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The Effect of Anthocyanins on Blood Pressure

A PRISMA-Compliant Meta-Analysis of Randomized Clinical Trials

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Abstract: The findings of clinical studies concerning the association between anthocyanins supplementation and blood pressure (BP) are inconsistent.

In order to provide a more precise estimate of the overall effect of anthocyanins on systolic blood pressure (SBP) and diastolic blood pressure (DBP), we conducted a meta-analysis of clinical trials about anthocyanins supplementation and BP.

PubMed, Web of Science, Wanfang Database, and China National Knowledge Infrastructure (CNKI) (until October 2015) were searched to identify potential studies with information on anthocyanins extract supplementation and arterial BP. The weighted mean difference (WMD) and 95% confidence interval (CI) were used as a summary statistic. Net changes in SBP and DBP between anthocyanins supplementation and placebo groups were calculated by subtracting the values at end of follow-up from those at baseline. Meta regression was used to explore the potential moderators of effect size. The publication bias was assessed using Begger's Funnel plots and Egger's tests; $P < 0.05$ was considered to be statistically significant.

Finally, 6 clinical studies with 472 participants for the effect of anthocyanins consumption on BP were included in the present meta-analysis. There is no significant effect on either SBP (WMD: 1.15 mm Hg, 95% CI: −3.17 to 5.47, $I^2 = 56\%$) or DBP (WMD: 1.06 mm Hg, 95% CI: −0.71 to 2.83, $I^2 = 0\%$) following supplementation with anthocyanins.

In summary, results from this meta-analysis do not favor any clinical efficacy of supplementation with anthocyanins in improving blood pressure. Further well-designed large randomized controlled trials (RCTs) with long follow-up period are needed to verify the association of anthocyanins supplementation and blood pressure.

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Abbreviations: BP = blood pressure, CI = confidence interval, CNKI = China National Knowledge Infrastructure, DBP = diastolic blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MD = mean difference, RCT = randomized controlled trial, SBP = systolic blood pressure, SD = standard deviation, SE = standard error, SEM = standard error of mean, WMD = weighted mean difference.

INTRODUCTION

High blood pressure (BP) or hypertension, as commonly known, is a chronic disease which is responsible for 13% of all global mortality.[1] Some convincing evidences demonstrate that there are strongly and positively association between hypertension with increased risk of developing chronic diseases, including coronary heart disease, stroke, heart failure, and kidney disease.[2,3] Considering so many hypertension patients, it takes an enormously cost to treat hypertension and related complications. In addition to antihypertensive agents, we can also by way of lifestyle modification and alimentary control to prevent hypertension and related complications.[4] Evidence suggests that the increase of vegetables and fruit consumption can reduce the risk of hypertension.[5] As is known to us, researchers have a considerable interest in the foods rich in natural bioactive components and their contribution to decreasing cardiovascular risks as a promising alternative to pharmaceutical medications.

Anthocyanins are polyphenols responsible for many of the fruits and floral colors, and most common in plant foods such as pelargonidin, cyanidin, delphinidin, peonidin, malvidin, and petunidin.[6] To date, anthocyanins have been proved to be effective in preventing different diseases based on epidemiological and clinical studies. Cassidy et al[7] have demonstrated that, in young women, a higher intake of anthocyanins may reduce myocardial infarction risk. As for dyslipidemic subjects, it has been reported that anthocyanins supplementation can improve low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations and enhance cellular cholesterol efflux to serum.[8] A cross-sectional study reported that a higher intake of anthocyanins is associated with a lower arterial stiffness.[9] However, there is not a convincing conclusion about the anthocyanins' effect on blood pressure. Broncel et al suggested that after 2 months of therapy with 300 mg/d aronia extract rich in anthocyanins for metabolic syndrome patients, statistically significant decreases were observed in blood pressure,[10] whereas another study has reported that higher intake of these relatively pure anthocyanins does not reduce BP in healthy men with a high normal BP.[11] Regarding these inconsistent findings, we conducted a meta-analysis of clinical trials to provide a more precise estimate of the overall effect of anthocyanins on systolic blood pressure (SBP) and diastolic blood pressure (DBP).

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METHODS

Ethical approval and patient written informed consent are not required due to that this is a systematic review and meta-analysis of previously published studies. This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Literature Search

PubMed, Web of Science, Wanfang Database, and CNKI (until October 2015) were searched to identify potential studies with information on anthocyanins extract supplementation and arterial BP. We searched for articles by using the following keywords separately or in combination: ''anthocyanin'' or ''anthocyanins'' combined with ''blood pressure'' or ''hypertension'' or ''systolic blood pressure'' or ''diastolic blood pressure.'' Additionally, we evaluated all the relevant publications including research papers, reviews, and the references in all retrieved articles to retrieve additional eligible studies.

Study Selection

We scrutinized full text of each potentially relevant paper by using the following inclusion criteria to select studies for the meta-analysis: (1) studies are random clinical trials, (2) participants aged 18 years or older, (3) the interventions are pure anthocyanins or anthocyanins extracts, and (4) SBP and DBP data at baseline and after consumption of anthocyanins preparations were available. Studies were excluded under the following exclusion criteria: (1) reviews, case reports, and case series; (2) no numerical values were provided regarding SBP and/or DBP at baseline or study end; (3) the study did not include a control group; (4) intervention time is <1 week. Publications were discarded if they were duplicated or did not meet the initial objective.

Quality Assessment

The quality of included studies was methodologically assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions.[12] The following methodological domains were considered: adequacy of sequence generation, allocation concealment, blinding, drop-out rates (incomplete outcome data), addressing incomplete outcome data, selective outcome reporting, and other potential sources of bias. Labeling as ''L'' indicated low risk of bias, whereas ''H'' indicated high risk of bias. A judgment of ''U'' indicated unclear risk of bias.

Data Extraction

Two reviewers (YZ and YB) dependently conducted the literature search and screening process, and disagreements were resolved by a third investigator. The following data in each eligible study was extracted: the first author's last name, year of publication, location of the study, study design, age, sample size, duration of treatment period, type of intervention, and administered daily dose of anthocyanins. Additionally, mean SDs (or mean SEM) of blood pressure (SBP and DBP) at baseline and at the end of trial (or treatment period in the case of cross-over trials) were individually recorded.

Statistical Analysis

Meta-analysis was conducted using the Cochrane Program Review Manager (v.5.0; Oxford, England) and STATA software (version 12.0; StatCorp, College Station, TX). The unit of BP levels was mm Hg. The WMD and 95% CI were used as a summary statistic. The following formula was used to calculate the mean difference: mean difference $= \text{mean}_{\text{pre-treatment}} - \text{mean}_{\text{post-treatment}}$. And the following formula was used to calculate the standard deviations (SDs) for the net changes: SD = square root ([SD pretreatment]^2 + [SD post-treatment]^2 – [2R × SD pretreatment × SD post-treatment]), assuming a correlation coefficient (R) = 0.5.[13,14] For studies with multiple measurements that reported data at different time points, the values of the longest duration of treatment were used. Sensitivity analyses were used to test the robustness of overall analyses. The I^2 index was used to assess heterogeneity. Values of 25%, 50%, and 75% were used for the I^2 analysis and correspond to low, moderate, and high heterogeneity, respectively. If $I^2 > 50\%$, a random effect model were used for quantitative data synthesis; otherwise, a fixed model was chosen. Meta regression was used to explore the potential moderators of effect size. The publication bias was assessed using Begger's Funnel plots and Egger's tests; $P < 0.05$ was considered to be statistically significant.[14,15]

RESULTS

Literature Search and Study Characteristics

We initially screened 413 articles from different searches, of which 261 duplicate were removed, and 152 articles were examined. After reviewing full text, 140 articles which did not fulfill inclusion criteria were excluded; only 12 trials seemed worthy of being further scanned were obtained. Six articles were eliminated for the following reasons: 1 article is a retrospective study, 2 articles did not report baseline blood pressure values, and 3 articles did not report blood pressure values after intervention. Hence, the meta-analysis finally included remaining 6 clinical studies[8,11,16–19] with 472 participants for the effect of anthocyanins consumption on BP. The identification processes of our literature search are shown in Figure 1.

The key characteristics of the included studies are presented in Table 1. Of the 6 studies, 3 were conducted in Asia (all Chinese trials[8,16,18]) and 3 in Europe (1 in England,[17] 1 in Norway,[11] and another one in Italy[19]). There were 472 participants randomized in the 6 trials, of whom 232 were allocated to the anthocyanins supplementation group and 240 to the placebo group. The number of participants in these trials ranged from 42 to 146. The anthocyanins capsule as the main type of intervention was administered to the individual at the range of doses from 162 mg/d to 640 mg/d in the included trials. Five studies were designed as randomized clinical trial, 1 as cross-over study.

Risk of bias Assessment

The assessment of the risk of bias was summarized in Table 2. All included studies had a low risk of bias for blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. All the studies are unclear about the risk bias for allocation concealment. And 2 out of the 6 studies have a low risk bias for sequence generation; the other 4 studies are unclear about the risk bias for sequence generation.

Effect of Anthocyanins on Blood Pressure

The meta-analysis of data showed no significant effect on either SBP (WMD: 1.15 mm Hg, 95% CI: −3.17 to 5.47, $I^2 = 56\%$) or DBP (WMD: 1.06 mm Hg, 95% CI: −0.71 to 2.83, $I^2 = 0\%$) following supplementation with anthocyanins.

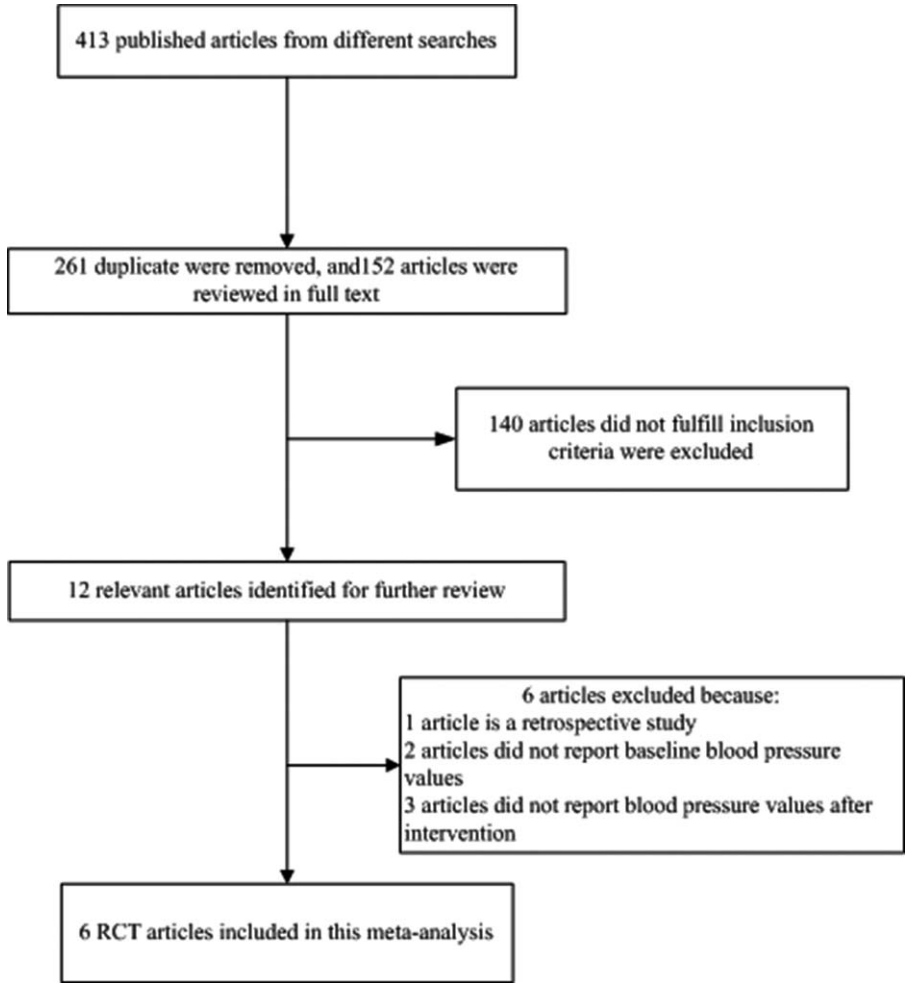

FIGURE 1. Flow diagram for identification processes.

The detail efficacy of anthocyanins in SBP and DBP among and the meta-analysis are shown in Figure 2.

Meta regression and sensitivity analysis

There was a moderate heterogeneity for SBP ($I^2 = 56\%$). Hence, possible association between the net effect of anthocyanins on SBP and putative moderators (anthocyanins dose, baseline SBP, location, and duration of supplementation) was assessed using random effects meta-regression analysis. However, changes in SBP showed no direct association with these above factors ($P > 0.05$). Sensitivity analyses performed to assess the effect on overall results of the meta-analysis also did not alter the results. The leave-one-out analysis showed that the key contributor to this moderate heterogeneity was 1 study conducted by Zhu et al.[16] After excluding it, the heterogeneity was reduced to $I^2 = 0\%$, and the pooled mean difference for SBP was 3.25 (95%CI = −0.08 to 6.59), which was similar to the main finding.

Publication Bias

Funnel plot of the study suggested a little asymmetrical but acceptable range of symmetry for the impact of anthocyanins supplementation on SBP and DBP (Figure 3). Besides, Egger's test showed no evidence of significant publication bias for this meta-analysis with BP and anthocyanins supplementation, with $t = 1.67$, $P = 0.17$ for SBP, and $t = 1.63$, $P = 0.178$ for DBP respectively.

DISCUSSION

Our meta-analysis of data from 6 eligible random clinical trials showed no significant effect of anthocyanins supplementation on the change of either SBP or DBP from baseline. To our acknowledgement, this is the first meta-analysis to evaluate the effects of anthocyanins on blood pressure.

Anthocyanins as an important active ingredient constitute a diverse group of polyphenolic compounds, which is present in fruits, vegetables, berries, and red wine.[20] Previous meta-analysis has suggested that green tea or green tea extract supplementation can cause a small but significant reduction in BP (SBP:WMD = −1.42 mm Hg, 95% CI = −2.37 to −0.36, $I^2 = 52\%$, and DBP: WMD = −1.25 mm Hg, 95%CI = −2.32 to −0.19, $I^2 = 74\%$).[21] Khalesi et al found significant reductions in both SBP (WMD: −2.85 mm Hg, 95%CI: −5.37 to −0.33, $P = 0.027$) and DBP (WMD: −2.39 mm Hg, 95%CI: −3.78 to −0.99, $P = 0.001$) following supplementation with flaxseed product.[22] Another mate-analysis conducted by Onakpoya et al

TABLE 1. Demographic Characteristics and Baseline Parameters of Studies Included in this Study

Study (Year)	Location	Design	Inclusion Criteria	Duration (week)	Daily Dose (mg)	Participants	Age (years)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)
Zhu (2011)[16]	China	R, D, PC	Total cholesterol concentration between 200 and 310 mg/dL.	12	320	*I*: 73; *P*: 73	*I*: 40–65; *P*: 40–65	*I*: 26.8 ± 2.0; *P*: 26.4 ± 2.1	*I*: 124.3 ± 16; *P*:126.2 ± 14.9	*I*: 82.8 ± 10.5; *P*: 84.7 ± 10.7
Hassellund et al (2012)[11]	Norway	R, D, PC, Cross-over	Aged between 35 and 51 years old, with resting office SBP of >140 and/or DBP >90 mm Hg or daytime average BP of >135/85 mm Hg if they had recently undergone a 24-h ambulatory BP recording.	4	640	*I*: 27; *P*: 27	*I*: 41 ± 3; *P*: 41 ± 3	*I*: 27 ± 3; *P*: 27 ± 3	*I*: 143 ± 13; *P*: 143 ± 13	*I*: 96 ± 6; *P*: 96 ± 6
Qin et al (2009)[8]	China	R, D, PC	The subjects should meet 2 of the following 4 criteria: TC >200 mg/dL, TG>150 mg/dL, LDL >100 mg/dL, or HDL >40 mg/dL.	12	320	*I*: 60; *P*: 60	*I*: 40–65; *P*: 40–65	*I*: 25.5 ± 3.1; *P*: 26.7 ± 4.0	*I*:126.5 ± 17.8; *P*:129.1 ± 19.0	*I*: 82.7 ± 10.0; *P*: 82.4 ± 10.6
Liu (2008)[18]	China	R, D, PC	The subjects should meet 1 or more of the following 4 criteria: TG≥1.70 mmol/L; TC≥5.20 mmo1/L; LDL≥3.12 mmol/L; HDL≤0.9l mmol/L◦	12	200	*I*: 30; *P*: 28	*I*: 58.1 ± 5.5; *P*: 55.2 ± 5.3	*I*: 26.8 ± 3.6; *P*: 26.2 ± 3.9	*I*: 131.7 ± 19.7; *P*: 128.1 ± 19.9	*I*: 85.0 ± 9.8; *P*:81.8 ± 10.5
Curtis (2009)[17]	England	R, D, PC	Postmenopausal women,70 y, not taking hormone replacement therapy for ≥6 mo, with BMI in the 20–32 kg/m^2 range and who were nonsmokers	12	500	*I*: 26; *P*: 26	*I*: 58.1 ± 5.5; *P*: 58.3 ± 5.8	*I*: 25.1 ± 3.8; *P*: 24.3 ± 3.4	*I*: 123 ± 15; *P*: 130 ± 14	*I*: 78 ± 7; *P*: 82 ± 11
Davinelli (2015)[19]	Italy	R, D, PC	Light smokers (<1 pack per day), inclusive age 45–65 years, good general health, and body mass index between 25 and 30 kg/m^2	4	162	*I*: 16; *P*: 26	*I*: 45–65; *P*: 45–65	*I*: 28.9 6 ± 4.1; *P*: 28.5 6 ± 4.7	*I*: 127.8 6 ± 21.2; *P*: 128.5 6 ± 22.2	*I*: 82.2 6 ± 12.5; *P*: 81.4 6 ± 12.1

Values are expressed as mean ± SD.

BB = Blueberry, BMI = body mass index, CVD = cardiovascular disease, D = double-blind, DBP = diastolic blood pressure, HDL = high-density lipoprotein, I = intervention group, LDL = low-density lipoprotein, NS = no stated, P = placebo group, PC = placebo-controlled, PL = placebo, R = randomized, SBP = systolic blood pressure, TC = total cholesterol concentration, TG = triglyceride concentration, USA = the United States of America.

TABLE 2. Assessment of Risk of Bias in the Included Studies Using Cochrane Criteria

Study	Ref	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Potential Threats to Validity
Zhu 2011	[16]	U	U	L	L	L	L	L
Hassellund et al 2012	[11]	U	U	L	L	L	L	L
Qin et al 2009	[8]	U	U	L	L	L	L	L
Liu 2008	[18]	L	U	L	L	L	L	L
Curtis 2009	[17]	L	U	L	L	L	L	L
Davinelli 2015	[19]	U	U	L	L	L	L	L

H = high risk of bias, L = low risk of bias, U = unclear risk of bias.

revealed a positive effect of chlorogenic acid on both SBP (mean difference [MD]: −4.31 mm Hg; 95% CI: −5.60 to −3.01; $I^2 = 65\%$) and DBP (MD: −3.68 mm Hg; 95% CI: −3.91 to −3.45; $I^2 = 97\%$).[23] However, there is no meta-analysis to explore the effect of anthocyanins on blood pressure. In the present meta-analysis, the nonsignificant effect of anthocyanins supplementation on the change in BP from baseline compared with the placebo groups, identified in our meta-analysis adds new evidence for the relationship between nutritional supplementation and BP.

Some clinical studies demonstrated that the consumption of anthocyanins rich supplementation (such as grape-wine extracts and Hibiscus sabdariffa L extracts) result a significant decrease in BP,[24,25] which is inconsistent with our findings. It might be ascribed the different ingredients of the supplementations, except for anthocyanins, the grape-wine extracts and Hibiscus sabdariffa L extracts also contain other polyphenols. Thus, there may be other polyphenols (such as catechins, flavonols, mg phenolic acids, and stilbenes) present in the above supplementations that are responsible for the responses antihypertensive effect. One systematic review conducted by Wallace et al explored the effect of anthocyanins and anthocyanin-rich extracts on blood pressure, which detected no effect of purified anthocyanins or anthocyanin-rich extracts on blood pressure,[26] also give compelling evidence for our conclusion that anthocyanins supplementation may have no significant effect on the change of either SBP or DBP.

Another possibility for the lack of significant effect of anthocyanins on the blood pressure could be the baseline characteristics of populations studied. The participants in included studies were classified as mild hypertension or high normal range. Some studies have indicated that the antihypertensive effect is greater in subjects with higher baseline BP.[27,28] Therefore, it may be more difficult to reduce a slightly elevated BP than to reduce a highly elevated BP.

One retrospective study[29] (mean treatment duration was 24.32 ± 10.43 months with 120 mg anthocyanins daily) suggested that anthocyanins can significantly reduce both

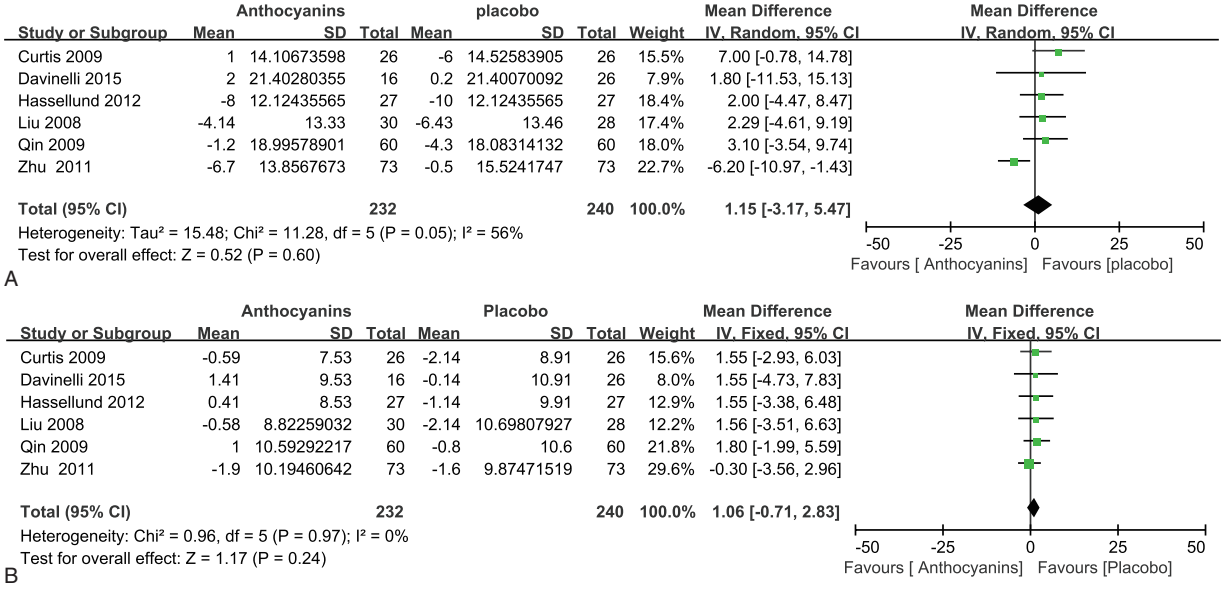

FIGURE 2. Forest plot detailing weighted mean difference and 95% CI for the impact of anthocyanins supplementation on blood pressure (A: SBP, B: DBP). CI = confidence interval, DBP = diastolic blood pressure, SBP = systolic blood pressure.

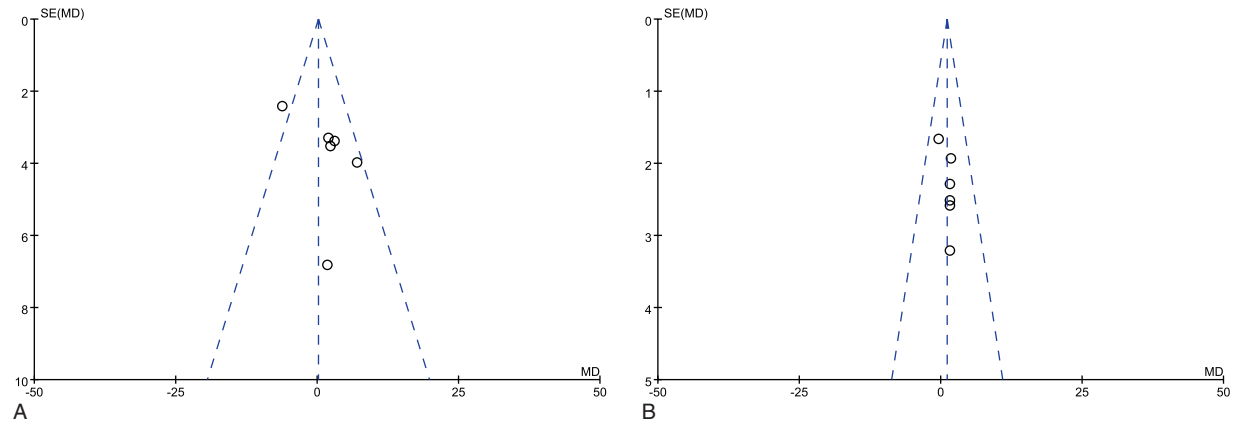

FIGURE 3. Funnel plot for publication bias of anthocyanins supplementation and blood pressure (A: SBP, B: DBP). DBP = diastolic blood pressure, SBP = systolic blood pressure.

SBP and DBP. Besides, 1 observational study conducted by Jennings et al demonstrated that a higher anthocyanin intake reduced central systolic blood pressure (mean ± SE: −3 ± 1.4 mm Hg for quintile 5 compared with quintile 1; *P*-trend = 0.02).[9] Compared with RCTs, observational studies have longer duration.[30] Thus, we can infer that longer intervention time with anthocyanins may result in further reductions in BP.

The present meta-analysis had several potential limitations. First, we could not perform subgroup analyses due to the small number of studies included in the meta-analysis. Second, there was a moderate heterogeneity when assessing the effect of anthocyanins supplementation on SBP, we screened possible explanations including anthocyanins dose, baseline SBP, location, and duration of supplementation to this observed heterogeneity. However, the systemic result was not affected by these characteristics. The leave-one-out analysis showed that the summary estimate of SBP was not substantially changed after excluding the study conducted by Zhu et al.[16] Furthermore, the studies included in this meta-analysis had short durations of follow-up.

CONCLUSION

In summary, results from this meta-analysis do not favor any clinical efficacy of supplementation with anthocyanins in improving blood pressure. Further well-designed large RCTs with long-follow-up periods are needed to verify the association of anthocyanins supplementation and blood pressure.

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