The Effect of Green Coffee Extract Supplementation on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Given the proliferation in studies investigating green coffee bean extract (GCBE) supplementation, the purpose of this study was to determine the efficacy and effectiveness of GCBE supplementation on indices of blood pressure. The literature search was performed in four databases including PubMed/Medline, Scopus, the Cochrane Library, and Google Scholar to identify clinical trials that examined the effects of green coffee supplements on SBP and DBP up to February 2019. Mean change and standard deviation (SD) of the outcome measures were used to estimate the mean difference between the intervention group and the control group at follow-up. Nine studies including reported SBP and DBP as an outcome measure. Results revealed significant reduction in SBP (WMD: -3.093 mmHg, 95% CI: -3.914, -2.273; $I^2 = 0.0\%$) and DBP (-2.170 mmHg, 95% CI: -2.749, -1.590; $I^2 = 46.5\%$) after green coffee supplementation with low heterogeneity among the studies. In addition, in sub-group analysis, a significant reduction in SBP and DBP in studies with hypertensive patients, green coffee dosage <400 mg, and administered for ≤4 weeks was identified. The results of current meta-analysis study support the use of GCBE supplementation for the improvement of blood pressure indices, with sub-group analysis highlighting improvements in hypertensive patients.

Keywords: Meta-analysis, Blood Pressure, SBP, DBP, Green-Coffee.

Introduction

High blood pressure is a major risk factor for cardiovascular disease (Stamler, Stamler, & Neaton, 1993), with global prevalence varying from less than 3.4% to over 72.5% (Kearney, Whelton, Reynolds, Whelton, & He, 2004). In the Framingham study, the risk of developing high blood pressure over a lifetime was 90%, whilst it is estimated that the global burden of hypertension will increase to 1.56 million by 2025 (Kearney et al., 2005). Hypertension is a primary risk factor for CHD, CVD and can lead to stroke, kidney problems, disability and early mortality (Chen et al., 2009). High blood pressure can be reduced by lifestyle changes such as changing diet, increasing physical activity, or through drug therapy (Suzuki, Kagawa, Ochiai, Tokimitsu, & Saito, 2002). Many studies have shown that antioxidant vitamins, supplements and many nutritional supplements can reduce blood pressure in humans and animals (Kazuya Kozuma, Shigemi Tsuchiya, Jun Kohori, Tadashi Hase, & Ichiro Tokimitsu, 2005), for example, polyphenols are food additives that are known as antioxidants and widely distributed in foods such as tomatoes, apples, chocolate, coffee and tea (Flament & Bessière-Thomas, 2002).

Coffee is one of the most commonly consumed drinks in the world, and has been reported to elicit a protective effect on liver function (Johnson et al., 2011), diabetes mellitus (van Dam, 2008) and degenerative diseases (Gaafar, El-Ghamery, & Mahmuod, 2013). Unroasted Green Coffee is rich in chlorogenic acid (CGA 2-5 gr/100 gr) (Haidari, Samadi, Mohammadshahi, Jalali, & Engali, 2017), which consists of caffeic acids or ferulic acids (Clifford, 1999), and possesses anti-diabetic (Meng, Cao, Feng, Peng, & Hu, 2013), anti-obesity (Cho et al., 2010; Gorji et al., 2019) and anti-lipidemic (Cho et al., 2010; Ong, Hsu, & Tan, 2013; Salamat et al., 2019) properties, with Yamaguchi et al, asserting that drinking a cup of coffee daily has an antihypertensive effect (Yamaguchi et al., 2008). In Kuzuya et al., male, hypertensive participants who supplemented with

Green coffee bean extract (GCBE) for 28 days significantly decreased SBP and DBP (Kazuya Kozuma et al., 2005); whilst in Dujaili et al., it was demonstrated that, following 7 days of supplementation with GCBE, SBP and DBP were significantly decreased (Al-Dujaili, Abuhajleh, & Al-Turk, 2016). However, contrastingly, Yeon et al., among others, have reported GCBE does not elicit any significant effect on blood pressure (Park, Kim, Lee, & Lee, 2010), and conclusions drawn from previous meta-analytical examinations may be regarded as premature, with only a small number of eligible studies analyzed (Onakpoya, Spencer, Thompson, & Heneghan, 2015). Given the proliferation in studies investigating GCBE supplementation, the purpose of this study is to determine the efficacy and effectiveness of GCBE supplementation on indices of blood pressure.

Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the conducting of this study (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

Search strategy

The literature search was performed in four databases including PubMed/Medline, Scopus, the Cochrane Library, and Google Scholar to identify clinical trials that examined the effects of green coffee supplements on SBP and DBP up to February 2019. The merging of MESH and non- MESH terms were used as follows: (((("green coffee"[Title/Abstract]) OR "green coffee extract"[Title/Abstract])) AND (((("Clinical Trials as Topic"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR RCT[Title/Abstract] OR "Intervention Studies"[Title/Abstract] OR "intervention"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR

"randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "random"[Title/Abstract] OR "randomly"[Title/Abstract] OR "placebo"[Title/Abstract] OR "assignment"[Title/Abstract]))). Moreover, we conducted hand searches of all reference lists of eligible articles, and related reviews in order to avoid missing any relevant article.

Eligibility criteria

We considered studies that were: (1) randomized placebo-controlled trials with crossover or parallel designs (2) publications that were carried out on adult individuals more than 18 years old (3) those that reported sufficient data on baseline and final trials of SBP or/and DBP in both green coffee and control groups (4) studies that did the intervention with any green coffee species. We excluded articles if they; (1) were conducted on children, pregnant women or animals (2) were not placebo-controlled trials (3) did not reported sufficient information for the outcomes in green coffee or control groups (4) examined the effects of green coffee along with other components. Grey literature, including conference papers, dissertations, and patents were omitted for purposes of this study.

Data extraction

Two independent investigators (A.N and HKV) performed the study selection, and a third, senior researcher (C.C.) was present to resolve any disagreements. In case of absence of reporting data in the published studies, we emailed the corresponding author to obtain the required data. The following data were acquired from each study; first study author's name, year of publication, age and gender of subjects, trial duration, study location, type and dosage of green coffee supplements, study design, health status of participants, number of participants in each group, mean and SD of outcome measures at baseline, post-trial and/or changes in outcome measures from baseline to the

end-of-study. If a study reported multiple data at diverse time points, only the most recent were included.

Quality assessment

Methodological quality and risk of bias of included studies was determined by using the Cochrane scoring system (Moher et al., 2009). This tool assesses possible sources of bias in randomized trials, including the random sequence generation; the concealment of allocation to conditions; the inhibition of awareness of the allocated intervention; blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Three scores of yes, no, and unclear could be given to each above-mentioned item, which are referred as high risk, low risk, and unknown risk respectively

Data synthesis and statistical analysis

Mean change and standard deviation (SD) of the outcome measures were used to estimate the mean difference between the intervention group and the control group at follow-up. If data were reported in a different format, standard calculations were performed to derive the mean and SD (Higgins, 2011; Hozo, Djulbegovic, & Hozo, 2005). In order to estimate effect sizes, the random-effects model (using DerSimonian-Laird method) was used and results were provided across weighted mean difference (WMD) and 95% CI. We conducted subgroup analysis to investigate potential sources of heterogeneity among the studies. The sensitivity analysis was performed using the leave-one-out method, to discover the impact of each study, individually, on the overall effect size. Publication bias was assessed by means of visual calculation of funnel plots and Egger's tests(Egger, Smith, Schneider, & Minder, 1997). If any publication bias was detected, it was tested via the 'trim and fill' approach (Palmer, Peters, Sutton, & Moreno, 2008). All statistical analyses were implemented using Stata software (Stata Corp. College Station, Texas, USA).

Results

Study selection

The initial database search returned 181 articles (in addition to 2 articles retrieved by a hand searching), and after duplicates were removed, 129 articles remained. After screening based on the title and abstract 26 articles yielded for full-text review. Finally, 5 articles (K. Kozuma, S. Tsuchiya, J. Kohori, T. Hase, & I. Tokimitsu, 2005; Ryuji Ochiai et al., 2004; Park et al., 2010; Roshan, Nikpayam, Sedaghat, & Sohrab, 2018; Yamaguchi et al., 2008) with 9 studies were included in this meta-analysis (**Figure 1**).

Characteristics of the included studies

The characteristics of the included studies are summarized in Table 1. These studies were published between 2004 and 2018 and were conducted in the Iran (Roshan et al., 2018), south Korea (Park et al., 2010), and Japan (K. Kozuma et al., 2005; Ryuji Ochiai et al., 2004; Yamaguchi et al., 2008). The follow-up period ranged from 4 to 16 weeks. Daily recommended dosage of green coffee varied between 46 and 800 mg in these studies. The design of all the included trials was parallel. All studies were done on both genders except for one trial that included women only (Park et al., 2010), and four studies on men only (K. Kozuma et al., 2005; Ryuji Ochiai et al., 2004). The sample size in the included trials ranged from 31 (Ryuji Ochiai et al., 2004) to 72 (Yamaguchi et al., 2008). Participants in include studies were patients with the metabolic syndrome (Roshan et al., 2018), healthy subjects (R. Ochiai et al., 2008; Park et al., 2010), and patients with hypertension (K. Kozuma et al., 2005; Yamaguchi et al., 2008).

Quality assessment

Methodological quality and risk of bias of included studies was provided in **Supplemental Table 1.** Most studies demonstrated adequate quality for key factors (Kazuya Kozuma et al.,

2005; Park et al., 2010; Yamaguchi et al., 2008). Two have fair quality for blinding of outcome assessment (Ryuji Ochiai et al., 2004) and selective outcome reporting (Roshan et al., 2018), respectively.

Meta-analysis results

Effect of green coffee extract supplementation on SBP

Nine studies including a total of 501 participants (case=251 and control=250) reported SBP as an outcome measure. Overall results from the random-effects model indicated that green coffee extract supplementation administration did result in significant change in SBP after green coffee supplementation WMD: -3.093 mmHg, 95% CI: -3.914, -2.273, p<0.001) with no significant heterogeneity among the studies ($I^2 = 0.0\%$, p = 0.454) (**Figure2**). In the subgroup analysis, we found that green coffee extract supplementation remained significant in hypertensive subjects, and metabolic syndrome patients. In addition, there was a greater significant reduction in SBP in studies with green coffee dosage ≥400 mg (WMD: -7.21 mmHg, 95% CI: -13.73, -0.69, p = 0.030) and a significant reduction with intervention duration ≤4 weeks (WMD: -3.12 mmHg, 95% CI: -3.96, -2.27, p<0.001) (**Supplemental figure 1**).

Effect of green coffee extract supplementation on DBP

9 studies including a total of 501 participants (case=251, and control=250) reported DBP as an outcome measure. Combined results from the random-effects model indicated that DBP did change significantly following green coffee extract administration (WMD: -2.170 mmHg, 95% CI: -2.749, -1.590, p<0.001) with low heterogeneity among the studies ($I^2 = 46.5\%$, p = 0.060) (**Figure 3**). When, we conducted subgroup analyses based on health status; green coffee extract administration reduced DBP only in hypertensive subjects (WMD: -2.179 mmHg, 95% CI: -2.524, -1.834,

p<0.001). In addition, green coffee extract administration reduced DBP in studies with intervention duration ≤4 weeks and green coffee dosage <400 mg (**Supplementary figure 2**).

Sensitivity analysis

To discover the impact of each single study on the combine effect size, we removed each trial from the analysis, step by step. We observed no significant effect of any individual study on the combine effect sizes of SBP and DBP (**Supplementary figure 3**).

Publication bias

Evaluation of publication bias by visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of green coffee extract supplementation on SBP and DBP (**Figure 4**).

Discussion

Bioactive phytochemicals of coffee have gained prominence due to their reputed biological properties, including; antioxidant and anti-inflammatory activities, increased fatty acid oxidation and insulin sensitivity, modulation of glucose absorption and utilization, and antihypertensive effects (Godos et al., 2014; Sudeep, Venkatakrishna, Patel, & Shyamprasad, 2016). Although coffee contains numerous bioactive phytochemicals, the traditional coffee roasting process inhibits significant amounts of the phytochemicals that are purportedly responsible for the biological actions, such as chlorogenic acid (Esquivel & Jiménez, 2012). To ameliorate loss of some compounds with beneficial, health-eliciting effects, coffee can also be used as GCBE (Esquivel & Jiménez, 2012). Green coffee bean extract is comprised of unroasted coffee beans and contains higher amounts of bioactive phytochemicals than that for the usual roasted coffee that is generally consumed (Esquivel & Jiménez, 2012; Sarriá, Martínez-López, Mateos, & Bravo-Clemente, 2016). The unroasted variant of coffee, the green coffee bean, has been purported to elicit

numerous, potential, positive effects on indices of blood pressure. Indeed, GCBE has been shown to elicit anti-hypertensive effects in spontaneously hypertensive rats [9], and in mildly hypertensive humans [10]. Given the health burden globally associated with hypertension and cardiovascular disease, and the dearth of consensus on the efficacy of GCBE in reducing blood pressure, the aim of the present study was to determine the efficacy and effectiveness of GCBE supplementation on blood pressure. In the present meta-analysis, we summarized results from nine studies which examined the effects of GCBE supplementation on SBP and DBP in adults. Our results indicated that GCBE supplementation can significantly reduce SBP and DBP. Whilst in the subgroup analyses, we found significant reductions in SBP and DBP for patients with pre-existing hypertension, particularly at dosages of ≥400 mg.

Polyphenols are abundant secondary metabolites in plants and are asserted to prevent, or at least ameliorate, diseases associated with oxidative stress and their associated complications. The glycosylated derivate forms of polyphenol, chlorogenic acids (ester of caffeic acid and quinic acid) are the principal polyphenol in coffee (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). There is agglomerative evidence that coffee positively impacts metabolic syndromes such as obesity, type 2 diabetes, atherosclerosis, and insulin-resistance (Dickson et al., 2015; Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014; Ho et al., 2012). Moreover, many pharmacological studies regarding GCBE supplementation demonstrate that the chlorogenic acids in green coffee regulates hypertensive, vasoreactivity, and glucose metabolism (Blum, Lemaire, & Lafay, 2007; Kazuya Kozuma et al., 2005). Indeed, in the present study we highlight that GCBE supplementation can significantly reduce SBP and DBP, and when stratified by health status, GCBE remains effective in reducing SBP and DBP in patients with preexisting hypertension, but not metabolic syndrome. Onakpoya et al, (Onakpoya et al., 2015) previously reported that GCBE

supplementation significantly reduces SBP and DBP; problematically, however, in Onakpoya et al, only five eligible studies were included, with only Asian populations represented and no stratification by health status (Onakpoya et al., 2015). Thus, the authors concluded SBP and DBP are reduced; however, in the present study we were able to include a larger sample, a more diverse population, and demonstrate that the hypotensive effects of GCBE supplementation, specific to DBP, are only evident in patients with preexisting hypertension and not metabolic syndrome; whilst both patient groups had favorable reductions in SBP.

Hypertension is associated with a variety of serious consequences and comorbidities, including; kidney disease, diabetes, stroke, heart disease and many others. It has been reported that for each 2 mmHg rise in SBP, this corresponds to a 7% increased risk of mortality from heart disease, in addition to a 10% increased risk of stroke ("Overview | Hypertension in adults: diagnosis and management | Guidance | NICE," 2019). Consumption GCBE has been reported to reduce BP and BMI via its' influence on 11β-HSD1 Enzyme Activity, through the reduction of the stress hormone level, cortisol ("Overview | Hypertension in adults: diagnosis and management | Guidance | NICE," 2019; Revuelta-Iniesta & Al-Dujaili, 2014). Mechanistically, CGAs are involved in the suppression of macrophage infiltration, and thus may be involved in blood vessel remodeling (Kanno et al., 2013). Furthermore, the blood pressure reducing properties of CGA constituents (caffeic or ferulic acid) have been studied in animals (Suzuki et al., 2002), where intravenous injections of these acids at higher relative doses revealed stronger hypotensive effects. Human studies have demonstrated that although there is inter-individual variability in the absorption and pharmacokinetics, CGA has high bioavailability when consumed orally (Farah, Monteiro, Donangelo, & Lafay, 2008; Monteiro, Farah, Perrone, Trugo, & Donangelo, 2007;

Stalmach, Steiling, Williamson, & Crozier, 2010). Supporting the assertion of high bioavailability when orally consumed, , we found a greater reduction in SBP at dosages of ≥400 mg.

Strength and limitations

The primary strength of this study was that this meta-analysis provided a comprehensive overview of the effect of GCBE supplementation of blood pressure indices, far beyond evidence thus far, manifest in human-based RCTs; and given the potential influence on the treatment or management of hypertension, this is worthwhile endeavor. The evidence base, prior to this meta-analysis, was relatively bereft of uniformity, with the preceding meta-analysis only including five studies of homogenous populations, and thus urgently required a summative, quantitative assessment, which we have provided. We demonstrated that there is sufficient evidence for GCBE supplementation to elicit positive effects on SBP and DBP. Another strength of the current meta-analysis is the assimilation of the heterogeneous sample of participants, with a range of demographic statuses, ethnicities and ages. We were also able to stratify analyses based on both duration of supplementation and dosage, in addition to health status, thereby providing foresight into expected outcomes based on such information and highlighting that reductions in DBP may only be manifest in patients with preexisting hypertension, and not metabolic syndrome.

Notwithstanding, the current study has some limitations. The extent to which concomitant lifestyle adjustments influenced the results seen in the meta-analyses is uncertain. Apart from coffee, CGA is available in a wide variety of foods including potatoes, fruits and peanuts; on the average, humans are thought to consume approximately 1g of CGA daily via food intake (Suzuki et al., 2006). Whether the extra amount of CGA consumed by trial participants led to an enhancement of its effect on blood pressure is not clear. The adverse event reports from the included studies suggest that CGA is generally safe. In a previous report, CGA consumption has

been reported to increase plasma total homocysteine concentration, which is a risk factor for coronary heart disease (Olthof, Hollman, Zock, & Katan, 2001).

The analyses were not restricted to solitarily include patients of one type, consequently, this permitted a larger number of studies and participants to be included for analyses, however could conceivably impact mechanism of action and effectiveness. Some included trials were small in sample size, and it has been demonstrated by Sterne *et al.* that it is probable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools (Sterne & Egger, 2001). Nevertheless, this was out of the operational control of the meta-analysis.

Conclusion

The results of current meta-analysis study support the use of GCBE supplementation for the improvement of blood pressure indices, with sub-group analysis highlighting greater improvements in dosages of ≥400 mg. However, notwithstanding the positive effect elicited by GCBE supplementation for SBP cross health statuses, it is evident that for DBP, significant effects only remain in patients with preexisting hypertension, and not metabolic syndrome. Moreover, there appears no deleterious or adverse side effects manifest as a result of GCBE supplementation; notwithstanding, however, further studies concerned with safe levels of GCBE consumption are warranted.

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Table 1. Characteristics of eligible studies.

Author, Country, year	Clinical trial design	Population	Sex	Sample size GCE/Placebo	Duration	Outcome	Intervention	
							Intervention group	**Placebo group**
Kazuya KOZUMA et al, Japan,2005 (a)	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	31/29	4 weeks	Weight, BMI	185 mg/d GCBE	NR
Kazuya KOZUMA et al, Japan,2005 (b)	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	28/29	4 weeks	Weight, BMI	93 mg/d GCBE	NR
Kazuya KOZUMA et al, Japan,2005 (c)	randomised double-blind clinical trial/parallel	Mildly hypertensive patient	Men	29/29	4 weeks	Weight, BMI	46 mg/d GCBE	NR
Yamaguchi et al, Japan, 2008	randomised double-blind clinical trial/parallel	mildly hypertensive men and women	Both	37/37	4 weeks	Weight, BMI	82 mg/d CGAs	The zero-dose coffee contained 0 mg of CGA
Yamaguchi et al, Japan, 2008	randomised double-blind clinical trial/parallel	mildly hypertensive men and women	Both	35/37	4 weeks		172mg/d CGAs	The zero-dose coffee contained 0 mg of CGA
Yamaguchi et al, Japan, 2008	randomised double-blind clinical trial/parallel	mildly hypertensive men and women	Both	37/37	4 weeks		299mg/d CGAs	The zero-dose coffee contained 0 mg of CGA

Ryuji OCHIAI et al, Japan, 2004	randomized, placebo-controlled, cross-over study	Normotensive males	Men	16/15	4 weeks	Weight	368ml coffee drink contain 598 mg/d CGAs	NR
Park Ju Yeon et al, south Korea, 2010	randomised double-blind clinical trial/parallel	Overweight women	women	23/20	8 weeks	Weight, BMI, WC	200 mg/d GCBE	NR
Hanieh Roshan et al, Iran, 2018	randomised double-blind clinical trial/parallel	patients with the metabolic syndrome	Both	21/22	8 weeks	Weight, BMI, WC	800 mg/d GCBE	NR