REVIEW

Effects of Anthocyanins on Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Numerous clinical trials have examined the role of anthocyanins on cardiometabolic health, but their effects have not been quantitatively synthesized and systematically evaluated. The aim of our study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the effects of anthocyanins on glycemic regulation and lipid profiles in both healthy populations and those with cardiometabolic diseases. The MEDLINE, EMBASE, Cochrane database, OVID EBM Reviews, and clinicaltrials.gov databases were searched until February 2017. RCTs with a duration of ≥2 wk that evaluated the effects of anthocyanins on glycemic control, insulin sensitivity, and lipids as either primary or secondary outcomes were included. The Cochrane Risk of Bias tool was used to assess the study quality. Standardized mean differences (SMDs) were determined by random-effects models. Meta-regression, sensitivity, and subgroup analyses were performed to explore the influence of covariates on the overall effects. Thirty-two RCTs (1491 participants) were eligible for meta-analysis. Anthocyanins significantly reduced fasting glucose (SMD: −0.31; 95% CI: −0.59, −0.04; I^2 = 80.7%), 2-h postprandial glucose (SMD: −0.82; 95% CI: −1.49, −0.15; I^2 = 77.7), glycated hemoglobin (SMD: −0.65; 95% CI: −1.00, −0.29; I^2 = 72.7%), total cholesterol (SMD: −0.33; 95% CI: −0.62, −0.03; I^2 = 86.9%), and LDL (SMD: −0.35; 95% CI: −0.66, −0.05; I^2 = 85.2%). Sensitivity analyses showed that the overall effects remained similar by excluding the trials with a high or unclear risk of bias. The significant improvements in glycemic control and lipids support the benefits of anthocyanins in the prevention and management of cardiometabolic disease. Further well-designed RCTs are needed to evaluate the long-term effects of anthocyanins on metabolic profiles and to explore the optimal formula and dosage. The protocol for this review was registered at https://www.crd.york.ac.uk/PROSPERO/#index.php as CRD42016033210. *Adv Nutr* 2017;8:684–93.

Keywords: anthocyanins, cardiovascular disease, meta-analysis, randomized controlled trial, type 2 diabetes

Introduction

Dietary modification or supplementation is a safe and cost-effective strategy for preventing and managing metabolic disease (1) and is being pursued as an alternative or supplement to pharmaceutical treatments. Anthocyanins are a subgroup of natural pigments in the major group of polyphenols that are responsible for dark color ranging from red-orange to blue-violet in plants, such as flowers, vegetables, grains, and fruits. The potential benefits of anthocyanins in prevention and management of cardiometabolic diseases have sparked substantial interest in recent decades (2). Epidemiologic evidence indicates that incorporating anthocyanin-rich foods into the diet may lower the risk of type 2 diabetes (3), blood pressure (4), and cardiovascular diseases (CVDs) (5). These findings are supported by animal experiments and clinical studies that have shown the improvement in cardiometabolic features after the consumption of anthocyanin supplements or berry fruits (6). Experimental studies suggest that the beneficial effect mechanisms of anthocyanins mainly involve insulin-dependent (7) and insulin-independent pathways (8).

Several reviews have summarized the effects of purified anthocyanins or anthocyanin-rich foods on metabolic markers or disease risk. A recent review reported the beneficial impacts of blueberries on insulin resistance and glucose intolerance (9). Wallace et al. (10) systematically reviewed 10 randomized

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Abbreviations used: CVD, cardiovascular disease; HbA1c, glycated hemoglobin; RCT, randomized controlled trial; SMD, standardized mean difference.

controlled trials (RCTs) on the effects of anthocyanin supplementation on lipids and blood pressure, and the results indicated that anthocyanins significantly improved LDL. Another systematic review (11) explored the potential action mechanisms and cardiovascular effects of anthocyanins in animal models and human trials and revealed significant improvements on lipids and antioxidant capacity. However, most of the systematic reviews on anthocyanins were based on observational studies. A number of RCTs have been performed to test the effects of anthocyanin-rich foods or supplements on cardiometabolic markers, and the findings have been ambiguous. To our knowledge, the meta-analysis assessing the effects of anthocyanins on cardiometabolic markers based on RCTs is limited. Current evidence from human trials has not yet been comprehensively evaluated and quantitatively synthesized. We therefore conducted a systematic review and meta-analysis to provide a more precise estimate of the overall effects of anthocyanins on glycemic regulation and lipid profiles and sought to improve clinical practice of using anthocyanins for the prevention and therapy of cardiometabolic disorders.

Methods

Search strategy and selection criteria

The current systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (12). The protocol was registered in the PROSPERO international prospective register of systematic review (CRD42016033210). Literature searches were performed until February 2017 from the database of MEDLINE, EMBASE, Cochrane Library, and OVID EBM Reviews, and clinical trial registries were searched in clinicaltrials.gov.

Published studies were screened by 2 reviewers based on their titles, abstracts, and full texts according to the following inclusion criteria: *1*) clinical RCTs using purified anthocyanins or anthocyanins-rich foods as treatment compared with a placebo or nonexposed concurrent controls and *2*) participants with cardiometabolic diseases, such as type 2 diabetes, metabolic syndromes, dyslipidemia, hypertension, or healthy individuals. Moreover, the references of the included studies or reviews were further screened to identify other eligible studies. Studies that were excluded fit the following criteria: participants younger than 18 y of age, or with end-stage diseases (such as carcinoma or organ failure) or hormone-related disorders (such as polycystic ovary syndrome or being post-menopause); trials that used multifactorial or crossover design without parallel controls or applied multistage interventions; a duration of <2 wk or just a single supplementation; and studies that used non-English language or provided incomplete data for data extraction.

Data extraction and quality assessment

Data extraction was carried out by 2 independent reviewers and then double checked. The differences were resolved by discussion with a third reviewer. The following information was extracted from each study: *1*) study characteristics, including study design, sample size, control varieties, duration of treatment, dosage, and sources of anthocyanins; *2*) participant characteristics, such as age, sex, and baseline BMI (in kg/m^2) ; and *3*) metabolic variables measured at baseline and posttreatment or the differences. The biomarkers included glycemic regulation markers, such as fasting blood glucose, fasting insulin, glycated hemoglobin (HbA1c), HOMA-IR; lipid profiles, such as LDL, HDL, total cholesterol, and TGs; inflammation markers, such as C-reactive protein, TNF-α, and IL-6; and blood pressure. The authors were contacted to request further data if they were not available in the paper.

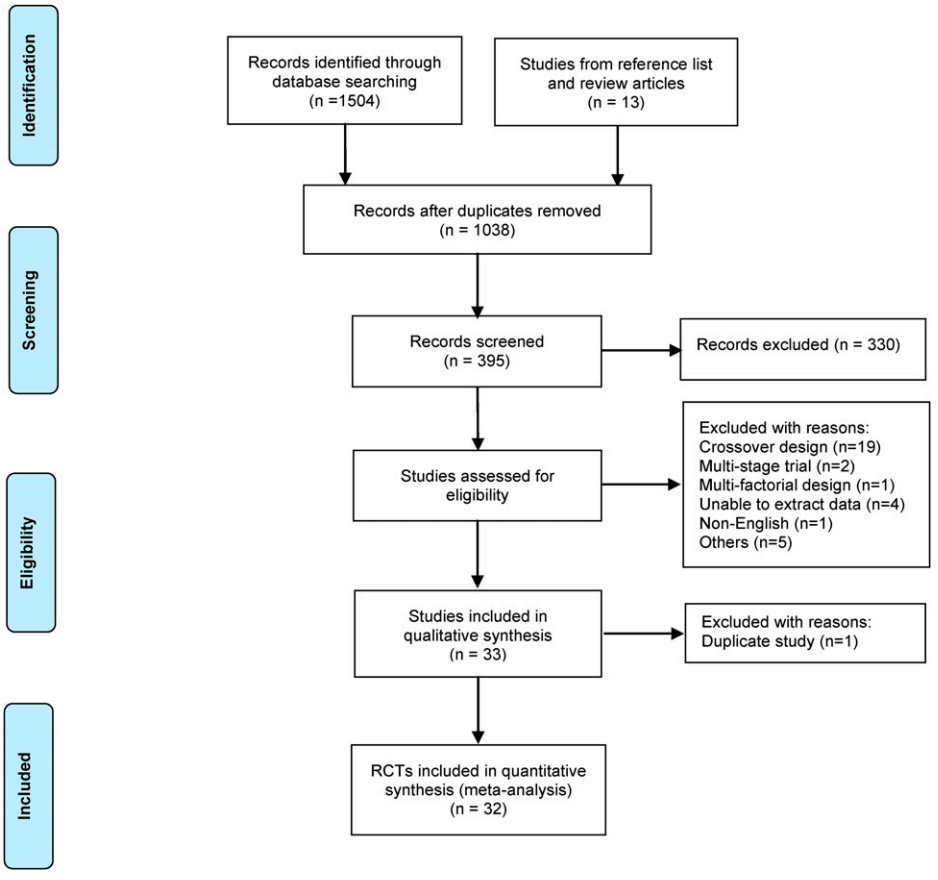

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection. RCT, randomized controlled trial.

The quality of the selected trials was assessed according to the criteria of Cochrane Handbook for Systematic Reviews of Interventions (13), which consisted of 4 main aspects: random-sequence generation, allocation concealment, blinding, and selective reporting. The risk of bias was classified as low, high, or unclear. The completeness of the data and potential selective reporting bias of each study were assessed by comparing the outcome of the published report with the original protocol registered in the database.

Data synthesis and analysis

This meta-analysis was performed by Stata (version 12.0; StataCorp) and Review Manager (Version 5.3; the Cochrane Collaboration). The means and SDs at the baseline and posttreatment had been directly extracted from articles. If not available, SDs were calculated from SEs or 95% CIs. Because some outcomes were measured by different methods or with different units, standardized mean differences (SMDs) were applied to estimate the effect size. Pooled SMDs and their 95% CIs are shown in forest plots to assess the overall effects of anthocyanins compared with controls. Heterogeneity between studies was tested by using Cochran's Q test (study by treatment interaction, $P < 0.1$), and an I^2 value >50% was considered significant heterogeneity across studies (14). In light of the significant heterogeneity, a random-effects model was used to estimate the pooled effects. For selected outcomes, SDs of mean differences between the initial and final values were calculated by using a conservative correlation coefficient of 0.5 (15).

Meta-regression, sensitivity, and subgroup analyses were conducted to evaluate the influence of potential confounding factors and sources of heterogeneity. These factors included participant characteristics (disease or risk), baseline BMI, dosage of anthocyanins, treatment duration, formula of supplements (purified or extracted anthocyanins or anthocyanin-rich foods), sources of anthocyanins (berry or nonberry sources), and the methodological quality (according to allocation concealment, adequate concealment of allocation is deemed a low risk of bias, and inadequate concealment a high or unclear risk of bias). Sensitivity analyses were performed by using the leave-one-out approach to examine whether the results are robust by removing individual trials. Potential publication bias was examined by visual inspection of the funnel plots as well as the Egger's test (16, 17). P values <0.05 were considered significant.

Results

Literature search and study selection

A total of 1504 potential studies were screened in the initial electronic search. After removing duplicate studies, the remaining 1038 articles were assessed for relevance according to the inclusion criteria for this review. The identification process for eligible studies is shown in **Figure 1** and is based on the Preferred Reporting Items for Systematic Review and

TABLE 1 Characteristics of included trials in the meta-analysis of the effect of anthocyanins on cardiometabolic health[1]

Study (ref), year	Cardiometabolic disease	Subjects, *n*, T/C	Duration	Intervention material	Total dose[2]	Anthocyanin, mg/d
Soltani et al. (19), 2015	T2DM	30/30	6 wk	*Cornus mas L.* fruit extracts	500 mg × 4	600
Li et al. (20), 2015	T2DM	29/29	24 wk	Purified anthocyanins	320 mg	307.2
Lee et al. (21), 2008	T2DM	15/15	12 wk	Cranberry extracts	1500 mg	NA
Kianbakht et al. (22), 2013	T2DM	37/37	4 wk	Whortleberry extracts	1050 mg	7.35
Fukuda et al. (23), 2015	T2DM	41/39	8 wk	Brazilian green propolis	226.8 mg	NA
Shidfar et al. (24), 2012	T2DM	29/29	12 wk	Cranberry juice	240 mL	NA
An et al. (25), 2016	Prediabetes	17/13	12 wk	Black raspberry extracts	1800 mg	NA
Wright et al. (26), 2013	Overweight and obesity	8/8	4 wk	Dried purple carrot	8.3 g × 3	118.5
Stull et al. (27), 2010	Obesity	15/17	6 wk	Blueberry powder	45 g	668
Rebello et al. (28), 2015	Overweight and obesity	14/14	4 wk	Blueberry anthocyanins	8.8 g × 2	325
Davinelli et al. (29), 2015	Overweight	26/16	4 wk	Maqui berry extracts	450 mg	162
Basu et al. (30), 2014 (LD)	Abdominal adiposity	15/15	12 wk	Freeze-dried strawberries	494 mL	78
Basu et al. (30), 2014 (HD)	Abdominal adiposity	15/15	12 wk	Freeze-dried strawberries	494 mL	155
Lee et al. (31), 2016	Overweight and obesity	32/31	8 wk	Black soybean extracts	2500 mg	162.5
Basu et al. (32), 2011	Metabolic syndrome	15/16	8 wk	Cranberry juice	480 mL	24.8
Basu et al. (33), 2010	Metabolic syndrome	25/23	8 wk	Freeze-dried blueberries	480 mL	742
Gurrola-Diaz et al. (34), 2010	Metabolic Syndrome	18/11	31 d	*Hibiscus sabdariffa* extracts	100 mg	19.24
Jeong et al. (35), 2014	Metabolic syndrome	39/38	12 wk	Black raspberry extracts	750 mg	NA
Puupponen-Pimiä et al. (36), 2013	Metabolic syndrome	20/12	12 wk	Berry constituents	300 g	70.7
Stull et al. (37), 2015	Metabolic syndrome	23/21	6 wk	Blueberry	45 g	580.6
Kianbakht et al. (38), 2014	Dyslipidemia	40/40	2 mo	Whortleberry extracts	1050 mg	7.35
Qin et al. (39), 2009	Dyslipidemia	60/60	12 wk	Purified anthocyanins	320 mg	307.2
Soltani et al. (40), 2014	Hyperlipidemia	25/25	4 wk	*Vaccinium arctostaphylos* extracts	1000 mg	90
Zhu et al. (41), 2013	Hypercholesterolemia	73/73	24 wk	Purified anthocyanins	320 mg	307.2
Zhang et al. (42), 2015	NAFLD	34/29	12 wk	Purified anthocyanins	320 mg	307.2
Asgary et al. (43), 2014	Hypertension	11/10	2 wk	Pomegranate juice	150 mL	8.7
Erlund et al. (44), 2008	Cardiovascular risk	35/36	8 wk	Berry constituents	150 g	515
Sumner et al. (45), 2005	Coronary heart disease	26/19	3 mo	Pomegranate juice	240 mL	NA
Karlsen et al. (46), 2007	None	59/59	3 wk	Purified anthocyanins	300 mg	300
Duthie et al. (47), 2006	None	11/9	2 wk	Cranberry juice	750 mL	2.2
Murkovic et al. (48), 2004	None	17/17	2 wk	Elderberry juice	1200 mg	120
Novotny et al. (49), 2015	None	29/27	8 wk	Cranberry juice	480 mL	21
Lynn et al. (50), 2014	None	25/21	6 wk	Tart cherry juice	250 mL	273.5

[1] Duration refers to the duration of treatment. HD, high dose; LD, low dose; NA, not available; NAFLD, nonalcoholic fatty liver disease; ref, reference; T/C, treatment/control; T2DM, type 2 diabetes.
[2] Amounts shown are for 1 dose/d unless otherwise indicated.

Meta-Analysis flow diagram (18). Sixty-five trials with anthocyanins as treatment were identified and further examined as full texts, and 33 were included for the meta-analysis. Among the 33 eligible studies, 6 enrolled patients with hyperglycemia, either type 2 diabetes mellitus (19–24) or prediabetes (25); 6 enrolled overweight or obese subjects (26–31); 6 included patients with metabolic syndromes (32–37); 4 studies included patients with dyslipidemia (38–41); and other studies included subjects with nonalcoholic fatty liver disease (42), hypertension (43), and CVD risk (44, 45) and healthy volunteers (46–50). Two publications came from the same trial with different treatment durations (41, 51). Only the one with the longer duration (41) was included. For studies with >2 groups within a study, the 2 comparisons (30) or only the higher dosage (25) compared with the control was extracted to avoid using duplicate control subjects. Most studies were placebo-controlled trials, except 3 that were diet (34) or water (33, 43) controlled. Finally, 32 eligible RCTs were included in the meta-analysis. A summary of the characteristics of all the included studies are presented in **Table 1**, and all excluded RCTs are listed in the **Supplemental Table 1**.

Study characteristics

A total of 1491 adults (759 in treatment groups and 732 in control groups) were included in the present meta-analysis, including 360 subjects with hyperglycemia and 396 with dyslipidemia. The variety of supplements included purified anthocyanins, composite anthocyanin extracts, and anthocyanins-rich foods, all of which were provided as powders, capsules, tablets, or beverages. The principal sources of anthocyanins were various berries, such as blueberries, strawberries, whortleberries, and cranberries. The dosage of pure anthocyanins ranged from 2.2 to 742 mg/d, and the treatment duration ranged from 2 to 24 wk. Of the included 32 RCTs in the meta-analysis, only 1 reported adverse events (25).

Risk of bias assessment

The graphs for the risk of bias are shown in **Supplemental Figures 1** and **2**. Most included studies (27 of 32) were double-blind. Allocation concealment was adequate in 22 trials, unclear in 5 studies, and not implemented in 5 studies. Twenty-five studies masked the participants, and 29 studies masked the outcome investigators. No obvious selective reporting bias was observed through comparison of the published outcomes and the limited available protocols. The funnel plots were symmetrical (figure not shown), and the Egger's tests suggested that no significant publication bias existed for the overall effects of most glycolipid metabolism markers (*P* values for Egger's testing are presented in **Table 2**).

Effects of anthocyanins on glycemic control and insulin sensitivity

The overall effect for all outcomes is displayed in Table 2. For heterogeneity testing, the I^2 ranged from 47.6% to 88.4%. Based on random-effects models, our meta-analyses suggested relevant favorable effects of anthocyanins on fasting and 2-h postprandial glucose and HbA1c. The pooled analyses suggested that anthocyanins significantly reduced fasting glucose concentrations (SMD: −0.31; 95% CI: −0.59, −0.04; I^2 = 80.7%). Four trials (189 subjects) reported the effect of anthocyanins on 2-h postprandial blood glucose (SMD: −0.82; 95% CI: −1.49, −0.15; I^2 = 77.7). Eleven trials, which included 510 subjects, reported results on HbA1c (SMD: −0.65; 95% CI: −1.00, −0.29; I^2 = 72.7%) (**Figure 2**). There were nonsignificant pooled effects of anthocyanins on fasting insulin (SMD: −0.002; 95% CI: −0.38, 0.38; I^2 = 78.2%) and HOMA-IR (SMD: −0.2; 95% CI: −0.8, 0.4; I^2 = 87.1%).

Effects of anthocyanins on lipid profiles and inflammation

Twenty-seven trials reported outcomes on lipid profiles and indicated that anthocyanin treatment was associated with decreased LDL (SMD: −0.35; 95% CI: −0.66, −0.05; I^2 = 85.2%) and total cholesterol (SMD: −0.33; 95% CI: −0.62, −0.03; I^2 = 86.9%) and marginally increased HDL (SMD: 0.24; 95% CI: −0.00, 0.49; I^2 = 81.1%). There was no significant pooled effect of anthocyanins on systolic blood pressure, diastolic blood pressure, or inflammatory markers, including C-reactive protein, TNF-α, and IL-6.

Subgroup and sensitivity analyses and meta-regression

Subgroup analyses (**Table 3**) revealed that anthocyanin treatment substantially reduced fasting glucose in subjects with hyperglycemia, LDL in subjects with dyslipidemia, and HOMA-IR among overweight and obese subjects (SMD: −0.65; 95% CI: −1.23, −0.06; I^2 = 45.2%) (**Figure 3**). Subgroup analyses among anthocyanin sources and formulas

TABLE 2 Meta-analysis for the effects of anthocyanins on cardiometabolic markers[1]

Outcome	Comparisons, *n*	Effect size	I^2, %	P^2
Fasting glucose	22	−0.31 (−0.59, −0.04)	80.70	0.37
2-h glucose	4	−0.82 (−1.49, −0.15)	77.30	0.92
HbA1c	11	−0.65 (−1.00, −0.29)	72.70	0.12
Fasting insulin	12	−0.002 (−0.38, 0.38)	78.20	0.52
HOMA-IR	9	−0.2 (−0.80, 0.40)	87.10	0.73
TGs	24	−0.2 (−0.45, 0.06)	76.50	0.08
Total cholesterol	30	−0.33 (−0.62, −0.03)	86.90	0.19
LDL cholesterol	27	−0.35 (−0.66, −0.05)	85.20	0.86
HDL cholesterol	29	0.24 (−0.00, 0.49)	81.10	0.51
apoA-I	6	0.21 (−0.12, 0.54)	65.90	0.81
apoB	6	−0.1 (−0.36, 0.17)	47.60	0.63
Systolic blood pressure	19	−0.17 (−0.55, 0.21)	87.90	0.63
Diastolic blood pressure	20	−0.17 (−0.56, 0.21)	88.20	0.29
TNF-α	7	−0.09 (−0.40, 0.21)	67.70	0.33
C-reactive protein	7	−0.51 (−1.14, 0.13)	88.40	0.3
IL-6	5	−0.1 (−0.43, 0.22)	52.50	0.1

[1] Data are pooled standardized mean differences (95% CIs) by a random-effects model. HbA1c, glycated hemoglobin; 2-h glucose, 2-h postprandial glucose by oral glucose tolerance test.
[2] Publication bias by Egger's regression.

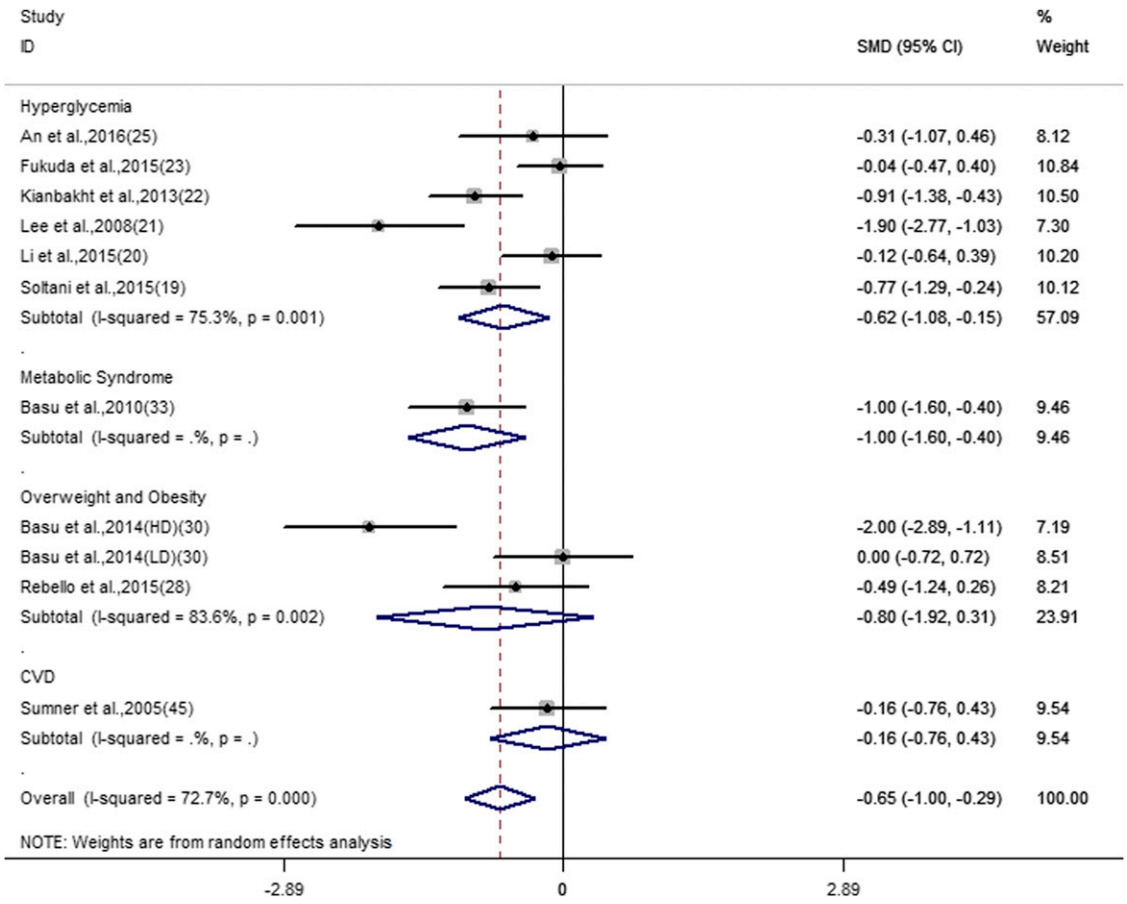

FIGURE 2 Forest plot of the meta-analysis for the effect of anthocyanins on glycated hemoglobin. Data are pooled SMDs with 95% CIs and are calculated by a random-effects model. Subgroup analysis was performed according to different cardiometabolic risk status. The 2014 trial by Basu et al. (33) has 4 study arms: HD, LD, and 2 placebo controls. CVD, cardiovascular disease; HD, high dose; ID, identifier; LD, low dose; SMD, standardized mean difference.

indicated decreased heterogeneity within subgroups. Meanwhile, a larger reduction of fasting glucose and LDL was observed in treatments that used purified anthocyanins or anthocyanin-rich extracts than in that of anthocyanin-rich foods, and in treatments that used berry sources than in other sources for anthocyanins.

Subgroup analysis by dosage of anthocyanins indicated reduced overall heterogeneity within strata (**Table 4**). A more notable effect was observed on HbA1c and TGs with a higher dosage of >400 mg/d than with lower dosages of anthocyanins. The optimal dosage for LDL reduction was at 200–400 mg anthocyanins/d. The overall effects on TGs and LDL had a dose-response trend, although it was nonsignificant. We did not assess the effect of an anthocyanin dose on 2-h postprandial glucose and inflammatory markers because there were inadequate studies for subgrouping or meta-regression. There were no clear effects of anthocyanin dose on blood pressure or other metabolic variables.

Sensitivity analyses, which exclude each study and subgroup analysis that was stratified by study quality (pooled separately from the trials with high or unclear risk of bias), were performed to test the robustness of the results. The studies with a low risk of bias had more marked effects on fasting glucose and LDL than did those with a high or unclear risk of bias. The exclusion of each study from the meta-analysis did not influence the overall effects on the main glucose and lipid metabolism measurements, such as fasting glucose, HbA1c, and LDL.

Discussion

This meta-analysis of the 32 RCTs revealed that anthocyanin treatment significantly improved fasting and 2-h postprandial glucose, HbA1c, total cholesterol, and LDL. No relevant effects were observed on blood pressure or inflammation markers. Subgroup analyses suggested that anthocyanins substantially decreased fasting glucose in subjects with hyperglycemia, LDL in subjects with dyslipidemia, and HOMA-IR among overweight and obese subjects. Sensitivity analyses showed that the overall effects of anthocyanins remained robust by excluding each trial or the trials with a high or unclear risk of bias.

Our study included a wide range of populations with different cardiometabolic statuses. The trials included in this meta-analysis also involved a large variety of dosages and sources of anthocyanins. To identify the sources of heterogeneity across the trials, we performed a range of analyses, including meta-regression, sensitivity, and subgroup analyses.

TABLE 3 Subgroup analyses for the effects of anthocyanins on fasting glucose and LDL cholesterol[1]

	Fasting glucose				LDL cholesterol			
Subgroups	**Comparisons, *n***	**Mean difference**	**I^2, %**	**P^2**	**Comparisons, *n***	**Mean difference**	**I^2, %**	**P^2**
Cardiometabolic disease								
Dyslipidemia	3	−0.05 (−0.26, 0.16)	0	0.91	5	−0.59 (−0.87, −0.31)	52.9	0.47
None	1	−2.61 (−3.33, −1.89)	—	0.004	3	−0.04 (−0.91, 0.83)	78.5	0.8
Hyperglycemia	7	−0.5 (−0.85, −0.15)	63.4	0.47	4	−1.27 (−2.59, 0.06)	93.5	0.23
Metabolic syndrome	4	0.01 (−0.94, 0.97)	87.6	0.76	6	−0.69 (−1.53, 0.16)	89.8	0.41
Overweight or obesity	5	−0.1 (−0.62, 0.43)	66.9	0.93	7	0.16 (−0.54, 0.86)	84.4	0.97
CVD	2	−0.11 (−0.6, 0.38)	0	—	2	0.28 (−0.21, 0.77)	0	—
Duration, wk								
2–11	12	−0.41 (−0.89, 0.07)	86.5	0.55	16	−0.37 (−0.75, 0.001)	81.3	0.99
12–24	10	−0.21 (−0.49, 0.08)	64.1	—	11	−0.33 (−0.86, 0.19)	89.5	—
BMI, kg/m^2								
<28	8	−0.1 (−0.27, 0.07)	0	—	11	−0.49 (−0.86, −0.13)	80.8	—
≥28	14	−0.41 (−0.87, 0.05)	87	0.46	15	−0.17 (−0.67, 0.33)	88.2	0.37
Source								
Berries	16	−0.36 (−0.74, 0.01)	85.7	—	21	−0.41 (−0.78, −0.04)	87.8	—
Other	6	−0.16 (−0.39, 0.07)	0	0.65	6	−0.17 (−0.54, 0.20)	47.8	0.67
Formula								
Purified or extracts	11	−0.28 (−0.49, −0.07)	44.6	0.86	13	−0.61 (−0.94, −0.29)	78.7	0.17
Nonpurified	11	−0.31 (−0.90, 0.27)	89	—	14	−0.04 (−0.55, 0.47)	86.7	—
Study quality, risk of bias								
Low	16	−0.47 (−0.76, −0.18)	79.8	—	19	−0.5 (−0.82, −0.16)	84.8	—
High or unclear	6	0.16 (−0.47, 0.79)	77.2	0.08	8	0.06 (−0.67, 0.8)	86.1	0.26

[1] Data are pooled standardized mean differences (95% CIs) by a random-effects model. BMI could not be extracted in some studies. Source means anthocyanins from berries or other sources, and the other sources include pomegranate juice, *Hibiscus sabdariffa* extracts, purple carrot, *Cornus mas L.* fruit extracts, *Vaccinium arctostaphylos* extracts, etc. Formula refers to purified anthocyanins or anthocyanins-rich extracts and nonpurified anthocyanins-rich food. The study quality was stratified by the risk of bias of allocation concealment. CVD, cardiovascular disease.

[2] Univariable meta-regression model.

The results suggested an approximate dose-response trend for TGs and LDL and decreased heterogeneity within subgroups. However, meta-regression showed no significant impact of the anthocyanin dose on the overall effects. This may be because the applied anthocyanins have different molecular structures and contain diverse bioactive constituents. Additionally, there are few dose-response studies. Further well-designed clinical trials are warranted to explore the dose-response relation of anthocyanin treatment within one study, as explored by Basu et al. (30).

Our results are consistent with the reports on whortleberry (22) and cranberry (21) that anthocyanins from berry sources had more marked effects than other sources on main glycolipid metabolism markers of fasting glucose and LDL. This could be because anthocyanins from berry sources contain more of certain active ingredients. Anthocyanins and proanthocyanins were mainly localized in the skin of fruits (52). Food processing may alter the components or molecule structure of anthocyanins (53). Moreover, we found that purified or extracted anthocyanins have more notable effects than nonpurified anthocyanin-rich foods, which could be because the presence of other components in anthocyanin-rich foods or the interaction between food ingredients may interfere with the effect of purified anthocyanins. The processing procedures in anthocyanin extraction or purification might be crucial for the biological functions of anthocyanins (54). Studies have shown that background dietary structure and physiological relevance could have an impact on the biological activity of anthocyanins (55). Further clinical trials are necessary to identify the specific molecular structure or certain processing methods that could affect the biological function of anthocyanins.

Our analysis indicated that anthocyanin treatment could significantly reduce markers of glycemic control. Subgroup analysis further suggested that anthocyanins improved fasting glucose and HbA1c with greater effects observed among patients with hyperglycemia. These findings would have important public health implications in primary and secondary prevention of type 2 diabetes (56) and CVDs (57). Studies suggested that postprandial hyperglycemia could be a better predictor of CVD than fasting glucose (58), and lowering postprandial blood glucose concentrations is an important clinical practice for diabetes control. Our analysis indicated that the 2-h postprandial glucose concentration was reduced by anthocyanin treatment. These findings support that anthocyanins could be a candidate for pharmacological management of hyperglycemia.

Insulin resistance occurs early in the progression of metabolic disorders and plays a pivotal pathogenic role in the development of type 2 diabetes. Animal and human studies have demonstrated that anthocyanins could improve insulin sensitivity (20, 59). Despite the nonsignificant effect that was observed in the overall effect of HOMA-IR, studies have shown that HOMA-IR could be significantly reduced by anthocyanins in patients with type 2 diabetes mellitus (19) and prediabetes (25), and the subgroup analysis showed a marked pooled effect of HOMA-IR in overweight and obese subjects. Obesity is considered a known risk factor of insulin resistance and type 2 diabetes (60, 61) as well as

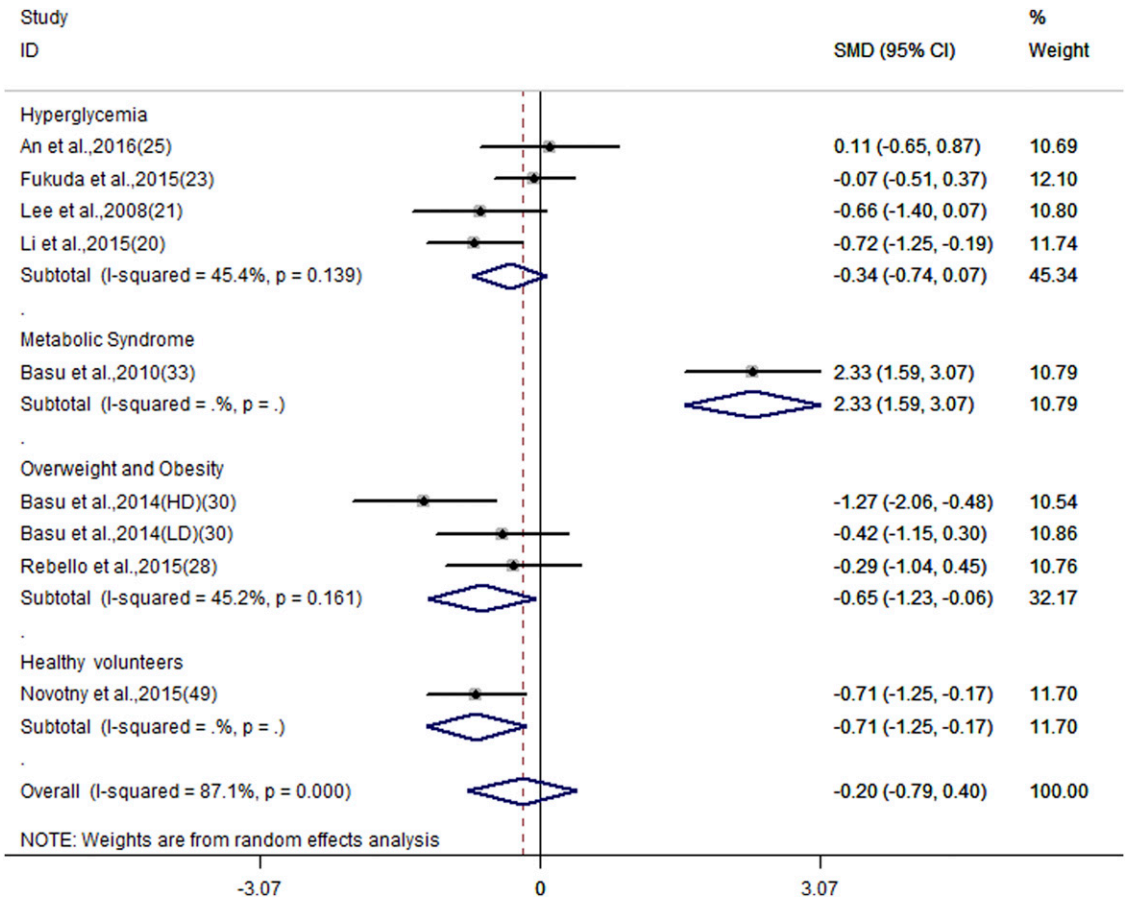

FIGURE 3 Forest plot of the meta-analysis for the effect of anthocyanins on HOMA-IR. Data are pooled SMDs with 95% CIs and are calculated by a random-effects model. Subgroup analysis was performed according to different cardiometabolic risk status. HD, high dose; ID, identifier; LD, low dose; SMD, standardized mean difference.

CVD (62–64). Adipose tissues could secrete certain cytokines or molecules, such as FFAs and adipokines that contribute to the development of metabolic disorders (65, 66). In an obese mouse model, blueberry anthocyanins had the potency to inhibit weight gain and body fat accumulation (67). Further clinical studies are required to confirm whether anthocyanins have additional benefits on insulin resistance and weight control among overweight or obese populations.

The present meta-analysis indicates that anthocyanins have favorable overall effects on LDL, which concurs with the previous systematic review (10). It was reported that anthocyanins could significantly improve LDL, but not other markers of CVD, among diseased individuals. Another systematic review discussed the cardiovascular protection of anthocyanins and revealed that the possible mechanism may be related to its effect on lipid peroxidation (11). These existing systematic reviews mainly focused on CVD molecular biomarkers, but a few reviews focused on glycemic regulation. Blumberg et al. (6) discussed the glucoregulation effect of cranberries from limited clinical trials. Stull (9) reported the improvements on insulin resistance but could not draw conclusions on the antidiabetic effect of blueberries because of the small number of clinical studies. Edirisinghe et al. (68) reviewed how the antidiabetic actions of berries might involve insulin-dependent or -independent mechanisms, such as the modification of inflammation, as demonstrated in experimental studies (69, 70). Several studies reported that anthocyanins could significantly reduce inflammatory biomarkers (25, 41, 46), whereas our meta-analysis showed a nonsignificant combined effect on inflammatory biomarkers. The inconsistencies could be due to the incomplete literature search on these outcomes, because the effect of anthocyanins on inflammatory markers was not our primary outcome, and only limited trials that reported the data on inflammation were included.

Our meta-analysis has several strengths. First, to our knowledge, this is the first meta-analysis that comprehensively assessed the effects of anthocyanins from available RCT data on cardiometabolic markers. We included a large number of studies with a randomized controlled design, extracted comprehensive cardiometabolic markers as outcomes, and included participants with a range of cardiometabolic risks. The relatively large number of participants allowed us a greater statistical power to detect a small treatment effect. Second, most of the included trials had a relatively good quality, and no significant publication bias was tested by Egger's regression. However, several limitations should be noted.

TABLE 4 Subgroup analyses for anthocyanin dose on the overall effects of cardiometabolic markers[1]

Outcome and anthocyanin dose, mg/d	Comparisons, *n*	Mean difference	I^2, %	P^2
Fasting glucose				
<200	8	−0.47 (1.19, 0.24)	89.1	0.59
200–400	5	−0.11 (0.30, 0.08)	0	—
>400	4	−0.1 (−0.92, 0.72)	86.4	0.85
HbA1c				
<200	3	−0.94 (−1.90, 0.03)	83.2	0.37
200–400	2	−0.24 (−0.67, 0.19)	0	—
>400	2	−0.87 (−1.26, −0.47)	0	0.42
HOMA-IR				
<200	3	−0.77 (−1.20, −0.34)	19.9	0.6
200–400	2	−0.58 (−1.00, −0.14)	0	—
>400	1	2.33 (1.59, 3.07)	—	—
Insulin				
<200	3	−0.42 (−1.12, 0.29)	70	0.67
200–400	3	−0.21 (−0.52, 0.10)	0	—
>400	3	0.26 (−0.52, 1.05)	80.3	0.3
TGs				
<200	12	0.04 (−0.47, 0.55)	86	0.51
200–400	3	−0.32 (−0.80, 0.17)	60.9	—
>400	5	−0.55 (−0.84, −0.26)	22	0.68
Total cholesterol				
<200	14	−0.18 (−0.73, 0.37)	88.5	0.93
200–400	7	−0.07 (−0.23, 0.09)	0	—
>400	4	−0.76 (−1.89, 0.37)	92.4	0.37
LDL cholesterol				
<200	14	−0.15 (−0.57, 0.28)	81.7	0.58
200–400	5	−0.49 (−0.69, −0.29)	3.4	—
>400	3	−0.8 (−2.78, 1.18)	95.7	0.67
HDL cholesterol				
<200	14	0.23 (−0.24, 0.70)	84.9	0.38
200–400	7	0.55 (0.09, 1.02)	86	—
>400	4	0.10 (−0.18, 0.38)	0	0.39
Systolic blood pressure				
<200	9	−0.19 (−1.04, 0.66)	91.8	0.95
200–400	5	−0.14 (−0.44, 0.16)	57.4	—
>400	4	−0.26 (−1.40, 0.87)	92.7	0.89
Diastolic blood pressure				
<200	9	−0.33 (−1.24, 0.58)	92.7	0.78
200–400	5	−0.04 (−0.23, 0.16)	6.2	—
>400	4	−0.42 (1.54, 0.70)	92.5	0.76

[1] Data are pooled standardized mean differences (95% CIs) by a random-effects model. Anthocyanin dose could not be extracted in some studies. HbA1c, glycated hemoglobin.
[2] *P* value for univariable meta-regression model.

First, the applied material of anthocyanins was heterogeneous in nature. To reduce the effect of heterogeneity, we conducted a number of subgroup and regression analyses. Standardized-pooled-effect (SMD) and random-effect models were also used to address the heterogeneity. Although there were wide CIs, the pooled effects were close to the average effect of each study but were still statistically significant. Second, there were limited studies with long-term durations and dose-response effects. In addition, a number of trials using anthocyanin-rich foods as treatment had an unclear or wide range of anthocyanin content, and there could be other non-quantified matrix compounds. It is possible that other components contained in these foods or their interactions with anthocyanins might have influenced the effects of anthocyanins. However, the inclusion of these studies in the current meta-analyses provided an additional perspective to the overall effect of anthocyanins. Finally, because of the missing medication-usage data of the selected RCTs, we could not analyze the influence of medication on the overall effects of anthocyanin treatment.

In conclusion, our meta-analysis of 32 RCTs indicated that anthocyanin supplementation or consumption of anthocyanin-rich foods has beneficial effects on glycolipid metabolism by reducing fasting and 2-h postprandial glucose, HbA1c, and LDL. The significant improvements in multiple cardiometabolic biomarkers support anthocyanins as an alternative for the prevention and treatment of cardiometabolic disorders. Further well-designed long-term trials are required to explore the optimal dosage, duration, and anthocyanins formula.

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