL-C, and one showed significant effects in the GTE group in comparison to the placebo group. A meta-analysis of 6 trials (Figure 2) failed to show a significant decrease in the LDL-C level in the GTE group in comparison to the placebo group (SMD:-0.169; 95% confidence interval [CI]:-0.414 to 0.076; $I^2=22.7\%$; $p=0.177$). A subgroup analysis revealed no significant differences in the LDL-C values between the subjects who received higher and lower doses of EGCG. A similar relationship was observed in the physical activity subgroup analysis. However, the heterogeneity in the higher-dose EGCG group was $I^2=61.9\%$ ($p=0.105$). Because only two studies were included, we were unable to perform a sensitivity analysis. According to Egger's test, there was no publication bias ($p=0.895$).

Two trials reported a significant decrease in TC after intervention in the GTE plus physical activity group, while one showed a significant reduction in the placebo group. The results of a meta-analysis of all of the included studies showed that GTE combined with physical activity was not associated with the serum value of TC (SMD:-0.219; 95%CI:-0.533 to 0.094; $I^2=48.1\%$; $p=0.170$). According to Egger's test, there was no publication bias ($p=0.239$). We divided the studies into subgroups for an analysis, and found non-significant decreases in the lower- and higher-dose GTE groups in comparison to the placebo group, with the same results obtained in the physical activity subgroups. Due to the higher heterogeneity in the subgroup analysis, we performed a sensitivity analysis by removing each study from the meta-analysis (SMD:-0.436; 95%CI:-0.770 to -0.102; $I^2=0\%$; $p=0.01$) (Figure 3), significant decreases were noted in the lower-dose EGCG group and in the daily activity group (SMD:-0.594; 95%CI:-1.012 to -0.177; $I^2=0\%$; $p=0.005$).

Effects of GTE on HDL-C and TG

Seven trials were included in the meta-analysis. The trials reported significant changes in the HDL-C levels of the GTE group after intervention;

only one reported a significant increase in the GTE and placebo groups. However, our meta-analysis found no significant increase in the HDL-C level in the GTE combined with physical activity group in comparison to the placebo group (SMD: -0.089; 95%CI: -0.384 to 0.205; $I^2=55.6\%$; $p=0.552$). According to Egger's test, there was no publication bias ($p=0.16$). A subgroup analysis revealed that higher-dose GTE was associated with a significant decrease in the HDL-C level in comparison to placebo (SMD:-0.743; 95%CI:-1.331 to -0.154; $I^2=0\%$; $p=0.013$). A subgroup and sensitivity analysis failed to show significant differences in the HDL-C level between the plan and daily groups (SMD: -0.177; 95% CI: -0.448 to 0.095; $I^2=33.3\%$; $p=0.202$).

Three trials reported a significant decrease in TG after intervention in the GTE group, while two showed a significant decrease with the GTE group and placebo group. Our meta-analysis found no significant decrease in the TG level in the GTE combined with physical activity group in comparison to the placebo group (SMD: 0.074; 95 % CI: -0.168 to 0.316; $I^2=36.8\%$; $p=0.547$). According to Egger's test, there was no publication bias ($p=0.593$). A subgroup analysis revealed that the TG level of subjects who received higher-dose GTE was not significantly decreased in comparison to placebo nor was any significant difference in the TG level noted between the exercise plan group and the daily activity group. We did not perform a sensitivity analysis, even though the subgroup analysis showed heterogeneity in the higher-dose EGCG group, because only two trials included a higher dose of GTE. A subgroup and sensitivity analysis failed to show a significant difference in the TG level between exercise group and daily activity groups (SMD: 0.044; 95 % CI: -0.378 to 0.466; $I^2=47.3\%$; $p=0.838$).

DISCUSSION

A total of seven RCTs were included in this meta-analysis, which found no significant differences in the serum HDL-C, LDL-C, and TG levels between the GTE combined with physical activity and the placebo groups. However, subgroup and sensitivity analyses revealed that the TC level was significant decreased in the lower-dose EGCG subgroup. The findings of the present meta-analysis contradict those of a previous

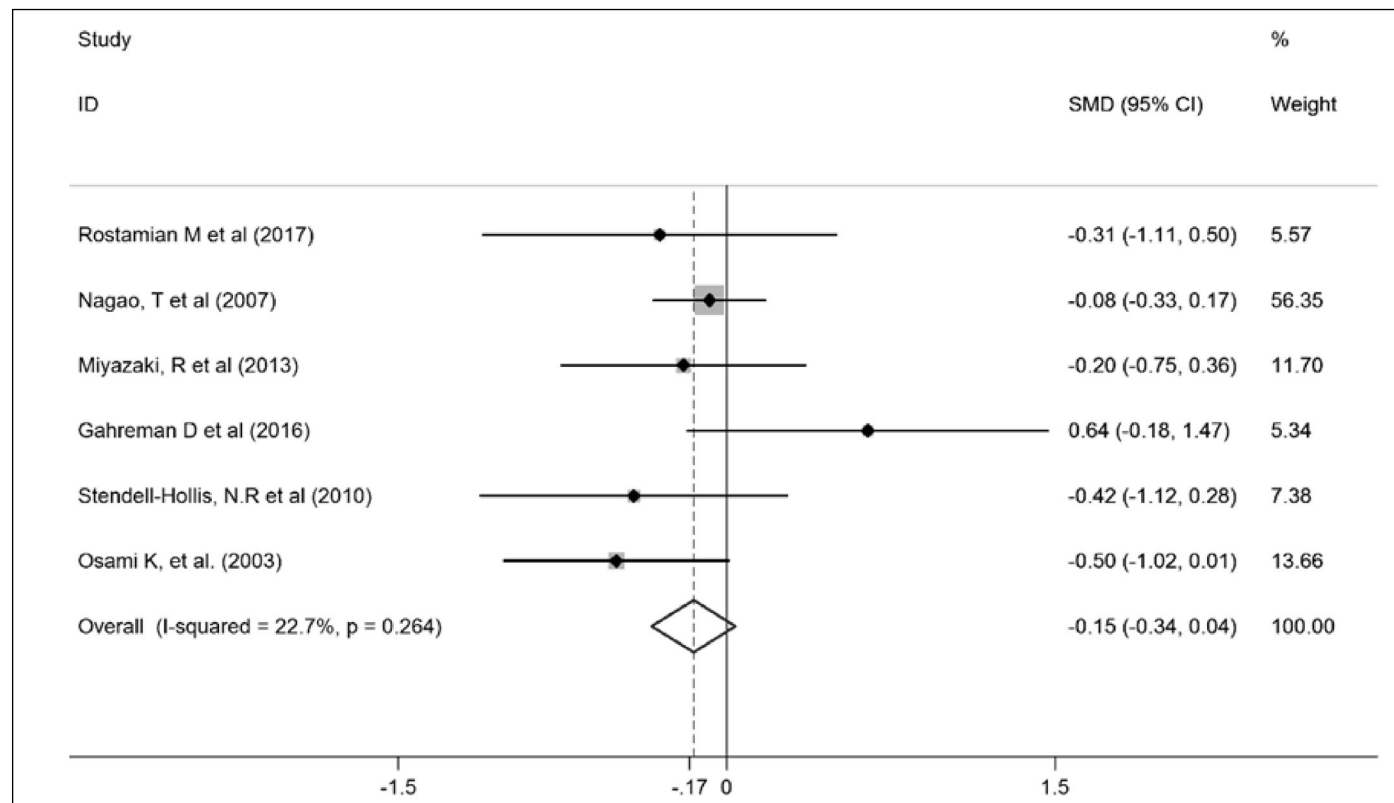


Figure 2. Results of evaluating the effect of GTE combined with exercise on LDL-C (mmol/L). Sizes of data markers indicate the weight of each study in the analysis.

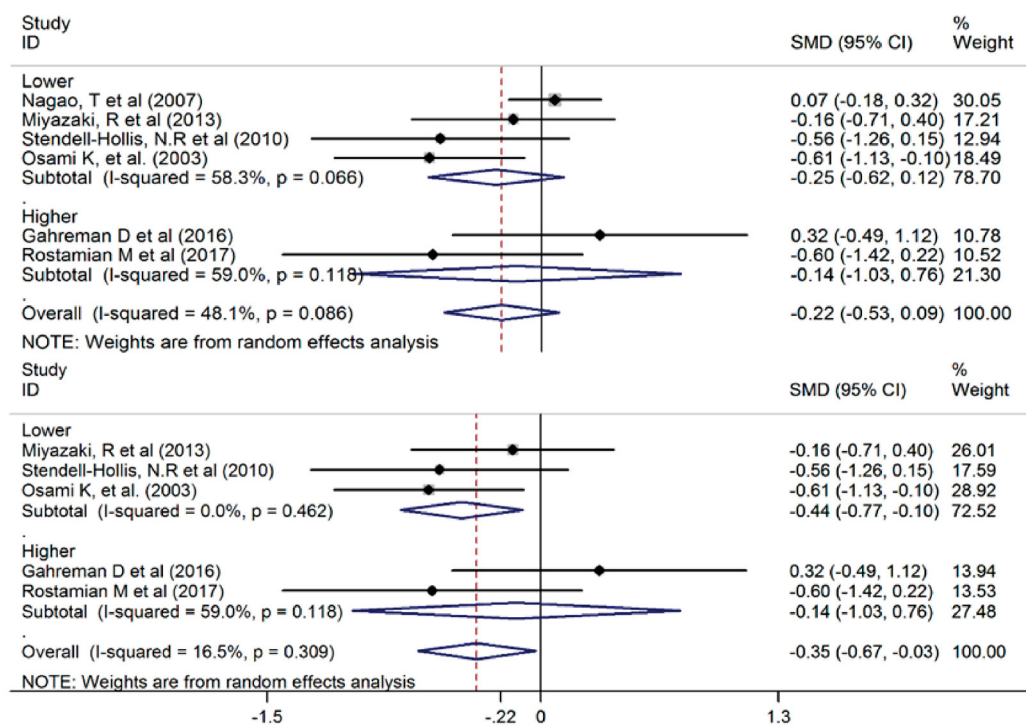


Figure 3. Results of subgroup and sensitivity analysis from difference dose EGCG evaluating the effect of GTE combined with exercise on TC (mmol/L). Sizes of data markers indicate the weight of each study in the analysis. (Lower subgroup = lower dose EGCG; Higher subgroup = higher dose EGCG).

meta-analysis, which revealed the beneficial effects of GTE on the lipid and lipoprotein profile.²⁸ In contrast to the previous review, our meta-analysis also assessed the effects of physical activity on the serum lipids. The studies evaluated here would have been different; thus, there might have been discrepancies between these reviews regarding the findings concerning the beneficial effects of GTE on the lipid and lipoprotein profile.²⁹ However, we did note some similarities in the lipid profiles of the subjects of our review and the subjects of the previous meta-analysis.

Protecting human LDL against oxidative attack is an important action of tea polyphenols; however, the mechanisms through which LDL oxidation is inhibited are unclear.⁴ GTE affects the human body via two major mechanisms: (1) tea polyphenols decrease the digestion and absorption of macronutrients in the gastrointestinal tract; and (2) tea polyphenols inhibit the anabolism and stimulate the catabolism of skeletal muscle, liver, and adipose tissues.³⁰ Studies have revealed that CVD is associated with oxidative stress induced lipid damage. Tea polyphenols therefore reduce this damage and enhance the endogenous defense system.³¹ However, we found no significant decrease in the LDL-C and TC levels in our review. Although the previous meta-analysis found that GTE did indeed reduce these levels.³² In comparison to the previous study, we considered physical activity as an important factor in our review. Increasing physical activity is effective for preventing CVD. However, in the present study, the combination of physical activity and GTE showed no significant effect. Of note, while we found no significant decrease in the LDL-C levels of the subjects in our meta-analysis. We did find a significant decrease in the TC levels in a sensitivity analysis. A study of tea polyphenols showed that EGCG, EGC, ECG, and EC are the main of tea catechins, along with their gallate esters (gallicocatechingallate, gallicocatechin, catechingallate, and catechin). A systematic review reported that the dose of EGCG in most studies exceeded 200 mg. An observational study review found that people who drank 1-3 cups of green tea enjoyed a reduced risk of CVD, and that an increase in green tea consumption by 3 cups daily was associated with a reduced risk of cardiac death.³³ Koutelidakis et al. showed that a lower dose of tea

catechins failed to improve the levels of LDL-C and TC.³⁴ In comparison to those previous studies, the studies included in the present meta-analysis might have involved a lower dose of EGCG; indeed, the lowest dose of EGCG was 39mg, and the highest was 375mg. This may explain the lack of any significant findings in our review.

Because of the limited number of studies available, we included all of the eligible human studies regardless of the subjects' health. This resulted in the inclusion of patients with metabolic syndrome, obese subjects, and breast cancer survivors in our review. The LDL-C levels varied markedly among our populations, which featured postmenopausal women, patients with hypercholesterolemia, and older subjects. The cholesterol concentrations also varied according to age and body mass index, which might be why our review revealed no significant finding.³⁵ Two RCT studies by Samavat et al.³⁶ and Wu et al.³⁷ showing that green tea catechins were able to reduce the level of LDL-C in postmenopausal women (high-dose EGCG[400-843mg/day]). This might have been a major confounding factor in our meta-analysis.

While several meta-analyses have reported significant improvement in the lipid and lipoprotein content with physical activity,³⁸⁻⁴⁰ few studies have shown significant changes in the TC and LDL-C levels specifically.⁴¹ Furthermore, these beneficial effects were typically noted in studies including diet intervention or obese participants.⁴⁰ A previous meta-analysis also reported non-significant decreases in the TC and LDL-C levels, although major cardio-protective improvements in the LDL-C subfractions may have occurred.³⁸ In our review, the sensitivity analysis revealed that the TC level was significantly decreased in association with daily activity. This may be due to the methods in studies that used physical activity combined with GTE. Studies have shown that many confounding factors can influence the effects of interventions targeting TC and LDL-C, including body characteristics, energy expenditure, food supplements, health status, and lifestyle. Consequently, the results obtained in our analysis might be because the eligible studies all included population with differences in health status, age, and degree of physical activity.

Aerobic exercise has been shown able to improve the TG and HDL-C levels, although a less-marked response is observed for LDL-C and TC.^{42,43} However, we found no significant differences in the HDL-C and TG levels between the GTE combined with physical activity, and exercise subgroups and the daily activity group. A meta-analysis reported that a large amount of high-intensity exercise exerted a beneficial effect on the HDL-C and TG levels (including high-amount and high intensity, low-amount and high intensity or low-amount and moderate intensity exercise).⁴⁴ Furthermore, Kodama et al.⁴⁵ reported that regular aerobic exercise increased the HDL-C levels, with greater improvement seen with a longer duration of exercise. In our included studies, more than half articles used regular exercise. However, three of the RCTs in our meta-analysis included overweight or obese subjects, and caloric restriction was not reported. A previous study reported that regular exercise has beneficial effects on the lipoprotein profile, and that a higher amount of exercise has a much greater beneficial effect on the serum lipid content than a lower amount of exercise.⁴⁶ In addition, there was difference health statuses of the individuals included in our review. This may explain why we failed to observe a significant improvement in the TG and HDL-C levels in the exercise subgroups. Exercise also reduces the TG levels and increases the HDL-C level. However, there no significant differences were noted in the TG levels of the exercise subgroup in our review. Endurance exercise and acute exercise studies have shown that aerobic exercise combined with resistance training was effective in reducing the TG level.^{47,48} A study of the effects of the amount and intensity of exercise on the plasma lipoprotein levels reported that the TG level was significantly changed, in response to high-amount-high-intensity, low-amount-high-intensity, and low-amount-moderate-intensity exercise. In contrast, although a trend toward a reduction in the TG level was found, exercise combined with GTE had no significant effect on the TG level.

A few studies have reported significant effects of GTE on the levels of HDL-C and TG, Vinson⁴⁹ showed that GTE was able to increase the HDL-C level in normal and high-cholesterol-diet hamsters. Guo et al. further confirmed that GTE improved the HDL-C and TG levels in high-cholesterol-diet mice.⁵⁰ However, meta-analyses of 7 trials failed to show significant effect on the HDL or TG. A systematic meta-analysis showed that green tea had no significant differences in the HDL-C and TG levels in humans.³² Similarly, another study reported that GTE for 3 weeks had no effects on serum lipid markers, such as HDL-C and TG.⁵¹ Our study also showed no

significant changes in the HDL-C and TG levels following GTE treatment, and in subgroup and sensitivity analysis. Furthermore, Bogdanski et al.⁵² and Hsu et al.⁵³ showed that a higher dose of GTE increased the levels of HDL-C and TG in their RCTs. Few studies have confirmed the beneficial effects of GTE on HDL-C and TG. More animals and/or human studies are needed to evaluate the relationship between with the GTE or GTE in combination with physical activity and HDL-C and/or TG.

Strengths and limitations

In comparison to the previous meta-analysis, the strength of this review is mainly that this is the first systematic review and meta-analysis focusing on the effects of GTE combined with physical activity on the lipid and lipoprotein content in humans. Furthermore, our findings contradict the results of the effects of GTE that were reported in previous reviews. However, there are several limitations that should be acknowledged. First, the eligible studies included data on GTE and physical activity from only a few RCTs, which restricted the accurate assessment of the type-response relationship between GTE combined with physical activity and the serum lipid content in humans. Second, due to the limitations of the included studies, we were unable to restrict the characteristics of the subjects enrolled. This represents an important confounding factor that affected the results or meta-analysis. Third, only one study reported the energy expenditure of its subjects. Thus we cannot evaluate the intensity of exercise, which is known to be associated with the degree of improvement in the serum lipid level. Finally, a few studies only used a pedometer to assess physical activity, and they did not report the detailed results of the daily activity of their subjects. These limitations might have undercut the strengths of this review.

CONCLUSION

The findings from previous studies collectively suggest that GTE combined with physical activity does not seem to be associated with the lipids and lipoprotein content of humans. However, due to the limited number of eligible studies, we could not obtain a clear result. These complex issues should be explored in better designed RCTs in the future.

All authors declare no potential conflict of interest related to this article

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. TZ: conceived of this study, collected the data, designed and performed the statistical analysis and interpretation and wrote the initial draft of the manuscript; SC: collected the data and performed the statistical data analysis; AS: provided scientific guidance for the study design. All authors read and approved the final version of the article.

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