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ORIGINAL ARTICLE

The effect of ginseng (genus *Panax*) on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials

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Pre-clinical evidence indicates the potential for ginseng to reduce cardiovascular disease risk and acutely aid in blood pressure (BP) control. Clinical evidence evaluating repeated ginseng exposure, however, is controversial, triggering consumer and clinician concern. A systematic review and meta-analysis were conducted to assess whether ginseng has an effect on BP. MEDLINE, EMBASE, Cochrane and CINAHL were searched for relevant randomized controlled trials $\geqslant$ 4 weeks that compared the effect of ginseng on systolic (SBP), diastolic (DBP) and/or mean arterial (MAP) BPs to control. Two independent reviewers extracted data and assessed methodological quality and risk of bias. Data were pooled using random-effects models and expressed as mean differences (MD) with 95% confidence intervals (CIs). Heterogeneity was assessed and quantified. Seventeen studies satisfied eligibility criteria ($n = 1381$). No significant effect of ginseng on SBP, DBP and MAP was found. Stratified analysis, although not significant, appears to favour systolic BP improvement in diabetes, metabolic syndrome and obesity (MD = −2.76 mm Hg (95% CI = −6.40, 0.87); $P = 0.14$). *A priori* subgroup analyses revealed significant association between body mass index and treatment differences ($\beta = -0.95$ mm Hg (95% CI = −1.56, −0.34); $P = 0.007$). Ginseng appears to have neutral vascular affects; therefore, should not be discouraged for concern of increased BP. More high-quality, randomized, controlled trials assessing BP as a primary end point, and use of standardized ginseng root or extracts are warranted to limit evidence of heterogeneity in ginseng research and to better understand its cardiovascular health potential.

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INTRODUCTION

Hypertension (HTN) remains a significant risk factor for cardiovascular disease, affecting more than 1 billion individuals worldwide and accounting for ~9.4 million deaths per year.[1] Despite improvement in detection and treatment strategies, blood pressure (BP) control remains elusive. With pursuit for more effective management strategies, there has been growing interest in the use of medicinal herbs, with ginseng emerging as a serious contender.

The herb ginseng has long-been considered by Asian pharmacopeia as a 'cure-all' tonic and valued for its exceptional therapeutic properties. Consequently, ginseng has been studied extensively, with growing evidence attributing its pharmacological effects to the presence of triterpenoid saponins, known as ginsenosides. Despite its therapeutic promise, ginseng is often unwarrantedly avoided by consumers and practitioners, because of clinically unproven concerns from an early observational study suggesting it may adversely affect BP.[2] Pre-clinical research has consistently contradicted these findings, suggesting ginseng and its individual ginsenosides have the potential to acutely reduce BP.[3–6] Clinical evidence to support these findings, however, remains controversial.[7–14] To clarify uncertainty and to assess whether ginseng has an effect on systolic (SBP), diastolic (DBP) and mean arterial (MAP) BPs, a systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted.

MATERIALS AND METHODS

The Cochrane Handbook for Systematic Reviews of Interventions was used as a guideline for this meta-analysis and reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[15] The review protocol is available at the ClinicalTrials.gov (registration no. NCT01913210).

Study selection

Relevant RCTs were identified using MEDLINE, EMBASE, Cochrane Central and CINAHL, through 28 April 2014, with the search strategy: *Panax* OR *ginseng* OR *ninjin* OR *renshen* OR *shinseng* OR *jen shen* OR *schinseng* OR *quinquefolius* OR *ginsenosides* AND *Blood Pressure* OR *BP* OR *diastolic pressure* OR *systolic pressure* OR *SBP* OR *DBP* OR *MAP* OR *mean arterial pressure*. Manual searches of references cited by published studies supplemented the electronic search. Eligible RCTs were those that investigated the effect of ginseng of the genus *Panax* on SBP, DBP and/or MAP, for minimum 4 weeks. Trials less than 4 weeks in duration, lacked suitable control, had no viable end point data and where ginseng was part of a multi-herbal treatment were excluded. Duration of 4 weeks was chosen as it is suggested to be a minimal recommended period to

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estimate the effect size of a dose of an antihypertensive agent.[16] No restriction was placed on language.

Data extraction and management

Data were extracted by two independent reviewers (AMK and ES), using a standardized *pro forma*. The Heyland Methodological Quality Score (MQS) was used to assess study quality, where a score $\geqslant 8$ was considered high quality.[17] Each study was also assessed using the Cochrane Risk of Bias Tool (sequence generation, allocation concealment, blinding, outcome data and reporting).[18] Disagreements between reviewers were resolved by consensus.

Baseline and end mean ± standard deviation (s.d.) or mean change from baseline ± s.d. for SBP, DBP and MAP were extracted when possible. Missing s.d. were calculated from 95% confidence interval (CI), *P* values, *t* or F statistics using standard formulae, if available.[18] When neither s.d. of end value nor s.d. of change from baseline could be calculated, change from baseline values was used and s.d. of change from baseline was imputed. Standard deviation of change from baseline was imputed by pooling available s.d. of change from baseline values from other studies included in the analysis. If available, mean end difference ± standard error (s.e.(MD)) or mean change from baseline difference ± s.e.(MD) values between groups were also extracted. When MAP was not reported directly, it was calculated using the formula: MAP = 2/3 DBP+1/3 SBP. The s.d. for calculated MAP were imputed as:

$$\frac{1}{\sqrt{N}} * \sqrt{\left(\frac{1}{3}\right)^2 s^2_{\text{SBP}} + \left(\frac{2}{3}\right)^2 s^2_{\text{DBP}}}$$

where *N* is sample size and *s* is the s.d.[19]

All crossover trials underwent paired analyses. If s.e.(MD) were missing for crossover trials, a coefficient of 0.50 was assumed, as it is a conservative estimate for an expected range of 0–1, because of insufficient data, to impute s.e.(MD) of between-treatment end value or change from baseline differences. Sensitivity analyses were performed using correlation coefficient of 0.25 and 0.75 (Supplementary Table 1). Authors were contacted whenever possible to request additional information ($n = 5$).[9,11,13,20,21]

Statistical analysis

Data were analyzed using Review Manager 5.2.7 (The Cochrane Collaboration, Copenhagen, Denmark). Pooled analyses were conducted using the Generic Inverse Variance Method with random-effects models. Analyses were further stratified in to three groups based on study inclusion criteria: (1) diabetes, metabolic syndrome or obesity (DM/MetS/Obesity), those who had type 2 diabetes, metabolic syndrome or were obese, as they share co-morbidities, (2) established HTN, those who did not have type 2 diabetes or metabolic syndrome as part of the inclusion criteria and (3) otherwise healthy (OH), those who did not meet the primary criteria for the other major groups. Data were expressed as mean differences (MD) with 95% confidence intervals (CIs). To mitigate the unit-of-analysis error including trials with multiple intervention arms, we combined arms to create single pairwise comparisons ($n = 4$).[14,22–24]

Inter-study heterogeneity was assessed by the Q-statistic (χ^2) and quantified by I^2 with $P < 0.10$ significant. An $I^2 \geqslant 50\%$ indicated 'substantial' heterogeneity and $\geqslant 75\%$ indicated 'considerable' heterogeneity.[18] Sources of heterogeneity were explored with *a priori* subgroup analyses of respective baseline BP values, study design, duration, MQS and ginseng preparation, and species. Continuous and dichotomous meta-regressions further assessed the significance of subgroup effects. Studies that included multiple comparisons were separated for subgroup analyses. Sensitivity analyses were performed to determine whether any single study exerted particular influence on the overall results by removing each individual study from the meta-analysis and re-calculating the effect size of the remaining studies. Publication bias was assessed by visual inspection of funnel plots and formally tested using Egger and Begg tests, where $P < 0.10$ was considered evidence of small-study effects. To attempt to identify and correct for funnel plot asymmetry, Trim-and-Fill analyses were used. Meta-regressions and publication bias assessment were performed using STATA 12 (StataCorp, College Stations, TX, USA).

RESULTS

Search results and study characteristics

Figure 1 shows the flow of literature. The search identified 731 reports, of which 17 studies ($n = 1381$ participants) were selected for analysis with a median duration of 9 weeks (range: 4–16 weeks).[8,9,11–14,20–30] Three reports were deemed irretrievable following unsuccessful library and database requests and attempts to contact the authors.

Table 1 displays the characteristics of included reports. The majority of studies (76.5%) were parallel in design. Seven studies (41%) were conducted in individuals with reported diabetes, metabolic syndrome and/or obesity, 2 (12%) in individuals with established HTN and 8 (47%) in OH individuals. The median reported age of participants was 44 years (range: 22–64 years). Twelve studies (70.6%) investigated *Panax ginseng* species, 5 (29.4%) investigated *Panax quinquefolius* and 1 (5.9%) investigated *Panax notoginseng*. One study investigated both *Panax quinquefolius* and *Panax ginseng* independently.[24] Seven studies (41.2%) reported using ginseng extract, 4 (23.5%) reported using full ginseng root or rootlets and the ginseng preparation used in 6 studies (35.3%) were undetermined. Based on Heyland MQS, 9 studies (52.9%) were high quality (MQS $\geqslant 8$; Supplementary Table 2) and using the Cochrane Risk of Bias Tool, studies were found to have low or unclear risk of bias in the majority of measured domains (Supplementary Figure 1). Only three studies included a dietary assessment of study participants, and reported no change in diet within or between groups over the study period.[13,23,30]

Systolic blood pressure

Sixteen studies ($n = 924$ ginseng, 537 control) provided data on ginseng and SBP (Figure 2). Ginseng did not have a significant effect on SBP in the pooled (MD = − 0.38 mm Hg (95% CI = − 1.86, 1.11); $P = 0.62$) and stratified analyses: DM/MetS/Obesity: (MD = − 2.76 mm Hg (95% CI = − 6.40, 0.87); $P = 0.14$), HTN: (MD = 0.49 mm Hg (95% CI = − 2.18, 3.16); $P = 0.72$), OH: (MD = 0.67 mm Hg (95% CI = − 0.57, 1.92); $P = 0.29$). No significant difference between strata effects was observed. There was significant evidence of inter-study heterogeneity in the overall analysis ($I^2 = 54\%$; $P = 0.005$) and the DM/MetS/Obesity stratum ($I^2 = 68\%$; $P = 0.005$). Sensitivity analysis did not modify the overall effect for SBP, however, with removal of one study,[9] there remained no significant evidence of heterogeneity in the overall analysis ($I^2 = 0\%$; $P = 0.70$) or DM/MetS/Obesity stratum ($I^2 = 0\%$; $P = 0.78$). Continuous meta-regression analysis revealed a significant negative linear association between intervention differences with ginseng and baseline body mass index, per 1 mmHg, relative to control ($\beta = -0.95$ mm Hg (95% CI = − 1.56, − 0.34); $P = 0.007$). Additional *a priori* subgroup analyses were not significant (Supplementary Table 3 and Supplementary Figure 2).

Diastolic blood pressure

Sixteen studies ($n = 924$ ginseng, 537 control) provided data on ginseng and DBP (Figure 3). Ginseng did not have a significant effect on DBP in the pooled analysis (MD = 0.17 mm Hg (95% CI = − 1.04, 1.38); $P = 0.79$) or stratified analyses: DM/MetS/Obesity: (MD = − 0.95 mm Hg (95% CI = − 2.47, 0.58); $P = 0.22$), HTN: (MD = 1.43 mm Hg (95% CI = − 1.41, 4.26); $P = 0.32$), OH: (MD = 0.69 mm Hg (95% CI = − 1.38, 2.76); $P = 0.51$). No significant difference between strata effects was observed. There was significant evidence of inter-study heterogeneity in the pooled analysis ($I^2 = 69\%$; $P < 0.001$), the DM/MetS/Obesity stratum ($I^2 = 71\%$; $P = 0.002$) and the OH stratum ($I^2 = 76\%$; $P = 0.0004$). Sensitivity analysis did not modify the overall effect for DBP, however, with removal of one study,[13] there remained no

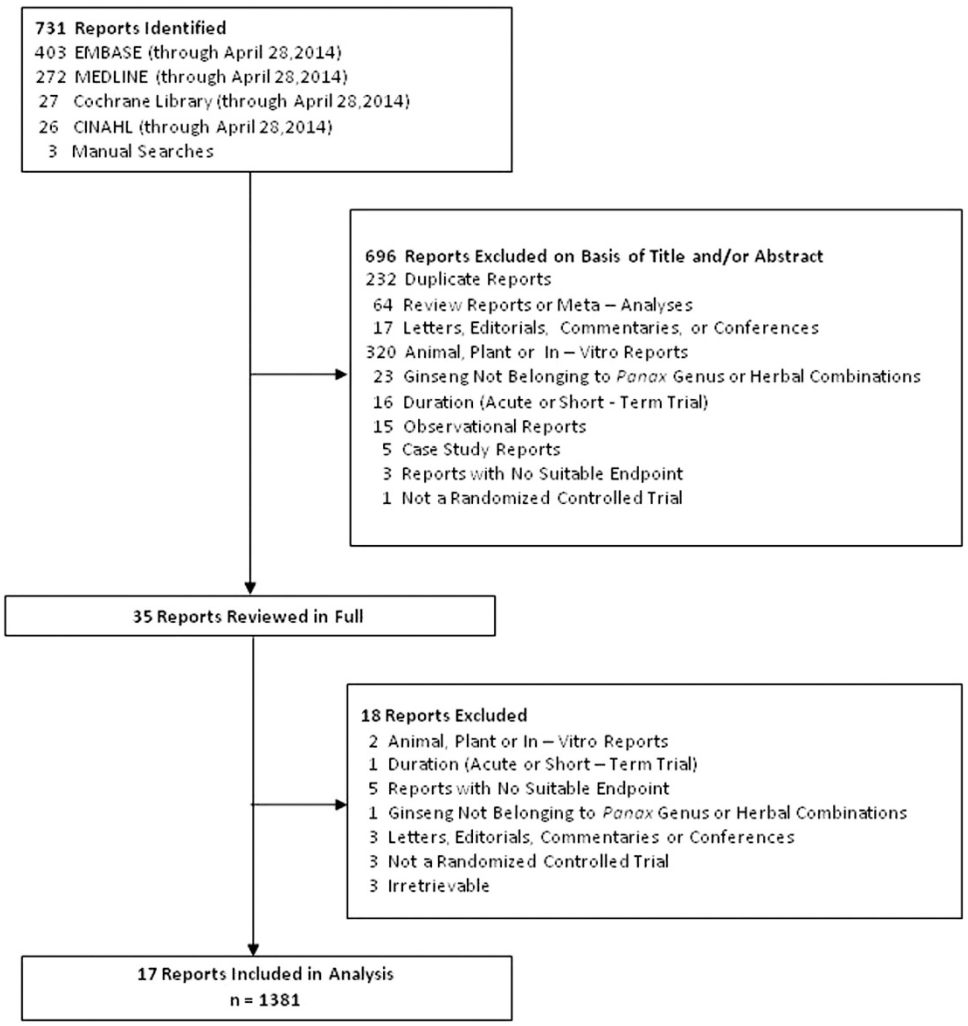

Figure 1. Flow of the literature search.

significant evidence of heterogeneity in the DM/MetS/Obesity stratum ($I^2 = 0\%$; $P = 0.74$). *A priori* subgroup analyses were not significant (Supplementary Table 3 and Supplementary Figure 3).

Mean arterial pressure

The data from sixteen studies ($n = 454$ ginseng, 265 control) were used to assess the effect of ginseng on MAP (Supplementary Figure 4). Ginseng did not have a significant effect on MAP in the pooled analysis (MD = 0.07 mm Hg (95% C = − 1.28, 1.43); $P = 0.91$), or stratified analyses: DM/MetS/Obesity: (MD = − 0.62 mm Hg (95% CI = − 2.98, 1.73); $P = 0.60$), HTN: (MD = 0.31 mm Hg (95% CI = − 0.95, 1.57); $P = 0.63$), OH: (MD = 0.69 mm Hg (95% CI: − 0.99, 2.37); $P = 0.42$). No significant difference between strata effects was observed. There was significant evidence of inter-study heterogeneity in the pooled analysis ($I^2 = 98\%$; $P < 0.00001$), the DM/MetS/Obesity ($I^2 = 99\%$; $P < 0.00001$) and OH ($I^2 = 92\%$; $P < 0.00001$) strata. Continuous meta-regression analysis revealed a significant negative linear association between intervention differences with ginseng and baseline body mass index, per 1 mmHg, relative to control ($\beta = -0.62$ mm Hg (95% CI = − 1.20, − 0.04); $P = 0.038$). Additional *a priori* subgroup analyses were not significant (Supplementary Table 3 and Supplementary Figure 5).

Publication bias

Visual inspection of funnel plots revealed asymmetry favouring studies with increasing SBP and MAP effects (Supplementary Figure 6). Egger test was not significant for SBP ($P = 0.344$), however; Begg test was significant ($P = 0.027$) for SBP. Egger and Begg tests were not significant for MAP (Supplementary Figure 6). Trim-and-Fill analysis identified five 'missed' studies for SBP (Supplementary Figure 7). Imputation of these studies resulted in a significant adjusted intervention effect of ginseng for SBP (MD = − 2.64 mm Hg (95% CI = − 4.81, − 0.46); $P = 0.02$). Trim-and-Fill identified two 'missed' studies for MAP that when imputed did not result in a significant adjusted intervention effect (Supplementary Figure 7). No significant evidence of publication bias was revealed for DBP (Supplementary Figure 6).

DISCUSSION

We conducted a systematic review and meta-analysis of 17 RCTs in 1381 individuals with and without HTN, with median trial duration of 9 weeks, in order to evaluate the effect of ginseng on BP control. Pooled analyses determined an overall neutral effect of ginseng on SBP, DBP and MAP, compared with control. Further stratification revealed no significant between or within strata effects of ginseng on SBP, DBP or MAP, although analysis appears to favour ginseng for improved SBP within the DM/MetS/Obesity stratum. *A priori* subgroup analyses revealed significant evidence of a linear baseline-response association for SBP (per 1 mmHg), suggesting great SBP improvements with ginseng supplementation in individuals with higher baseline BP values.

Table 1. Characteristics of included studies

Study[a]	*Design*	*Blinding*	*Duration (weeks)*	*Participants*[b]	*Age*[c] *(years)*	*BMI (kg m^{-2})*	*SBP*[c] *(mmHg)*	*DBP*[c] *(mmHg)*	*Method*[d]	*Species*[e]	*Preparation*	*Dose*[f] *(g per day)*	*Control*	*BP medication (%)*	*Setting*	*MQS*[g]
Caron *et al.*[25]	P	Double	4	29 (13M:17F)	21.6	NA	112.7	73.3	Method A	PG	Extract	0.20	Lactose monohydrate	0	USA	7
Caso Marasco *et al.*[26]	P	Double	12	501 (232M:269F)	38.0	NA	115.0	74.5	NA	PG	Extract	0.04	Multi-vitamins	NA	Mexico	6
Cherdrungsi *et al.*[20]	P	Double	8	20 (20M:0F)	22.6	NA	106.5	65.5	Method A	PG	Extract	0.30	NA	NA	Thailand	9
Dickman *et al.*[27]	P	Double	16	25 (0M:25F)	62.0	24.7	123.2	76.5	Method A	PQ	Root	0.50	Rice powder	NA	USA	7
Kaneko *et al.*[22]	C	NA	9	29 (2M:27F)	41.0	NA	NA	NA	Method C	PG	NA	6.0	NA	NA	Japan	9
Kim *et al.*[28]	P	Double	12	38 T2DM (23M:15F)	53.7	24.4	121.7	74.7	NA	PG	NA	0.78	Cellulose	NA	Korea	6
Kim *et al.*[23]	P	Double	8	57 (23M:34F)	36.2	23.4	117.2	78.5	Method C	PG	NA	3.0 6.0	Corn starch	0	Korea	6
Kwon *et al.*[21]	P	Double	8	45 OB (0M:45F)	43.8	28.0	122.9	77.4	Method B	PG	Extract	6.0	Corn starch	NA	Korea	8
Liang *et al.*[29]	P	Double	4	29 (15M:14F)	22.5	NA	NA	101.8	Method B	PN	NA	1.35	Starch	0	USA	7
Mucalo *et al.*[11]	P	Double	12	64 T2DM (22M:42F)	63.1	33.4	145.0	84.0	Method C	PQ	Extract	3.0	Corn starch	100	Croatia	8
Park *et al.*[9]	P	Double	12	48 MetS (0M:48F)	44.7	NA	132.8	85.7	Method B	PG	Root	4.5	NA	0	Korea	8
Rhee *et al.*[8]	P	Double	12	64 HTN (28M:36F)	59.6	24.7	138.0	85.4	Method C	PG	NA	3.0	NA	100	Korea	7
Seo *et al.*[24]	P	NA	4	280 (280M:0F)	21.7	22.4	NA	NA	NA	PG PQ	NA	3.0	NA	NA	China, Korea	9
Stavro *et al.*[12]	C	Double	12	37 HTN (30M:7F)	58.4	28.6	130.0	79.8	Method D	PQ	Root	3.0	Corn starch	86	Canada	10
Vuksan *et al.*[13]	C	Double	12	19 T2DM (11M:8F)	64.0	28.9	134.3	77.5	Method C	PG	Rootlets	6.0	Corn starch	NA	Canada	8
Xu[30]	C	Double	8	24 T2DM (14M:10F)	64.0	NA	134.2	82.0	Method B	PQ	Extract	3.0	Corn flour	NA	Canada	7
Yoon *et al.*[14]	P	Double	8	72 T2DM (44M:28F)	52.8	25.3	125.1	77.8	NA	PG	Extract	1.5 2.0 3.0	NA	NA	Korea	10

Abbreviations: BMI, body mass index; C, crossover design; F, female; HTN, hypertension; M, male; MetS, metabolic syndrome; MQS, Heyland Methodological Quality Score; NA, not available; OB, obese; OP, outpatient; P, parallel design; PG, *Panax ginseng*; PN, *Panax notoginseng*; PQ, *Panax quinquefolius*; T2DM, type-2 diabetes mellitus. [a]Kaneko *et al.*,[22] Kim *et al.*,[23] Seo *et al.*[24] and Yoon *et al.*[14] contained multiple comparisons, and to mitigate unit-of-analysis error, we combined groups to create a single pairwise comparison. [b]MetS included participants with three or more risk factors defined by National Cholesterol Education Program Adult Treatment Panel III. M:F ratio for Caron *et al.*[25] is based on pre-dropout. [c]Baseline values provided. When multiple values were reported, weighted mean was calculated. Data are expressed as mean ± s.d. Caso Marasco *et al.*[26] did not report s.d. [d]Method of BP measurement: Method A = indirect ausculatory method using stethoscope and sphygmomanometer; Method B = standard mercury sphygmomanometer; Method C = measured in triplicate using automatic blood pressure monitor; Method D = 24-h ambulatory measurements. [e]Ginseng species is reported individually for trials with multiple treatment groups. [f]Ginseng dose is reported individually for trials with multiple treatment groups. All ginseng doses were compared with placebo or an adequate control. [g]Study quality was assessed by MQS and trials with a score ⩾8 were considered to be of high quality.

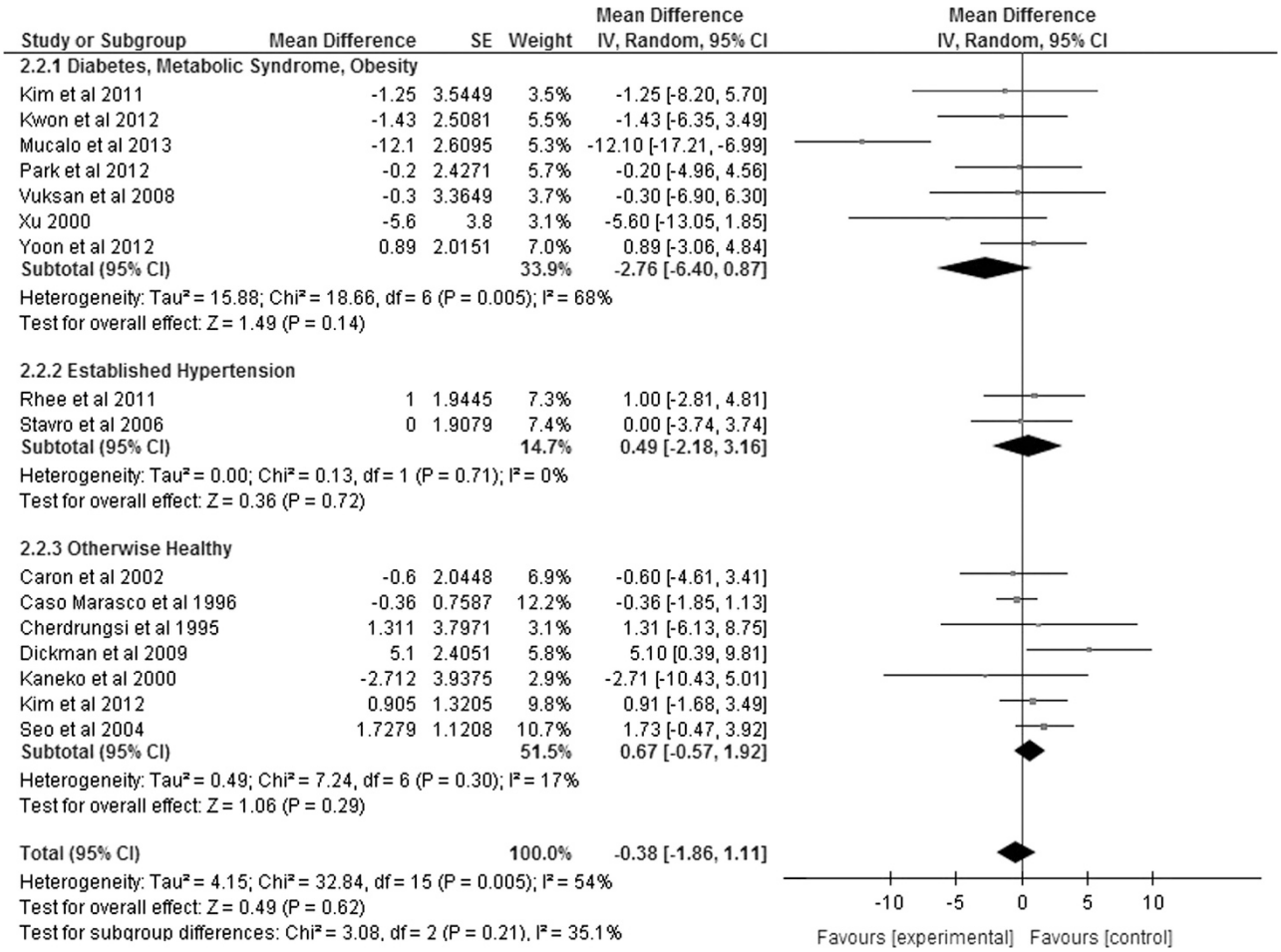

Figure 2. Forest plot of randomized controlled trials investigating the effect of ginseng on systolic blood pressure (SBP). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MDs with 95% CIs. *P* values are for generic inverse variance random-effects models. Inter-study heterogeneity was accessed by Q-statistic (χ^2) and quantified by I^2 with significance $P < 0.10$ and $I^2 \geqslant 50\%$ indicated substantial heterogeneity and $\geqslant 75\%$ indicated considerable heterogeneity.

To our knowledge, one additional meta-analysis has been conducted specifically looking at the effect of ginseng on BP.[31] The analysis, consisting of only five RCTs, provides limited evidence of the effectiveness of ginseng on BP, as the number of included RCTs and total sample size were insufficient to draw conclusions. Furthermore, diversity is lacking as the same research group performed the majority of included trials. Despite limitations, the findings do align with those of our meta-analysis, reporting overall no significant effect of ginseng on BP. Subgroup analyses for the other study did show an acute effect of Korean Red Ginseng (steamed *Panax ginseng*) on DBP. Our subgroup analyses do not support this finding; however, we did not limit our species analysis to the steamed variety only and we did not include BP effects in acute single-dose administration trials. Regardless, no adverse effect of ginseng on BP was found in either analyses, as was previously reported in an early observational study where increased BP, was self-reported by some participants, after consuming an array of ginseng species, formulations, doses, routes and administrations.[2] Although limited in design and extensive pre-clinical research has since contradicted its results, the findings from the study continue to be influential on the health community, leading to avoidance of ginseng by consumers. In this systematic review and meta-analysis, our group did not further assess the safety and tolerability of ginseng supplementation. Findings from systematic reviews specifically evaluating the safety and tolerability of ginseng use in clinical trials, however, have reported that ginseng appears to be generally safe and free of any serious adverse events.

The findings of our study also complement those of a systematic review assessing the effect of ginseng on cardiovascular disease risk factors, including BP.[32] The review, consisting of 12 studies that reported on BP outcomes, found that the majority of studies, showed either no substantial change or a slight improvement in SBP and/or DBP. The interpretation of this review is complicated by its limitation to studies published in English only and the inclusion of a variety of study designs.

Our findings are not consistent with pre-clinical research, which support a potential BP lowering effect of ginseng. These studies suggest that ginseng exerts a direct vasodilatory effect on isolated blood vessels via the generation of endothelium-dependent nitric oxide and consequent enhancement of cyclic guanosine monophosphate.[4,33] The individual ginsenosides Rg_3, Rg_1, Rb_1, Rb_3 and Re have been reported to display antihypertensive and cardioprotective effects.[3,6,34,35] It is unclear why this discrepancy exists between pre-clinical and clinical data. It may be explained by poor standardization of ginseng and consequent high variability in ginsenoside content, which has been shown to correlate with variability in ginseng efficacy.[36] As compositional analysis was not provided by the majority of included trials in our analysis, it is possible that variations in those ginsenosides reported to display vasodilatory effects, had an impact on our

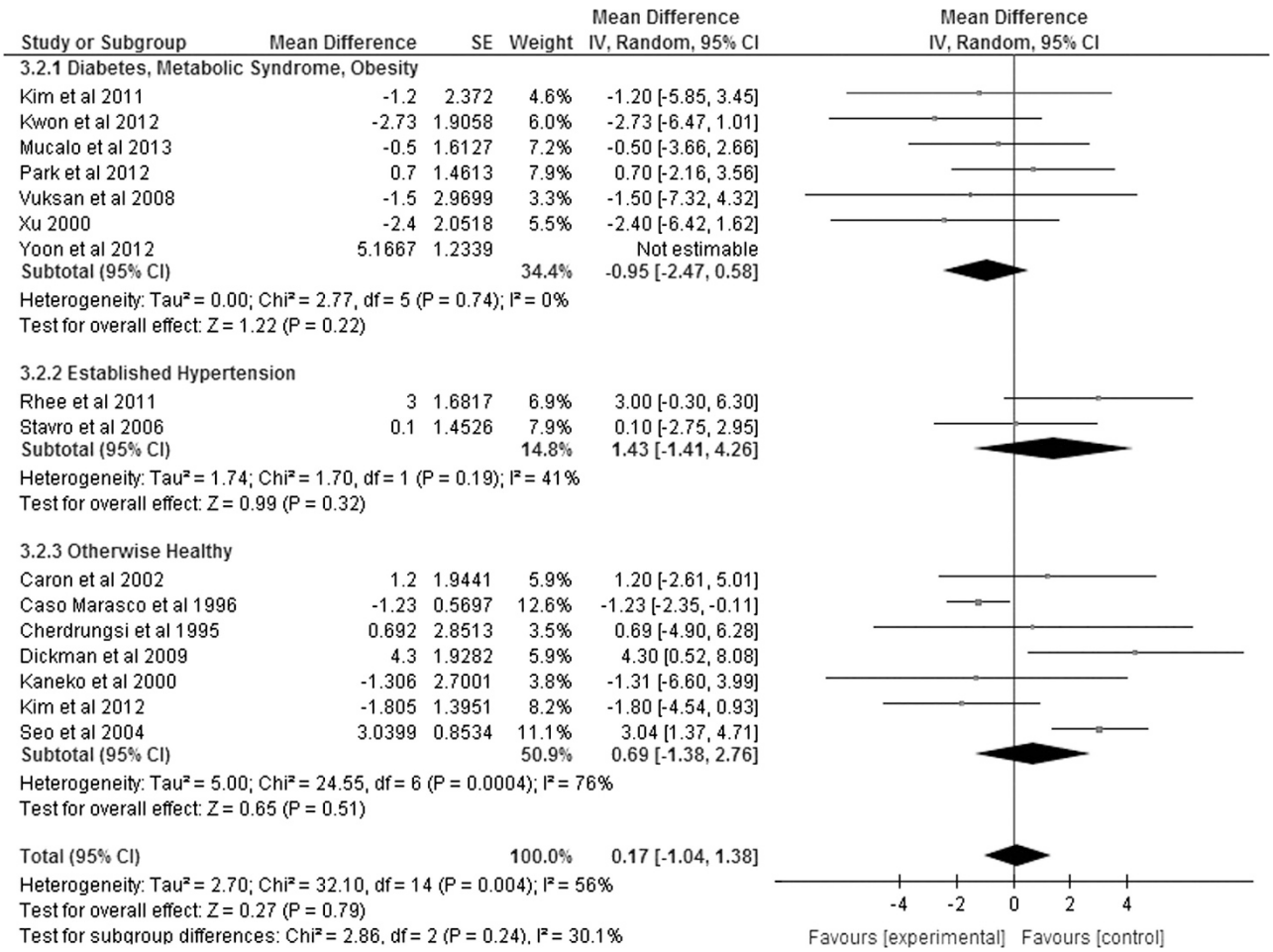

Figure 3. Forest plot of randomized controlled trials investigating the effect of ginseng on diastolic blood pressure (DBP). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MDs with 95% CIs. *P* values are for generic inverse variance random-effects models. Inter-study heterogeneity was accessed by Q-statistic (χ^2) and quantified by I^2 with significance $P < 0.10$ and $I^2 \geqslant 50\%$ indicated substantial heterogeneity and $\geqslant 75\%$ indicated considerable heterogeneity.

findings. The divergence in pre-clinical and clinical data may also be explained by variability in ginsenoside bioavailability and individual differences in intestinal microbiota.

We reported significant evidence of inter-study heterogeneity in the pooled analysis and DM/MetS/Obesity stratum for SBP. Sensitivity analysis revealed that removal of one study,[11] resulted in no evidence of heterogeneity. The effect size for the study was strongly in favour of SBP reduction with ginseng and was significantly greater than other studies included in our analysis. It is unclear why this difference exists. Potentially, the ginseng used had a more favourable ginsenoside profile or the difference may be attributed to the higher baseline SBP reported in the study. We also found significant evidence of heterogeneity in the pooled analysis and the DM/MetS/Obesity stratum for DBP. Sensitivity analysis revealed that with removal of one study,[14] there remained no significant evidence of heterogeneity. A potentially unique ginsenoside profile of Ginsam, the *Panax ginseng* vinegar extract used in the study, may account for this result.

The limitations of this meta-analysis should be considered. First, quality was low (MQS < 8) in 47% of the included studies; although, no effect of MQS (< 8 vs $\geqslant 8$) was revealed in subgroup analyses. Second, there was significant evidence of inter-study heterogeneity in our analyses, although sensitivity analyses explained the majority of heterogeneity in SBP and DBP, however; significant heterogeneity was unexplained for MAP. Third, the lack of standardization of ginseng and variability in ginsenoside profiles remains a challenge when interpreting ginseng research. Although isolated ginsenosides have been shown pre-clinically to benefit BP control, the optimal ginsenoside profile required to reproduce these benefits in a clinical setting is unknown. As the majority of studies in our analyses did not report specifics pertaining to the ginsenoside content of the intervention, it is difficult to generalize findings across studies. Moreover, lack of dietary assessment in most of the studies may introduce unknown confounders. Finally, publication bias remains a possibility, as we observed asymmetry favouring studies with SBP, in addition to a significant Begg test for SBP. Further, Trim-and-Fill analysis identified 'missed' studies that when imputed, resulted in a significant improvement in SBP. This highlights the need for further research in the area, with specific focus on the effect of ginseng on BP. Estimations derived from Trim-and-Fill should be interpreted with caution, however, as the method is less reliable when substantial evidence of inter-study heterogeneity is present.[37]

CONCLUSION

Findings of this systematic review and meta-analysis revealed an overall non-significant and neutral effect of ginseng (genus *Panax*) on SBP, DBP and MAP, relative to control. Stratified analyses although not significant, suggest that ginseng may have a more

favourable effect on SBP in individuals with diabetes, metabolic syndrome or obesity. This may have important clinical implications, as BP control remains elusive in the global population and HTN continues to be a significant risk factor for cardiovascular disease risk and mortality. Subgroup analyses suggest that ginseng may be more beneficial particularly for SBP, in individuals with higher baseline BP. The findings from this study also contribute to the present understanding of ginseng safety. Notably, ginseng had no significant adverse effect on BP, as was previously reported in early research. Although subject to limitations, findings suggest ginseng should not be avoided for concern of increased BP and may be explored safely in individuals with or at risk of HTN for its other associated health benefits, including diabetes control. Lack of ginseng standardization in clinical research, variability in ginsenoside bioavailability and individual differences in intestinal microbiota may account for the discrepancy between pre-clinical and clinical findings. Significant evidence of inter-study heterogeneity highlights the necessity for ginseng standardization in clinical research. Future long-term, high-quality, RCTs specifically investigating the effect of ginseng on BP and cardiovascular outcomes are warranted.

What is known about this topic?

- Despite widespread use, clinical evidence on the effect of ginseng on blood pressure is controversial.
- Use of ginseng in hypertension has been questioned.

What this study adds?

- Meta-analysis of 17 RCTs revealed a neutral effect of ginseng on systolic, diastolic or mean arterial pressure.
- Ginseng may be of some benefit in individuals with higher blood pressure.
- No adverse effects of ginseng on blood pressure were found in RCTs.

CONFLICT OF INTEREST

VV is holder of an American (No. 7,326,404 B2) and Canadian (No. 2,410,556) patent for use of viscous fibre blend in diabetes, metabolic syndrome and cholesterol lowering; currently holds grant support for ginseng research from the Canadian Diabetes Association (CDA), Canada and the National Institute of Horticultural and Herbal Science, RDA, Korea. JLS has received research support from the Canadian Institutes of Health Research (CIHR), the Calorie Control Council, Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and the International Tree Nut Council Nutrition Research and Education Foundation. He has received travel funding, speaker fees and/or honoraria from the American Heart Association, the American College of Physicians, the American Society for Nutrition, the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, the CDA, the Canadian Nutrition Society, the Calorie Control Council, the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, the International Life Sciences Institute North America, the International Life Sciences Institute, Brazil, the Abbott Laboratories, Pulse Canada, Dr Pepper Snapple Group and Coca-Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of both the CDA and the European Association for the study of diabetes, as well as being on the American Society for Nutrition writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high-fructose corn syrup. He is an unpaid scientific advisor for the International Life Science Institute North America, Food, Nutrition and Safety Program. His wife is employed by Unilever Canada. RJdS is funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to the WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of two systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. ES received funding from the Embassy of the State of Kuwait, Kuwait University. VH has received research support from the Ontario Graduate Scholarship (OGS) and the CIHR. AK, EJ and SBM have declared no conflict of interest.

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Supplementary Information accompanies this paper on the Journal of Human Hypertension website (http://www.nature.com/jhh)