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Effect of green tea supplementation on blood pressure among overweight and obese adults: a protocol for a systematic review

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ABSTRACT

Introduction: Emerging randomised controlled trials (RCTs) exploring the effect of green tea (GT) supplementation or GT extract (GTE) on blood pressure (BP) among overweight and obese adults yielded inconclusive results. We aim to conduct a systematic review to summarise the evidence of RCTs until now, to clarify the efficacy of GT supplementation or GTE in BP in overweight and obese populations.

Methods and analysis: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and ClinicalTrials.gov will be searched to retrieve potential RCTs. Unpublished studies will be identified by searching the abstract books or websites of the three major conference proceedings: the International Society of Hypertension, the Nutrition & Health Conference and the World Congress of Nutrition and Health. A random-effects meta-analysis will be performed to pool the mean difference for the change in BP from baseline (ie, postintervention BP minus baseline BP) between intervention groups and placebo groups of the included studies, presenting the pooled results with 95% CIs. Subgroups analyses will be conducted according to different doses of GT or GTE, trial duration, geographic regions, overweight versus obese participants, and participants with versus without change in body weight after intervention. Sensitivity analysis will be performed by excluding studies classified as having a high risk of bias, applying a fixed-effects model, using the postintervention BP for analyses and excluding trials with non-study cointerventions.

Ethics and dissemination: This systematic review will be published in a peer-reviewed journal. It will be disseminated electronically and in print. Summarising the RCT evidence to clarify the efficacy in BP among overweight and obese adults will aid in making the dietary recommendation of GT and improving the clinical management of hypertension.

Trial registration number: PROSPERO CRD42014007273.

Strengths and limitations of this study

- Our research group has great experience in conducting a systematic review with meta-analysis.
- This systematic review is the first to explore the efficacy of green tea or green tea extract in blood pressure among the overweight and obese populations.
- Summarising the evidence of randomised controlled trials to clarify the efficacy in blood pressure among overweight and obese adults will aid in making the dietary recommendation of green tea and improving the clinical management of hypertension.
- Small studies with high heterogeneity and varying quality may limit the quality of evidence for this systematic review.

BACKGROUND

Overweight and obesity are becoming a severe public health issue globally. The prevalence of overweight and obesity has nearly doubled since 1980, with an estimation of 35% and 11% in 2008 worldwide for overweight and obesity, respectively, in adults aged 20 and older.[1] Well-established evidence corroborates that obesity is one of the most important risk factors for the development of hypertension and increases the cardiovascular morbidity and mortality associated with hypertension.[2–4]

Tea is one of the most commonly consumed beverages, although in various amounts in different countries.[5 6] Green tea (GT) is rich in antioxidant polyphenols such as catechins and flavonols,[5 7] and the extract of tea has been shown to have a vasodilator effect,[8–10] both of which lead to benefits on cardiovascular health.[11–13] The physiological effect of GT on the risk factors for cardiovascular disease, including blood pressure (BP), is therefore promising and of interest.

In rodents, GT supplementation and epigallocatechin gallate (EGCG) as the major catechin species in GT have been reported

to prevent BP increase.[14 15] In human subjects, on the other hand, while evidence from observational studies suggested a significant inverse relationship between GT intake and cardiovascular diseases,[16–18] systematic reviews or meta-analyses of randomised controlled trials (RCTs) reported an inconclusive effect of GT on BP.[19–21] No protective effect of GT supplementation could be found in Hooper *et al*'s[19] or Taubert *et al*'s[20] meta-analyses, whereas GT produced a significant reduction in BP in Hartley *et al*'s[21] systematic review. Nevertheless, all the three reviews failed to investigate the effect of GT on BP among the overweight and obese populations. Furthermore, according to the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) criteria,[22] the two meta-analyses did not consider the grey literature systematically.[19 20] Moreover, since Hartley *et al*[21] restricted trials to those with a duration of at least 3 months, there were only three RCTs identified with a small sample size (ie, less than 200).

Emerging RCTs among overweight and obese adults yielded inconclusive results—with some suggesting a positive relationship between GT and lowered BP[23–25] while others showing no associations.[26–28] Thus, in the light of these discrepancies and given the high prevalence of hypertension and consumption of GT, in order to clarify the efficacy of GT supplementation or GT extract (GTE) in preventing the development of hypertension or treating hypertension among overweight and obese adults, we will conduct a systematic review to summarise the evidence of RCTs until now.

OBJECTIVES

In this systematic review, the overall purpose is to determine the efficacy of GT supplementation or GTE in BP among overweight and obese adults based on the data of RCTs. The primary objective is to assess the effect of oral GT supplementation or GTE compared with placebo on the change in BP from baseline (ie, postintervention BP minus baseline BP) among overweight and obese adults. The secondary objectives are to determine the effect on quality of life, adverse events and treatment discontinuation rates.

METHODS

Study eligibility

Types of studies

All RCTs including parallel and crossover RCTs will be eligible for inclusion. For crossover RCTs, we will only extract and analyse data from the first half as a parallel trial design.

Types of participants

Adults aged 18 or older with a body mass index (BMI) of 25 kg/m^2 and more[1] will be included for analysis. However, given that there may be different cut-off points of BMI to define overweight and obesity in the trials from the WHO definition, we will also accept varied BMI values to include overweight and obese participants based on the authors' definition. If the cut-off points are unclear, we will contact the authors for clarification. However, if the above approaches are not successful, we will use the criteria from WHO with a BMI of 'between 25 and 29.9 kg/m^2' as overweight and with a BMI of 'no less than 30 kg/m^2' as obese.[1]

If the same participants are investigated in multiple studies or at different time points, we will extract and analyse all the data from different follow-up periods, and choose those with the largest sample size of the same follow-up period for analysis.[29]

Types of interventions

At least one of the intervention arms has to include oral intake of GT or GTE as a monointervention. All doses and durations of GT supplementation or GTE will be eligible for inclusion. Studies that combined GT or GTE with antihypertensive drugs, or any other dietary supplements, or other lifestyle interventions will be excluded, because we want to isolate the intervention effect due to GT and obtain its efficacy by direct comparison with placebo in the absence of any other hypertension intervention.[29] However, to retrieve all potential eligible evidence in our systematic review, we will also include studies with cointerventions if the non-study cointerventions are the same in both the intervention and placebo groups.

Types of comparisons

Only trials using placebos in their control groups will be included. Specifically, the comparison will be oral GT supplementation or GTE versus placebo. For those trials with the same cointerventions in the intervention and control groups, the comparison will be oral GT or GTE plus cointervention versus placebo plus cointervention.

Types of outcome measures

The primary outcome will be the change in BP from baseline. Our secondary outcomes will include quality of life, adverse events associated with GT and treatment discontinuation rates.

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and ClinicalTrials.gov will be searched to retrieve potential RCTs. No limitations of language, publication status or setting will be added to our searches. The reference lists of articles and other reviews obtained in the search will be searched for relevant articles. In our searches, we will use descriptors that include synonyms for green tea, blood pressure and randomized controlled trials in various combinations, for example, 'tea or green tea or green tea extract or camellia sinensis or catechin or epigallocatechin gallate' and 'blood pressure or hypertension or cardiovascular or cerebrovascular' and 'RCT or placebo or clinical trial or intervention'.

Unpublished studies will be identified by searching the abstract books or websites of the three major conference proceedings: the International Society of Hypertension (http://ish-world.com), the Nutrition & Health Conference (http://nutritionandhealthconf.org) and the World Congress of Nutrition and Health (http://www.bitlifesciences.com/wcnh2013). Any abstract of interest will be assessed for further details by contacting the authors. Furthermore, we will try to contact the authors of included studies to obtain other data that may either be informally published or unpublished or ongoing and which is associated with efficacy of GT or GTE in BP.

Data collection and analysis

Selection of studies

We will summarise the identification, screening and inclusion of studies according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram.[30]

Two reviewers (GL and YZ) will independently screen and select studies for possible inclusion in the study. The titles and abstracts of RCTs identified from search will first be independently reviewed and compiled for further screening. Then the full text of all trials identified from the title and abstract screenings will be examined by the independent review authors. Finally, the two reviewers will pool a list of included studies and document the number and reasons of excluded studies. Any disagreement will be resolved by consensus, and a third reviewer (LM) will be consulted if disagreement persists. Agreement between authors will be quantified using the κ statistic.[31]

Data extraction and management

Two reviewers (GL and YZ) will independently extract data using specially developed data extraction forms. The data extraction form will be piloted prior to its use. Information will be collected on participants, interventions and outcome measures:

1. Participant characteristics (age, gender, number of total participants randomised, baseline BP, methods to measure BP, baseline BMI and quality of life, comorbidity, study setting, geographic region where the study was conducted, inclusion and exclusion criteria in the included studies, washout periods for antihypertensive drugs or other supplements);
2. Intervention details (number of arms, sample size for each arm, randomisation and allocation concealment method, blinding, dose and type of GT supplementation, trial duration, and source of funding) and
3. Outcome measures (description of measures used, postintervention BP and BMI, postintervention quality of life, change in BP from baseline, change in BMI and quality of life from baseline, treatment compliance, treatment discontinuation including withdrawals and drop-outs, and adverse outcomes).

Any disagreement will be resolved by discussion and consensus. Furthermore, when necessary we will try to contact the authors of included studies to obtain relevant information additionally.

Assessment of risk of bias in included studies

We will assess risk of bias for each included study using the Cochrane Collaboration 'Risk of bias' assessment tool which includes sequence generation, allocation concealment, blinding, incomplete outcome data and loss to follow-up, selective outcome reporting and other issues.[32] The reviewers (GL and YZ) will rate each domain of the included studies as having low, high or unclear risk of bias. We will discuss any disagreement in the assessment of risk of bias to reach a consensus.

Measures of treatment effect and data synthesis

A random-effects meta-analysis will be performed to synthesise the data by pooling the results of the included studies. We will analyse the data using Review Manager (RevMan) V.5.2 for Windows (the Nordic Cochrane Center, the Cochrane Collaboration, Copenhagen, Denmark). We will calculate and pool the mean difference (MD) for the change in BP from baseline between intervention groups and placebo groups, presenting the pooled results with 95% CIs. If the GT or GTE is efficacious in BP reduction, a dose-response analysis will be performed to measure the effect of daily dose of the total catechins or EGCG on the change in BP from baseline, using the STATA metareg command.[32]

Dealing with missing data

For missing or unclear data, the authors of the included studies will be contacted. If data are only available in graphic format, we will impute approximations of the means. Furthermore, if the SDs of the change in BP from baseline were not provided, we will estimate the approximations of the SDs as described in section 16.1.3.2 in the Cochrane Handbook for Systematic Reviews of Interventions.[32] Moreover, if no information on SDs of the change in BP from baseline or the postintervention BP is available, and if the effort to seek further information from original authors is not successful, we will borrow SDs from other trials included in this meta-analysis,[32 33] in order to estimate the SDs.

Assessment of heterogeneity

We will first assess clinical heterogeneity by determining whether the studies are similar enough to pool in terms of populations, interventions and outcome measures. If they are similar to be meta-analysed clinically, statistical heterogeneity will be evaluated using the I^2 statistic, with a value of $I^2 > 50\%$ or $p<0.1$ taken as implying significant heterogeneity.[34 35] If statistical heterogeneity is found, it will be examined by subgroup and sensitivity analyses.

Subgroup analysis

Results will be stratified by the following subgroup analyses:

1. Different doses of GT or GTE: the cut-off point will be chosen as 5 cups per day (1 cup=237 mL) in GT adopting the upper desirable GT intake in Boehm *et al*'s[36] systematic review, or equivalently 450 mg catechins or 250 mg EGCG per day in GTE approximately.[37–39]
2. Different trial duration: the RCTs with long time periods (ie, no less than 3 months) will be compared with trials of short duration.
3. Different geographic regions: results from various locations where studies were conducted (eg, Asia and Europe) will be stratified for subgroup analyses.
4. Overweight versus obese participants (ie, separating obese participants from overweight adults with a cut-off point of BMI based on the authors' definition in the included studies, or categorising adults with a BMI of between 25 and 29.9 kg/m^2 versus those with a BMI of no less than 30 kg/m^2 according to the WHO criteria).[1]
5. Participants with versus without change in body weight after intervention. Since there may be the effect of GT on weight loss in overweight and obese adults,[40] and a concurrent decrease in body weight may reduce BP,[20 41] a subgroup analysis will be conducted to examine whether the effect on BP is different in participants with significant weight loss (in kg) versus those without weight reduction.

Sensitivity analysis

We will carry out sensitivity analyses by excluding studies classified as having a high risk of bias. Also, a fixed-effects model will be performed for sensitivity analysis. Moreover, we will pool the MD for postintervention BP between intervention groups and placebo groups in all the included trials for meta-analysis. Another sensitivity analysis will be conducted by excluding the included trials with non-study cointerventions, to examine the robustness of the results.

Assessment of publication bias

We will construct a funnel plot to investigate the potential for publication bias for the primary outcome, by means of visual inspection for signs of asymmetry, Begg's rank correlation and Egger's regression tests,[32] using the STATA metabias command.

Assessment of quality of evidence across studies

We will assess the quality of evidence in this systematic review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[42] with GRADEprofiler (GRADEpro) V.3.6 software, defining the quality of evidence for each outcome as the extent to which one can be confident that an estimate of effect or relation is close to the quantity of specific interest.[32]

There are four levels rating the quality of evidence across studies in the GRADE system: very low, low, moderate and high. RCTs are categorised as high quality but can be downgraded for several reasons, including limitation in study design, indirectness of evidence, imprecision of results, unexplained heterogeneity or inconsistency of results or high probability of publication bias.[42]

DISCUSSION

The effect of GT including antioxidation and vasodilation on BP has been investigated in large quantities of observational studies and trials for decades. Meta-analyses based on observational studies indicated the significant inverse relationship between GT and cardiovascular diseases including stroke, myocardial infarction and coronary artery disease.[16–18] However, the conclusion could compromise the relationship by the observational design, the potential confounding factors, the publication bias of small positive studies, etc.[16 20 43] A systematic review based on RCTs will yield a better understanding of the efficacy of GT or GTE in BP, which will be helpful in making recommendations or establishing guidelines for implementation in general practice and other relevant settings. Two meta-analyses summarising evidence from RCTs reported no protective effect of GT or GTE on BP,[19 20] while Hartley *et al*[21] found a significant reduction in systolic and diastolic BP after pooling trials with a duration of no less than 3 months. Given the discrepancies in their conclusions, and taking into account that more trials were conducted and published, an up-to-date systematic review is needed to retrieve available evidence to clarify the efficacy of GT or GTE in preventing the development of hypertension or treating hypertension.

In this systematic review, we will focus on overweight and obese adults. Obesity is a high-risk factor for hypertension, and the number of obese adults has rocketed alarmingly.[44 45] Throughout the large obese populations, even a small reduction in BP may lead to a large reduction in cardiovascular disease events.[46] However, no previous meta-analyses or systematic reviews examine the effect or GT or GTE on BP in the overweight and obese populations. Furthermore, given that the sample sizes of dietary trials are usually small and the long-term dietary RCTs are difficult to implement on a practical basis,[20 21] it is reasonable to choose overweight and obese adults as high-risk and highly responsive (to intervention) participants,[47] to better clarify the efficacy of dietary intervention.

This systematic review and meta-analysis is the first to explore the efficacy of GT or GTE in BP in the overweight and obese populations, to the best of our knowledge. Summarising the RCT evidence to clarify the efficacy in BP among overweight and obese adults will aid in making the dietary recommendation of GT and improving the clinical management of hypertension.[3 45]

We anticipate that the review will provide valuable evidence of the beneficial efficacy of GT supplementation or GTE in BP among overweight and obese adults. If GT can significantly prevent the development of hypertension or treat hypertension in overweight and obese populations, GT supplementation will be a simple and acceptable intervention given its popularity, high rate of compliance and rare adverse effects.[21]

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Contributors GL and LT were responsible for the study conception and design. GL, YZ and LM were responsible for the drafting of the manuscript. AH, MAHL and LT made critical revisions and provided professional and statistical support. All authors read and approved the final version of the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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