REVIEW

The Nitrate-Independent Blood Pressure–Lowering Effect of Beetroot Juice: A Systematic Review and Meta-Analysis

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ABSTRACT

Beetroot is considered a complementary treatment for hypertension because of its high content of inorganic NO_3. This systematic review and meta-analysis aimed to clarify several aspects of beetroot juice supplementation on systolic blood pressure (SBP) and diastolic blood pressure (DBP). We searched PubMed, Scopus, and Embase databases, and the reference lists of previous reviews. Randomized clinical trials that investigated the effects of beetroot juice on resting blood pressure in humans were recruited for quality assessment, meta-analyses, subgroup analyses, and meta-regressions; of these, 22 were conducted between 2009 and 2017 and included a total of 47 intervention ($n = 650$) and 43 control ($n = 598$) groups. Overall, SBP (−3.55 mm Hg; 95% CI: −4.55, −2.54 mm Hg) and DBP (−1.32 mm Hg; 95% CI: −1.97, −0.68 mm Hg) were significantly lower in the beetroot juice–supplemented groups than in the control groups. The mean difference of SBP was larger between beetroot juice–supplemented and control groups in the longer than in the shorter (≥14 compared with <14 d) study durations (−5.11 compared with −2.67 mm Hg) and the highest compared with the lowest (500 compared with 70 and 140 mL/d) doses of beetroot juice (−4.78 compared with −2.37 mm Hg). A positive correlation was observed between beetroot juice doses and the mean differences of blood pressures. In contrast, a smaller effect size of blood pressures was observed after supplementation with higher NO_3 (milligrams per 100 mL beetroot juice). A weak effect size was observed in a meta-analysis of trials that used NO_3-depleted beetroot juice as a placebo compared with other interventions (−3.09 compared with −4.51 mm Hg for SBP and −0.81 compared with −2.01 mm Hg for DBP). Our results demonstrate the blood pressure–lowering effects of beetroot juice and highlight its potential NO_3-independent effects. *Adv Nutr* 2017;8:830–8.

Keywords: beetroot, nitrate, blood pressure, hypertension, NO

Introduction

Hypertension is a major global health challenge with a high prevalence and undesirable complications, including cardiovascular disease and chronic kidney disease; the global age-standardized prevalence of hypertension in adults was ~31.1% in 2010 (1). Monotherapy is the initial approach for reducing blood pressure [overall expected mean reduction: 10–15 mm Hg in systolic blood pressure (SBP) and 8–10 mm Hg in diastolic blood pressure (DBP)], although the use of combination therapy has shown the highest mean reductions (overall expected mean reduction: 20–25 mm Hg in SBP and 10–15 mm Hg in DBP) (2, 3). Several complementary and alternative medicine therapies, including dietary supplements, functional foods, traditional herbs, and meditation, are regularly used for treating hypertension (4, 5).

Beetroot (*Beta vulgaris*) has been highlighted as an ergogenic compound and a multitargeted supplement in vascular dysfunction, atherosclerosis, cardiorespiratory disorders, and diabetes (6–8). Because of its high content of inorganic NO_3, beetroot has also been considered as a complementary treatment for hypertension (9, 10). To our knowledge, there is no evidence regarding the regular consumption of beetroot among hypertensive patients, but it has been shown that ~36% of people regularly use complementary and alternative medicine for blood pressure reduction (4). It has been proposed that inorganic NO_3 supplementation may compensate NO-disrupted pathways in hypertension and increase NO bioavailability, an

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Abbreviations used: DBP, diastolic blood pressure; RCT, randomized clinical trial; SBP, systolic blood pressure.

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important physiologic mediator in regulating blood pressure (11). Acute and short-term hypotensive effects of inorganic NO_3 have been reported in several clinical studies (8, 12–14). A meta-analysis of these trials showed a reduction in SBP but not DBP after supplementation with sodium/potassium NO_3 and beetroot juice (15); more recently, Ashor et al. (16) investigated the medium- and long-term blood pressure–lowering properties of NO_3 and indicated a −4.1- and −2.0-mm Hg reduction in SBP and DBP, respectively, after medium-term (≥7 d) dietary NO_3 supplementation. Both of these meta-analyses used beetroot juice that was similar to sodium or potassium NO_3 supplements. However, beyond inorganic NO_3, beetroot is a rich source of several other biologically active phytochemicals, including betalains (betacyanins and betaxanthins), flavonoids, and polyphenols (17).

Thus, in this systematic review and meta-analysis, we investigated the efficacy of beetroot juice supplementation on blood pressure in humans with the aim of introducing a new approach to highlight the potential blood pressure–lowering properties of beetroot as a medicinal food. To elucidate our hypothesis regarding the possible NO_3-independent hypotensive effect of beetroot juice, further subgroup analyses were also conducted to investigate the dose-dependent effects of beetroot and its standardized NO_3 content in relation to observed effect sizes, the results of which could help develop targeted interventions for hypertensive patients.

Methods

Search strategy, identification, and quality assessment

This review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to report study findings (18). All English-language medical literature was searched with the use of PubMed, Scopus, and Embase databases. A structured search strategy with the use of various combinations of keywords (beetroot, red beet, *B. vulgaris*, blood pressure, and hypertension) and Boolean terms were conducted to identify records in each database. Reference lists from previous reviews and randomized clinical trials (RCTs) that investigated the potential effect of beetroot supplementation on resting blood pressure in apparently healthy humans or those with hypertension, type 2 diabetes, chronic obstructive pulmonary disease, heart failure, or hypercholesterolemia were also observed.

In the initial screening phase, based on the titles and abstracts, irrelevant records, animal studies, reviews, and conference papers were excluded because these studies investigated the acute effects of single doses of a beetroot supplement, assessed nonresting blood pressure, or used beetroot alongside other interventions (dietary supplements, iodide, or antibacterial mouth wash). To assess study eligibility, we independently reviewed the records for initial inclusion and exclusion criteria, and potentially relevant full-text articles were retrieved for data extraction (**Figure 1**). The quality of the articles was independently assessed with the use of the Jadad scale (**Supplemental Table 1**), which includes reporting of the randomization method, allocation concealment, blinding of outcome assessment, and completeness of follow-up (19).

Data collection and synthesis

To complete the data extraction form, we used the first author's name, date of publication, number of participants in the RCT groups, age, sex, dose of beetroot, NO_3 concentration of beetroot dose, frequency and duration of the supplementation, placebo used in control groups, mean values, and SDs of baseline and final values for blood pressures in the treatment and control groups; if a study had several intervals for follow-up measurements of blood pressures, each time interval was considered as a separate study. Furthermore, in studies with a subgroup analysis, each subgroup was included as a separate study. The primary outcomes of the analyses were mean differences of both SBP and DBP after beetroot supplementation between intervention and control groups; secondary outcomes were mean changes in SBP and DBP in the beetroot-supplemented groups (in studies reporting baseline values of blood pressures).

Statistical methods

Data were quantitatively assessed based on the weighted mean differences and 95% CIs after obtaining treatment levels of both SBP and DBP between

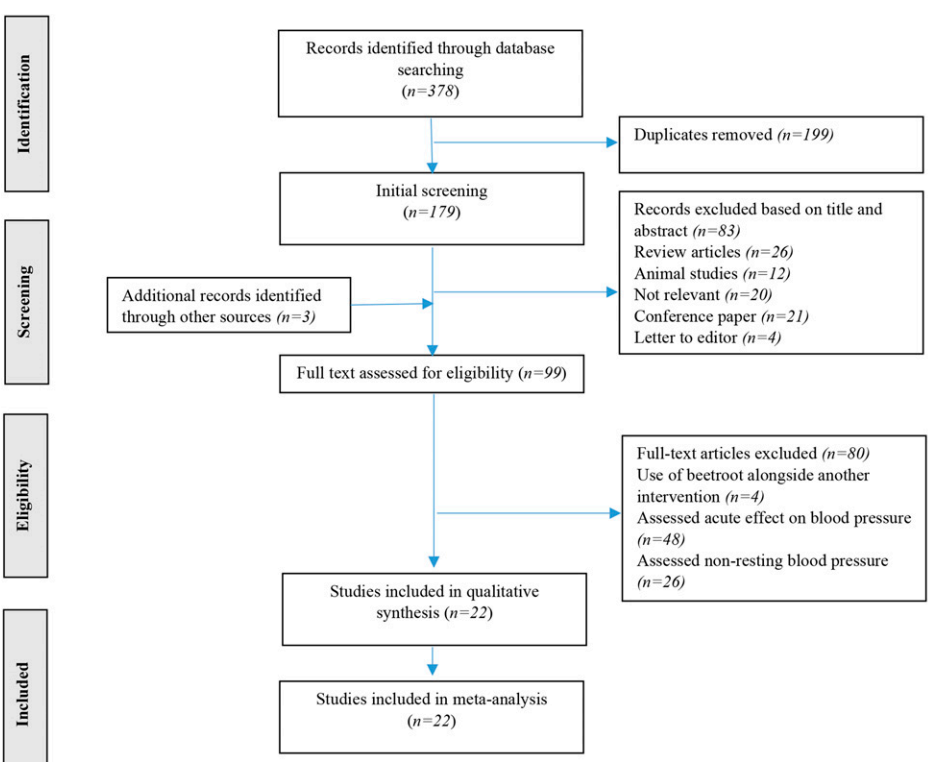

FIGURE 1 Flow chart of the literature search.

the intervention and control groups. We also conducted a meta-analysis with the use of the absolute mean difference of blood pressures relative to baseline values in the beetroot-supplemented groups. To assess statistical heterogeneity in the meta-analysis, the I^2 statistic and Cochran's Q statistic were used according to specific categories (low = 25%, moderate = 50%, high = 75%) and significance levels ($P < 0.10$), respectively (20). Although both the fixed- and random-effects models were used to calculate the pooled mean difference of blood pressures in response to beetroot, findings from the random-effects model were reported because of significant heterogeneity between studies. To investigate potential sources of heterogeneity and to evaluate whether mean differences in blood pressures might be affected, we conducted subgroup analyses for the supplement dose, study duration, and types of placebo. Treatment effects were assessed in the following predefined subgroups: study duration (<14 and ≥14 d); dose of beetroot juice (low doses: 70 and 140 mL/d; medium dose: 250 mL/d; high dose: 500 mL/d); dose of NO_3/100 mL beetroot juice (low: <150 mg/100 mL; medium: 151–249 mg/100 mL; and high: ≥250 mg/100 mL); and types of placebo used in the controls (NO_3-depleted beetroot juice compared with others, including blackcurrant juice, low-calorie juice, and a low-NO_3 diet).

To identify the potential moderators that explained blood pressure variance in response to beetroot supplementation, random-effect meta-regression models were used. Accordingly, with the use of meta-regression, we analyzed the effect of baseline values of blood pressures (because of different physiologic or pathophysiologic statuses of study participants), age, BMI (in kg/m^2), and study duration on the pooled-effect size of both SBP and DBP.

To evaluate potential publication biases, we used funnel plots and Eggers's regression test asymmetry. Sensitivity analyses were also conducted by excluding trials, investigating the effects of beetroot supplementation in physically active subjects (primarily measured effect of beetroot on exercise performance), and publications with low Jadad scores (≤2). Statistical analyses were conducted with the use of Stata version 11 (StataCorp). All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

Results

Study characteristics

After initially screening and assessing the full texts, 19 eligible studies (7, 9, 10, 21–36) of the 378 identified were included in the qualitative and quantitative analysis; 3 studies (37–39) without control groups for beetroot juice were included only for a

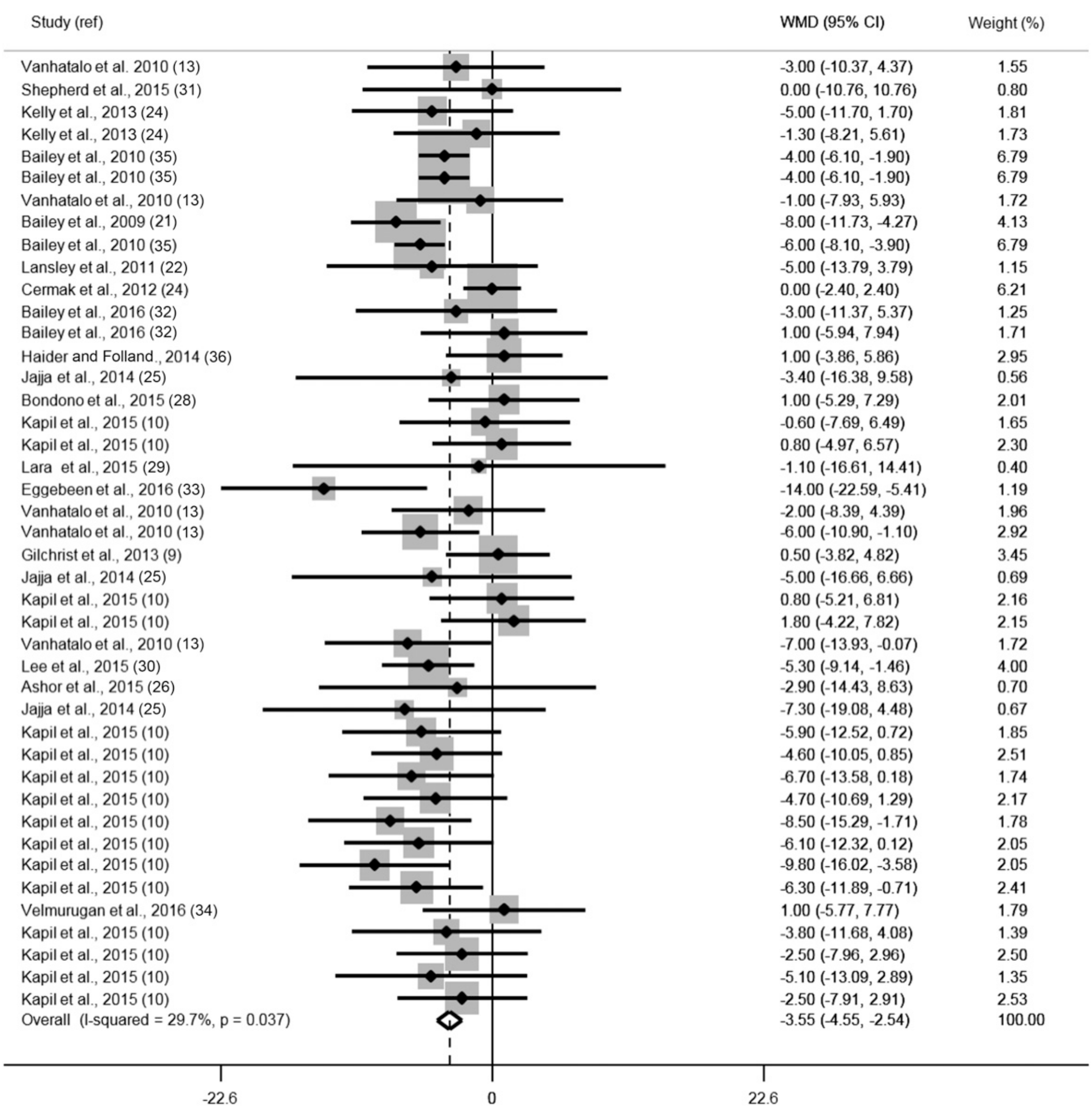

FIGURE 2 Forest plot of mean differences of systolic blood pressure in beetroot juice–supplemented groups and controls. Ref, reference; WMD, weighted mean difference.

pooled estimation of blood pressure changes in intervention groups. The results of the quality assessment of the studies according to Jadad criteria are provided in Supplemental Table 1. All trials were conducted between 2009 and 2017 and included a total of 47 intervention (n = 650) and 43 control (n = 598) groups. Nine trials (21–24, 27, 29, 30, 35, 36) investigated the effect of beetroot juice on exercise performance as a primary outcome and resting blood pressure as a secondary outcome. Trial durations ranged from 2 to 56 d; the main characteristics of the studies included in the final analysis are provided in **Supplemental Table 2**.

The mean ± SD age of participants ranged from 21 ± 3 to 69 ± 7 y. The daily doses of beetroot juice consumed ranged from 70 to 500 mL, providing varying doses of NO_3 (316–860 mg/d per ~63–857 mg/100 mL beetroot juice).

Meta-analysis

Overall, SBP (−3.55 mm Hg; 95% CI: −4.55, −2.54 mm Hg; $P < 0.001$) (**Figure 2**) and DBP (−1.32 mm Hg; 95% CI: −1.97, −0.68 mm Hg; $P < 0.001$) (**Figure 3**) were significantly lower in beetroot-supplemented groups than in the control groups. The mean difference of SBP between beetroot-supplemented and control groups was larger in the longer than in the shorter (≥14 d compared with <14 d) study durations (−5.11 compared with −2.67 mm Hg) and highest compared with the lowest (500 compared with 70 and 140 mL/d) doses of beetroot juice (−4.78 compared with −2.37 mm Hg),

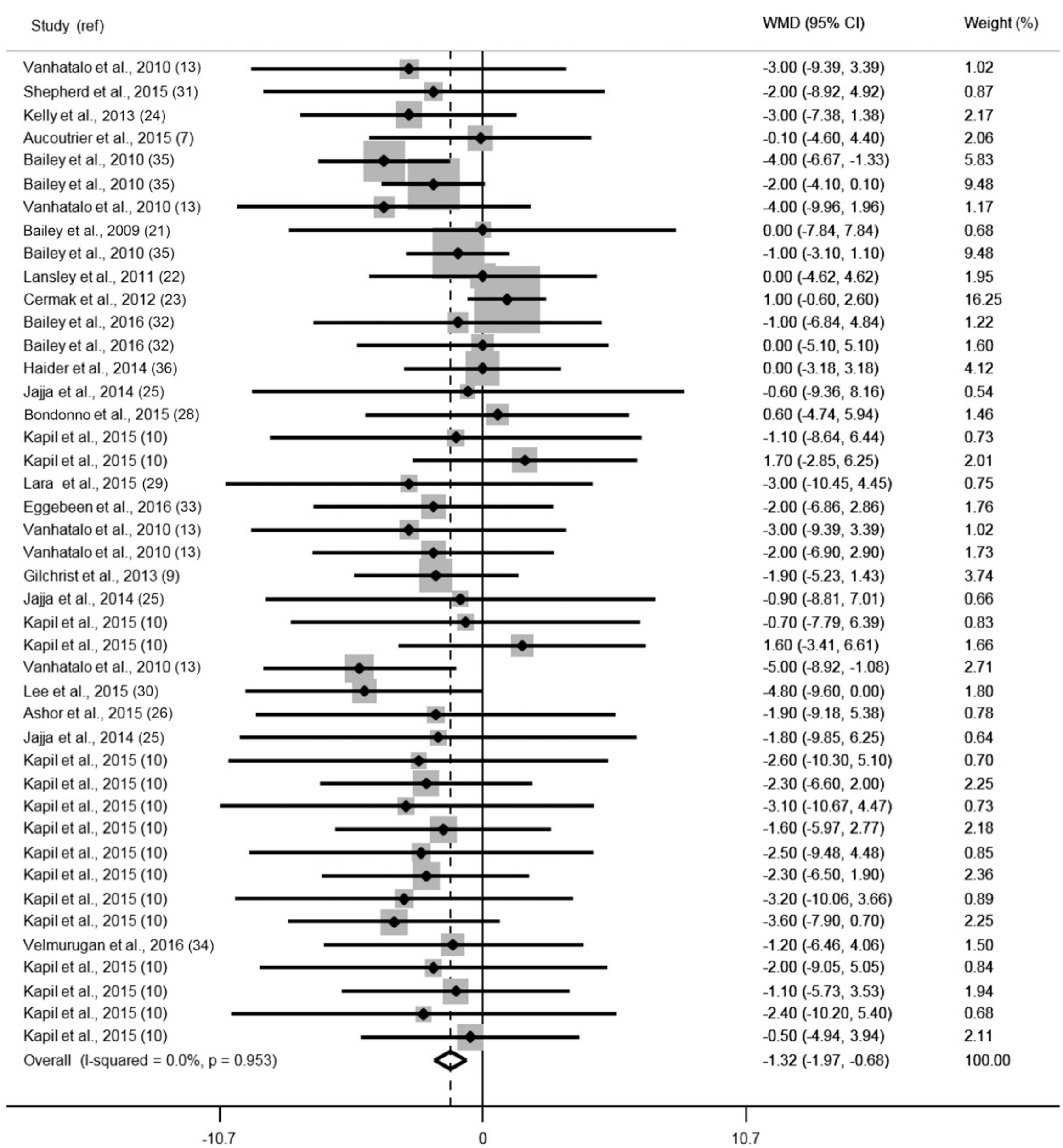

FIGURE 3 Forest plot of mean differences of diastolic blood pressure in beetroot juice–supplemented groups and controls. Ref, reference; WMD, weighted mean difference.

a similar trend to that observed for DBP (Table 1). The consumption of the lowest NO_3 concentration of beetroot juice (<150 mg/100 mL) resulted in a larger mean difference of both SBP (−4.63 compared with −2.27 mm Hg) and DBP (−2.11 compared with −0.29 mm Hg) than in the highest consumption of NO_3 concentration (≥250 mg/100 mL) between beetroot-supplemented and control groups. Furthermore, a lower mean difference of SBP (−3.09 compared with −4.51 mm Hg) was observed in studies that used NO_3-depleted beetroot juice as a placebo (Supplemental Figure 1) than in those that used blackcurrant or a low-calorie juice as well as a low-NO_3 diet; the effect size was not significant for DBP (−0.81; 95% CI: −1.66, 0.04; $P = 0.10$) in trials that used NO_3-depleted beetroot juice in the control groups (Supplemental Figure 2).

Mean SBP changes (−9.04; 95% CI: −10.5, −7.5; $P < 0.001$) and DBP (−5.36; 95% CI: −6.5, −4.2; $P < 0.001$) after beetroot supplementation are shown in Figures 4 and 5. Larger reductions in both SBP (−11.6 compared with −6.09 mm Hg) and DBP (−6.61 compared with −5.58 mm Hg) were observed in subjects with chronic diseases than in healthy subjects (data not shown). No major differences in the changes of DBP (−5.57 compared with −6.16 mm Hg) were observed between normal (BMI ≤25) and overweight subjects (BMI >25) after beetroot supplementation, although overweight subjects experienced a larger reduction in SBP than normal-weight subjects (−11.3 compared with −6.0 mm Hg) (data not shown).

A meta-regression analysis showed that mean changes in SBP were directly affected by its baseline values, age of participants, and study duration ($P < 0.05$ for all) but not by BMI; changes in DBP were not associated by baseline values or the age of participants but were positively correlated with study duration (Table 2).

Sensitivity analysis

Excluding trials that primarily investigated the impact of beetroot supplementation on exercise performance (21–24, 27, 30, 35, 36) did not change the results for either SBP (−3.15 mm Hg; 95% CI: −4.59, −1.72 mm Hg; $P < 0.001$) or DBP (−1.38 mm Hg; 95% CI: −2.42, −0.34 mm Hg; $P = 0.009$). Excluding studies with a higher risk of bias (Jadad score ≤2) from analyses had no significant impact on the mean differences of SBP (−2.95 mm Hg; 95% CI: −4.16, −1.74 mm Hg; $P < 0.001$) and DBP (−0.99 mm Hg; 95% CI: −1.77, −0.22 mm Hg; $P = 0.012$).

TABLE 1 Meta-analysis of the mean difference of blood pressure between beetroot-supplemented and control groups[1]

	Number of studies	WMD (95% CI)	*P* value*	*Q* value	*P* value**	I^2
Study duration, d						
SBP						
<14	26	−2.67 (−4.03, −1.31)	0.001	45.7	0.007	45.4
≥14	17	−5.11 (−6.63, −3.60)	0.001	9.30	0.90	0
DBP						
<14	26	−0.91 (−1.65, −0.16)	0.017	18.8	0.81	0
≥14	17	−1.32 (−1.97, −0.68)	0.001	4.37	0.99	0
Dose of beetroot, mL/d						
SBP						
70 and 140	14	−2.37 (−4.52, −0.22)	0.03	18.0	0.15	28.0
250	18	−3.22 (−4.87, −1.58)	0.001	22.2	0.17	23.3
500	11	−4.78 (−5.81, −3.73)	0.001	8.93	0.53	0
DBP						
70 and 140	14	−0.29 (−1.39, 0.79)	0.59	9.13	0.76	0
250	18	−1.48 (−2.69, −0.27)	0.016	5.54	0.99	0
500	11	−2.14 (−3.21, −1.09)	0.001	7.48	0.68	0
NO_3 content of beetroot, mg/100 mL per day						
SBP						
<150	12	−4.63 (−5.74, −3.52)	0.001	11.6	0.38	5.70
151–249	14	−3.43 (−5.11, −1.76)	0.001	20.6	0.19	22.6
≥250	17	−2.37 (−4.52, −0.22)	0.030	18.0	0.15	28.0
DBP						
<150	12	−2.11 (0.315, −1.07)	0.001	7.60	0.74	0
151–249	14	−1.50 (−2.74, −0.25)	0.018	5.53	0.99	0
≥250	17	−0.29 (−1.39, 0.79)	0.59	9.13	0.76	0
Types of placebo						
SBP						
NO_3-depleted beetroot	27	−2.91 (−4.34, −2.54)	0.001	37.2	0.07	30.1
Others[2]	16	−4.57 (−5.55, −3.59)	0.001	14.5	0.48	0
DBP						
NO_3-depleted beetroot	27	−0.71 (−1.96, 0.14)	0.10	13.7	0.97	0
Others[2]	16	−2.10 (−3.08, −1.12)	0.001	9.79	0.83	0

[1] To assess statistical heterogeneity, the I^2 statistic and Cochran's *Q* statistic were used according to specific categories (low = 25%, moderate = 50%, and high = 75%) and significance level ($P < 0.10$), respectively. *, *P* for WMD; **, *P* for *Q* value. DBP, diastolic blood pressure; SBP, systolic blood pressure; WMD, weighted mean difference.
[2] Blackcurrant juice ($n = 10$), low-calorie juice ($n = 5$), and control diet for NO_3 ($n = 1$).

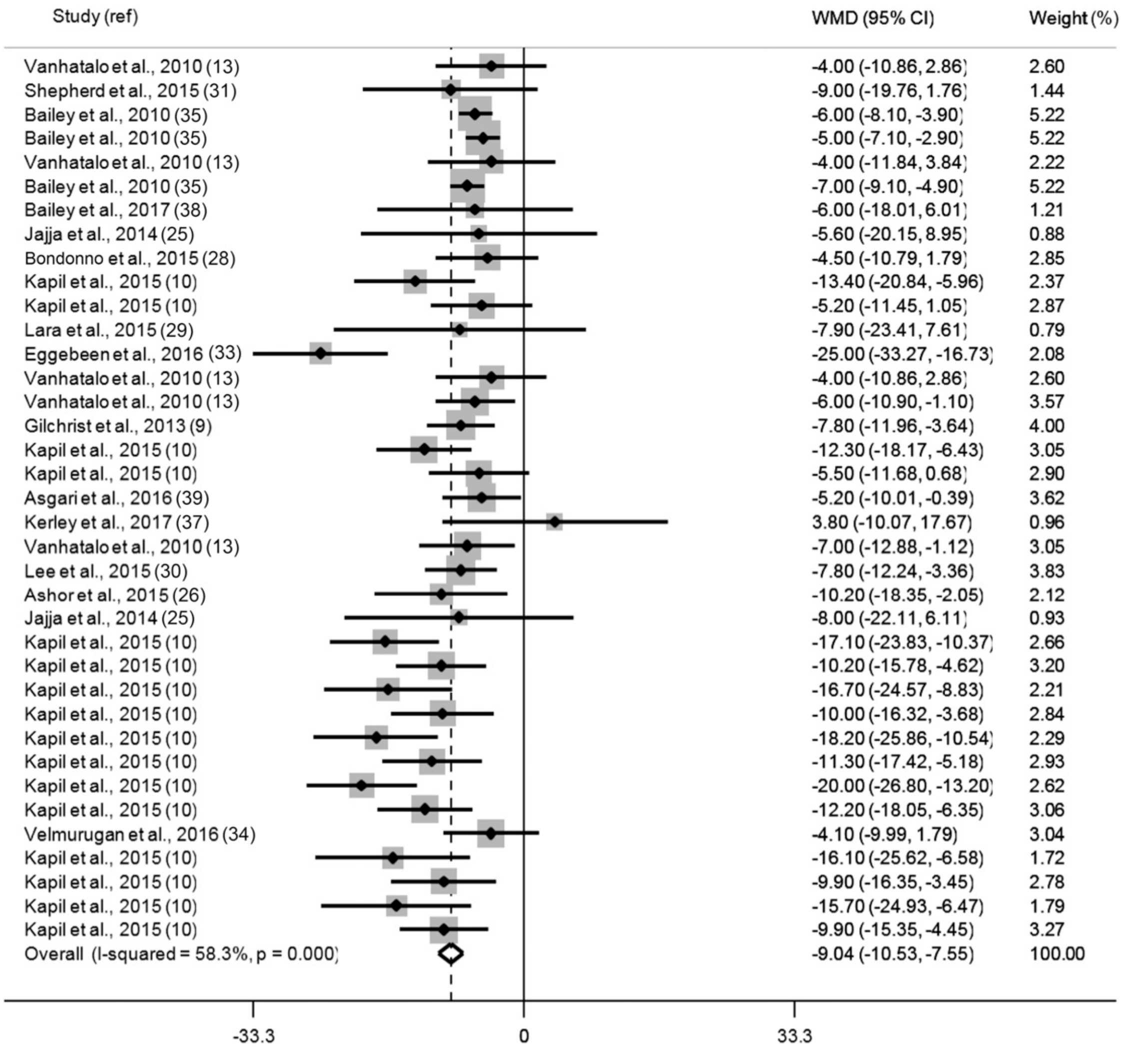

FIGURE 4 Forest plot of trials that investigated the effects of beetroot juice supplementation on systolic blood pressure in relation to baseline values. Ref, reference; WMD, weighted mean difference.

Publication bias and heterogeneity

An overall symmetric distribution of the studies around the mean effect size was observed in funnel plots for both SBP and DBP, indicating a low risk for publication bias (**Supplemental Figures 3** and **4**). According to the results of the Egger's regression test, no evidence was observed for both SBP and DBP ($P = 0.06$) outcomes regarding publication bias. There was moderate heterogeneity for SBP (I^2 = 29.7%; Q = 59.7; P = 0.037) and no heterogeneity for DBP (I^2 = 0%; Q = 27.9) in the meta-analysis models. The subgroup analysis (Table 1) indicated that trials with a shorter duration (<14 d) and those that used lower doses of beetroot juice (<500 mL) or NO_3-depleted beetroot as placebos might be potential sources of heterogeneity for SBP outcomes.

Discussion

Our meta-analysis of 43 RCTs showed that, compared with placebos, supplementation with beetroot juice might be related to significantly lower levels of both SBP and DBP (mean difference: −3.55 and −1.32 mm Hg, respectively). The treatment effects on SBP (−9.37 mm Hg) that were observed after beetroot juice consumption were relatively close to the overall expected mean reduction of 10–15 mm Hg in SBP after monotherapy (3), a value also similar to the SBP reduction observed after adherence to a dietary approach to stop the hypertension diet (40), and an ∼5-mm Hg decrease in SBP was associated with a considerable decrease in the risk of stroke and cardiovascular disease mortality.

Based on the findings from subgroup analyses, the best effect of beetroot juice supplementation on blood pressures was observed when the duration of trial was >14 d. Previous meta-analyses (15, 16) have reported only short- and medium-term blood pressure–lowering effects of beetroot juice.

Our results also demonstrate that the blood pressure–lowering effects of beetroot may be affected by chronic diseases; a greater reduction was observed in SBP and DBP after beetroot supplementation in nonhealthy than in healthy participants; in addition, overweight and obese subjects had a similar higher response to beetroot juice supplementation.

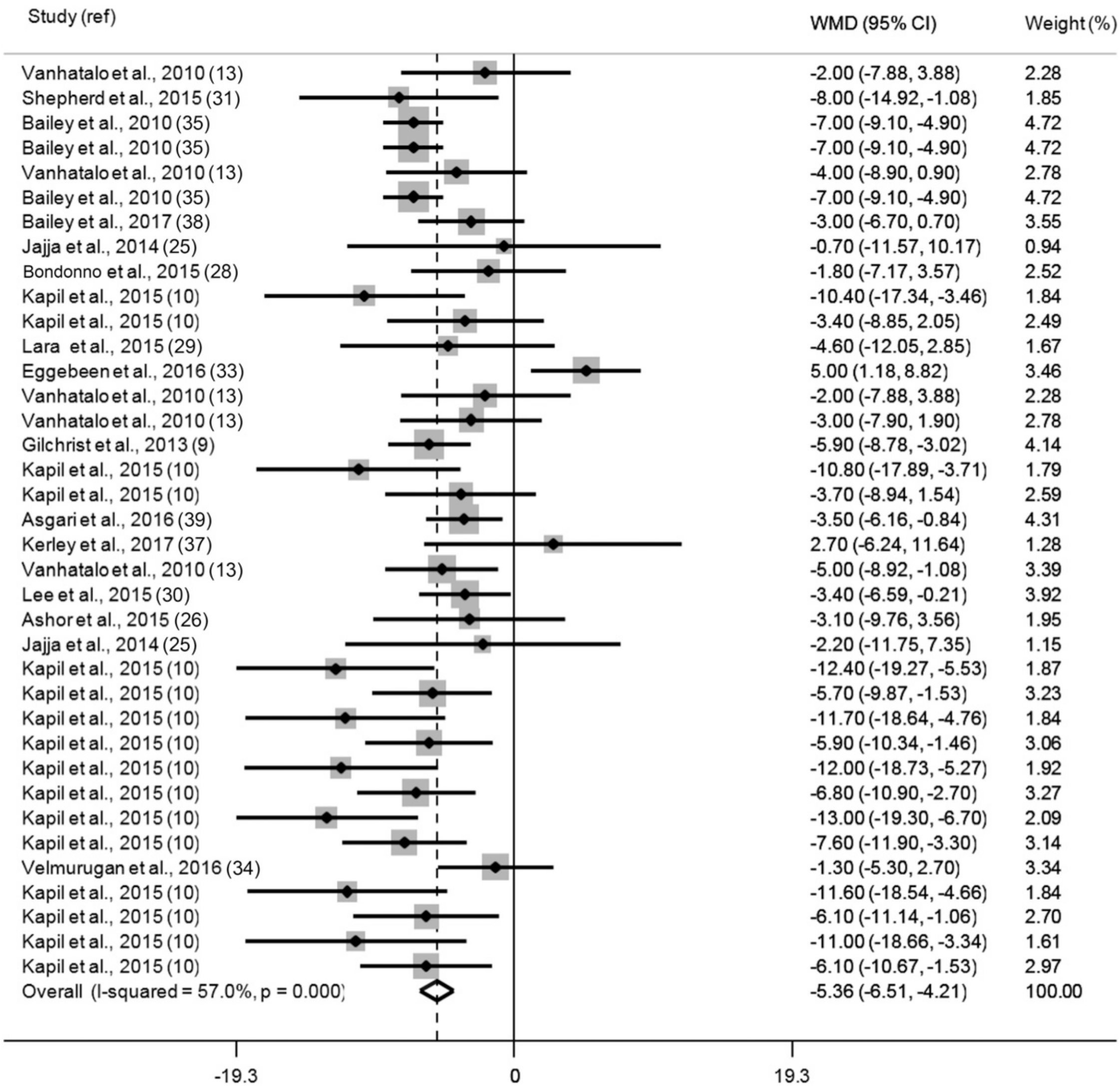

FIGURE 5 Forest plot of trials that investigated the effects of beetroot juice supplementation on diastolic blood pressure in relation to baseline values. Ref, reference; WMD, weighted mean difference.

One remarkable finding of our analyses was the positive correlation of beetroot juice doses with the mean differences of blood pressures and, in contrast, that of smaller effect sizes after supplementation with higher NO_3 doses for both SBP and DBP. Moreover, a weak effect size was observed in a meta-analysis of trials that used NO_3-depleted beetroot juice as a placebo. These observations are supported by results derived from a recent meta-analysis of trials that investigated the medium-term effect of dietary NO_3 on blood pressure (16) and that reported an inverse association between the daily dose of NO_3 and effect sizes for both SBP and DBP. Contrary to these findings, Siervo et al. (15) reported a significant association between daily doses of inorganic NO_3 and changes in SBP in a meta-regression of short-term trials, although plasma NO_2, a biomarker of NO bioavailability, was not related to SBP changes. Despite the fact that our results differ from current views that have attributed the hypotensive effect of beetroot to inorganic NO_3, apparently beyond NO_3 content, beetroot exerts its beneficial effects through other bioactive compounds such as polyphenols, a concept also supported by findings from previous studies that have indicated similar microvascular vasodilation after 14 d of consuming an NO_3-rich beetroot juice compared with a NO_3-depleted placebo (9). These data suggest that bioactive components other than NO_3, present

TABLE 2 Meta-regression of potential moderators of blood pressure changes in response to beetroot juice supplementation[1]

	Slope	95% CI	*P* value
SBP			
Baseline, mm Hg	0.232	0.001, 0.451	0.041
Age, y	0.166	0.019, 0.314	0.028
BMI, kg/m^2	0.743	−0.412, 1.89	0.200
Study duration, d	0.136	0.039, 0.232	0.007
DBP			
Baseline, mm Hg	−0.066	−0.186, 0.319	0.590
Age, y	0.025	−0.063, 0.114	0.560
BMI, kg/m^2	−0.155	−0.709, 0.358	0.570
Study duration, d	0.081	0.001, 0.161	0.047

[1] DBP, diastolic blood pressure; SBP, systolic blood pressure.

possibly in both the NO_3-depleted placebo and NO_3-rich beetroot juice, could mediate dilatory responses (41).

Our meta-regression showed that individuals with higher baseline SBP values exhibited a greater decline in SBP levels after beetroot supplementation, although the change in DBP was not significantly related to its baseline value. The age of the participants and study duration were also identified as other potential moderators of SBP changes in response to beetroot supplementation. We observed a significant positive relation between age and the observed treatment effect on SBP after beetroot juice consumption (slope = 0.166; $P = 0.028$), a finding that differs from that of previous reports by Siervo et al. (42) that indicated that beetroot juice had a significantly lower effect on nocturnal SBP variability and its decline during the night in older than in younger (≥65 y compared with <65 y) subjects; the authors concluded that vascular responsiveness to inorganic NO_3 may be modified by its decreased capacity to convert NO_3 into NO_2 and by tissue-specific responses to dietary NO_3 supplementation (42).

To our knowledge, this is the first meta-analysis that has focused exclusively on the blood pressure–lowering effects of beetroot per se rather than beetroot along with NO_3 supplements. The key strength of our study may be the inclusion of short-, medium-, and long-term trials that investigated the hypotensive effects of beetroot juice. Furthermore, the subgroup analysis undertaken adds to the data available regarding the dose-dependent relation of beetroot juice, its NO_3 content, and the consequent blood pressure–lowering effects. Our meta-regressions facilitate enhanced understanding of potential moderators of blood pressure (e.g., age, BMI, baseline values of blood pressures, and study duration) in response to beetroot supplementation.

Of course, our findings do have some limitations, specifically the high levels of heterogeneity, which were unavoidable because of the varying population groups of trials, varying doses of beetroot juice and NO_3 contents of supplements, differences in study durations, and the physiologic and pathophysiologic status of participants. Our broad inclusion criteria for selection and qualification of studies may have increased the heterogeneity between studies and made it difficult to apply our findings for specific patients such as those who have hypertension. With the use of subgroup analyses we tried to detect potential sources of heterogeneity; we also conducted sensitivity analyses to minimize potential sources of bias by excluding low-quality trials or studies conducted on athletes, although this exclusion had no major effect on pooled effect sizes of beetroot supplements. In addition, our searches were limited to English-language and published records, possibly increasing the risk of publication bias.

In conclusion, this meta-analysis confirms previous findings and contributes important new evidence that indicates the hypotensive properties of beetroot to be a potentially safe and cost-effective nutritional approach for managing hypertension and preventing undesirable cardiovascular outcomes. Our subgroup analyses, however, suggest a different paradigm regarding the dose-dependent relation between inorganic NO_3 and its blood pressure–lowering effects and highlight the potential NO_3-independent blood pressure–lowering effects of beetroot juice. Further clinical studies with larger sample sizes and longer durations with the use of a standardized beetroot supplement for NO_3 content and other bioactive compounds are required in hypertensive patients with predefined hypertension stages to confirm whether supplementation with beetroot juice may be a safe nutritional intervention for treating hypertension.

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