Meta-analyses

Effect of anthocyanin supplementation on cardio-metabolic biomarkers: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background: Several studies have shown effects of anthocyanin on blood pressure, blood glucose, and lipid profile in different conditions, but the results of these studies are controversial. We summarized evidence from randomized clinical trials (RCTs) that investigated the effects of anthocyanin supplementation on cardio-metabolic biomarkers in adults.
Methods: The literature searches of MEDLINE and EMBASE for published studies in English was performed up to August 2017. Results were summarized as mean differences (MD) with 95% confidence intervals (CI). Effect sizes of eligible studies were pooled using random-effects models (the DerSimonian-Laird estimator). Heterogeneity among studies was evaluated by the Cochrane Q test.
Results: Of 5370 papers, 19 RCTs met inclusion criteria. There was no significant effect of anthocyanin supplementation on weight, waist circumference (WC), body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP). Our results indicated that anthocyanin supplementation had no significant effects on HbA1c (MD: -0.32; 95% CI $= -0.64$, 0.00; p $= 0.050$) with no heterogeneity ($I^2 = 0.0\%$, p $= 0.966$, no significant heterogeneity), however anthocyanin supplementation had significant effect on HOMA-IR (MD: -0.21; 95% CI $= -0.36$, -0.07; p $= 0.004$) ($I^2 = 37.9\%$, p $= 0.200$, no significant heterogeneity) in adults. Intake of anthocyanin had no significant effects on FBS (MD: 0.25; 95% CI $= -5.70$, 6.21; p $= 0.933$) and serum insulin (MD: 0.09; 95% CI $= -0.92$, 1.11; p $= 0.860$) with high heterogeneity for these variables (p $= 0.000$, and $I^2 = 83.5\%$) and (p $= 0.098$, and $I^2 = 52.4\%$), respectively. Anthocyanin supplementation had significant effects on total cholesterol (TC) and low density lipoprotein (LDL) for more than 300 mg/day intervention for more than 12 weeks. The dose and duration of supplementation were the potential sources of heterogeneity among most of the trials.
Conclusion: The results demonstrate that supplementation with anthocyanin have beneficial effect on HOMA-IR in adults.

1. Introduction

Life-style changes together with several well-recognized risk factors including hypertension, hypercholesterolemia, diabetes and obesity, as well as dietary habits, are potentially modifiable to prevent chronic diseases like cardiovascular disease, diabetes and etc. [1,2]. Accumulating evidence from clinical trials and prospective studies suggest that the consumption of several foods and beverages is associated with a reduction of aforementioned risk factors for chronic diseases. According to the guidelines, healthy diet and consumption of higher fruits and vegetables have beneficial effects on human health due to their high content of vitamin-mineral, fiber, flavonoids, and polyphenols. These bioactive components can decrease low density lipoprotein cholesterol (LDL-C) oxidation and hypertension risk [3].

Anthocyanins are water-soluble plant pigments and the main polyphenol components in many kinds of dark-colored fruits

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particularly berries and cherries. Moreover some dark-colored vegetables such as purple potatoes, black beans, red onion and red radish are the sources of this polyphenol [4]. Anthocyanins are widely distributed active chemicals with antioxidant properties that can protect us against chronic disease such as diabetes, cancers, atherosclerosis, and cardiovascular disease. There are several studies that investigated the beneficial effect of sour cherry juice and berries on blood glucose and body weight [1,2]. It seems that anthocyanins can inhibit the expression of enzymes involved in fatty acid synthesis [5].

Although recent studies have support the beneficial effects of anthocyanin on blood pressure, blood glucose, and lipid profile in different conditions, the results are not consistent. These inconsistencies may be due to the inter-individual variability in the response to anthocyanin supplementation [6,7]. In the present study, we systematically reviewed all published randomized controlled trials (RCTs) which investigated the effect of anthocyanin supplementation on some cardio-metabolic biomarkers including weight, body mass index (BMI), waist circumferences (WC), blood pressure, lipids profile and glycemic status in adults.

2. Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used to conduct this systematic review meta-analysis (Supplemental Table 1) [8]. The PICOS-model [9], where the acronym PICOS stands for Population (all individuals except children under 18 years old and pregnant and lactating women), Intervention anthocyanin supplementation (without polyphenols or another substances with anti-oxidative capacity), Comparison (studies which had control group), Outcome (studies that reported weight, waist circumference, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS), Hemoglobin A1c (HbA1c), insulin resistance (HOMA-IR), serum insulin, LDL, high density lipoprotein (HDL), TC and triglyceride (TG), and Study design (RCT) were applied to formulate our question.

2.1. Search strategy

MEDLINE, EMBASE, and PubMed Central were searched for all relevant published articles up to 27 August 2017 with no time restriction. Only articles published in English were considered in this review. We used medical subject headings (MeSH) and text words to identify the potential interest studies. Search words included: ("Glycosylated Hemoglobin A" OR "Insulin Resistance" OR Insulin OR Glucose OR "Glucose Intolerance" OR "Waist Circumference" OR "Body Mass Index" OR Triglycerides OR "Cholesterol, HDL" OR "Cholesterol, LDL" OR "Blood Pressure" OR "Arterial Pressure" OR "Hypertension") AND (Anthocyanin* OR dietary anthocyanin*). Of all articles, RCTs were checked by reviewing titles, abstracts, population and study design in order to select relevant publications for inclusion and exclusion criteria. Literature searches were downloaded into EndNote (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA) to merge retrieved citations from different databases, eliminate duplications and to facilitate the review process.

2.2. Eligibility criteria

Studies were eligible for inclusion if they fulfilled the following criteria: a) the study design was RCT, b) the intervention was oral anthocyanin supplementation (we considered the studies that used supplements which contained only anthocyanin), c) the outcomes of interest were weight, BMI, WC, HbA1c, FBS, HOMA-IR, serum insulin, TG, LDL-C, HDL-C, TC, SBP, DBP d) the population of interest was adults (aged >18 years), e) Published English studies. We excluded studies if they were observational studies, review articles, duplicated publications, conference papers, animal or cell culture studies and unrelated studies. All retrieved articles in the initial search were read independently by two reviewers (ED and ZM). Any disagreements were discussed and resolved by consensus or by a third independent reviewer (SS-b) if necessary.

2.3. Data extraction

The following data from full text of selected studies were extracted: general characteristics of the study (first author's name, year of publication, the study design, the country where the study was conducted, number of cases and controls, type of supplement, total supplement dose and duration of follow-up), characteristics of the participants (study population, age, gender) and outcome results (means and standard deviations for weight, BMI, WC, HbA1c, FBS, HOMA-IR, serum insulin, TG, LDL-C, HDL-C, TC, SBP and DBP in baseline and after intervention). Where further detail was required, we contacted study authors for additional information.

2.4. Quality assessment

We evaluated the quality of the included studies using Jadad scoring system. This scale rate the trial studies with some questions which describe randomization, blinding and completeness of follow-up. Each study can get a point ranging from zero to five, based on Jadad scoring system. A score of less than two was classified as low quality studies and high quality studies received a score of ≥3 [10].

3. Statistical analysis

Stata software version 12 (StataCrop. College Station, Texas, USA) was used to perform all statistical analyses. The mean and SD of changes in cardio-metabolic risk factors from baseline was used to conduct meta-analysis in RCTs. The following approximations were also used: If a study provided standard error for variation of mean, SD was calculated by dividing $SE*\sqrt{n}$. If a study provided medians (interquartile ranges), we converted them to means (SD) as described by Hozo and colleagues [11]. A fixed-effect model was used to calculate pooled weighted mean differences (MD) by the generic inverse variance method by the user written "metan" command in Stata (version 12) software [12]. Heterogeneity of studies was assessed using Cochrane's Q test (significant with a P-value of <0.10) and I^2 statistic provided the relative amount of variance of the summary effect [13]. In case of heterogeneity, random-effects model (DerSimonian–Laird) was used. To evaluate the predefined sources of heterogeneity, subgroup analysis was performed. Small study effects was assessed using Egger's regression asymmetry test for the included studies with the user written "metabias" command in Stata (version 12) software [12,14]. P < 0.05 was considered to be statistically significant.

4. Results

4.1. Study selection

The flow chart of literature search is shown in Fig. 1. The initial search identified 5367 publications through Scopus and PubMed. Of those, 740 records were duplicates. After excluding duplicates, a total of 4627 studies were retrieved for title and abstract screening. The cited references of the retrieved articles were checked to find any potential eligible studies; consequently we found 3 other
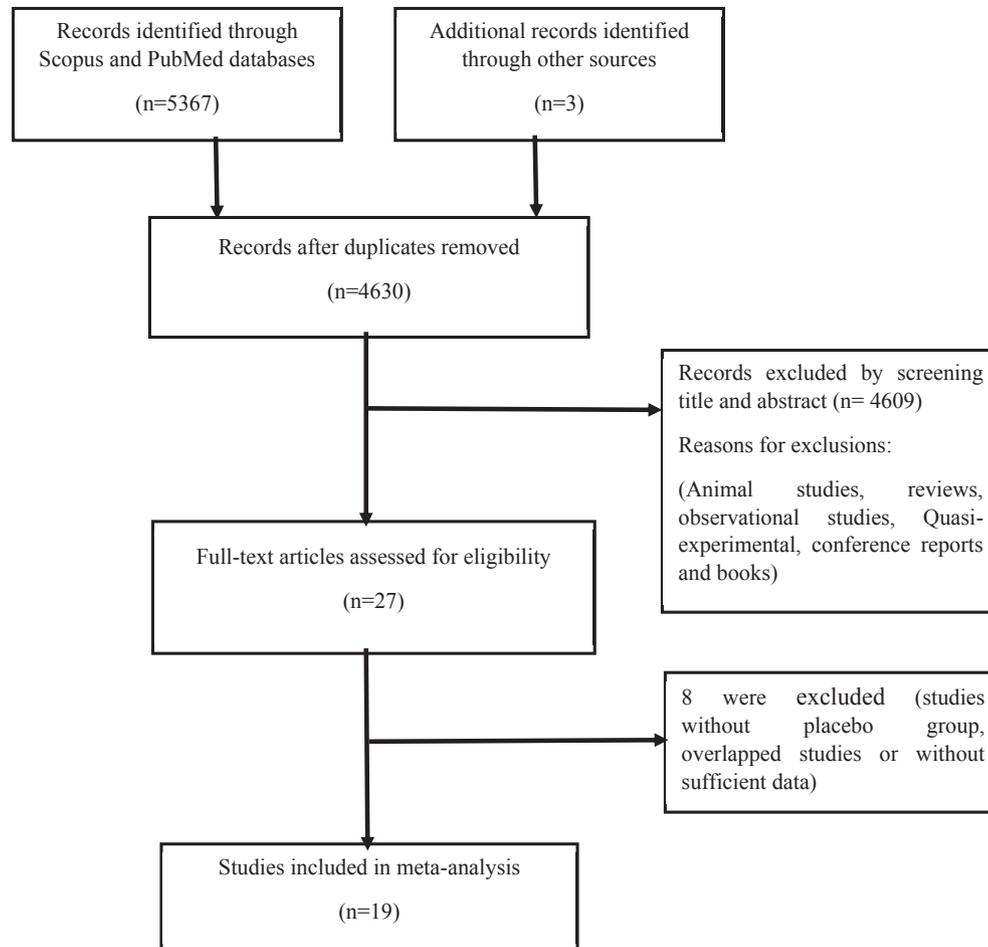
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┌─────────────────────────────┐   ┌─────────────────────────────┐
│ Records identified through  │   │ Additional records identified│
│ Scopus and PubMed databases │   │   through other sources     │
│                             │   │                             │
│          (n=5367)           │   │           (n=3)             │
└─────────────────────────────┘   └─────────────────────────────┘
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Records after duplicates removed

(n=4630)

Records excluded by screening title and abstract (n= 4609)

Reasons for exclusions:

(Animal studies, reviews, observational studies, Quasi-experimental, conference reports and books)

Full-text articles assessed for eligibility

(n=27)

8 were excluded (studies without placebo group, overlapped studies or without sufficient data)

Studies included in meta-analysis

(n=19)

Fig. 1. Flow diagram of study.

related articles through this searching backward for references cited in those articles after screening for title and abstract, 4602 articles were excluded and 25 papers were retrieved for full text review. Out of 25 retrieved papers, eight articles were excluded due to lack of information, quasi-experimental design or not having control group [1,3], without sufficient data [15–18] or overlapped by chosen studies [19,20]. Finally 19 studies were included in our meta-analysis.

5. Characteristics of included studies

Summarized characteristics of the included studies are presented in Table 1. These studies were published in Poland [21], United Kingdom [22,23], Italy [24], Korea [6,25], China [26–30], Japan [31], Norway [32], Austria [33], Mexico [34], USA [35], Australia [36], and Iran [7,37], which all were published between 2000 and 2016. The duration of follow-up in these studies was from one to 96 weeks. All studies had parallel design except two of them that were factorial randomized [34] and retrospective trial [6]. The participants of studies were of both genders except for Cook et al. study that was performed on men [22], and Curtis et al. study that was conducted on women [23]. The cases received daily anthocyanin supplement which contained various type of anthocyanins in the range of 31.45 mg–1050 mg and control group received placebo. Only one study calculated dietary intake of anthocyanin in participants [22]. All, except two studies [6,21] had high quality score (≥3).

6. Meta-analysis

6.1. Blood pressure and anthropometric measurements

The effects of anthocyanin supplementation on anthropometric measures and indices (weight, WC, BMI) and blood pressure measurements (SBP and DBP) are shown in Fig. 2. No significant effects of anthocyanin on SBP (MD: 1.80 mmHg; 95% CI = −0.92, 4.52; p = 0.195) (I^2 = 64.3%, p = 0.000) and DBP (MD: 0.66 mmHg; 95% CI = −0.82, 2.14; p = 0.382) (I^2 = 38%, p = 0.067) were observed in random-effect model. Sub-group analysis showed that none of predefined criteria were the sources of heterogeneity as shown in Supplemental Tables 2 and 3.

In the pooled analysis of seven trials with 572 participants, no significant pooled effects of anthocyanin on weight (MD: 1.71 kg; 95% CI = 2.14, 5.55; p = 0.385, I^2 = 79.6%, p < 0.0001) was observed. Effects of anthocyanin on BMI (MD: 0.71 kg/m^2; 95% CI = −0.88, 2.30; p = 0.380, I^2 = 93.1%, p < 0.0001), and WC (MD: 2.70 cm; 95% CI = −2.98, 8.38; p = 0.351, I^2 = 93.4%, p < 0.0001) were not significant in random-effect model. Sub-group analysis based on trial duration showed that those with anthocyanin intake for more than 12 weeks intervention had 2.42 kg weight reduction (MD: −2.42 kg; 95% CI: −4.46, −0.38; p = 0.020), (p = 0.654, and I^2 = 0%) and 0.75 kg/m^2 decrease in BMI (MD: −0.75 kg/m^2; 95% CI: −1.38, −0.23; p = 0.005), (p = 0.782 and I^2 = 0%), (Supplemental Tables 4, 5 and 6).

Table 1
Characteristics of included studies.

First author	Year	Country	Anthocyanin dose (mg)	Duration (weeks)	Sample size		Jadad score
Broncel et al. [21]	2010	Poland	300	8	I: 25	P: 22	2
Cook et al. [22]	2016	UK	105	1	I: 15	P: 15	3
Curtis et al. [23]	2009	UK	500	12	I: 26	P: 26	5
Davinelli et al. [24]	2015	Italy	162	6	I: 26	P: 16	5
Lee et al. [25]	2016	Korea	31.45	8	I: 32	P: 31	5
Li et al. [30]	2015	China	160	24	I: 29	P: 29	5
Murkovic et al. [33]	2004	Austria	120	2	I: 17	P: 17	5
Ohguro et al. [31]	2012	Japan	50	96	I: 19	P: 19	5
Preuss et al. [35]	2000	USA	200	8	I: 10	P: 9	5
Qin et al. [28]	2009	China	320	12	I: 60	P: 60	5
Shim et al. [6]	2012	Korea	60	96	I: 132	P: 97	1
Zhang et al. [27]	2015	China	320	12	I: 37	P: 37	5
Zhang et al. [26]	2016	China	320	24	I: 73	P: 73	5
Zhu et al. [29]	2011	China	320	12	I: 73	P:73	5
Kianbakht et al. [37]	2014	Iran	1050	8	I: 40	P: 40	5
Soltani et al. [7]	2015	Iran	600	6	I: 30	P: 30	5
Kent et al. [36]	2015	Australia	138	12	I: 21	P: 21	3
Karlsen et al. [32]	2007	Norway	300	3	I: 59	P: 59	3
CurrolaDiaz et al. [34]	2010	Mexico	100	4	I: 18	P: 26	3

I: Intervention, P: Placebo.

6.2. Lipid profile and related indices with blood glucose

Figures 3 and 4 have shown the effects of anthocyanin supplementation on lipid profile (TC, LDL-C, HDL-C and TG all in random-effect model) and blood sugar related factors (FBS, HbA1c, HOMA-IR and serum insulin), respectively. There was no significant effect of anthocyanin supplementation on lipid profile. Subgrouping by duration of interventions showed that the effect of anthocyanin on these variables for more than 12 weeks intervention was significant for HDL-C (MD: 7.40 mg/dl; 95% CI = 6.04, 8.75; p < 0.0001), (I^2 = 84.6%, p < 0.0001) and LDL-C (MD: −10.67 mg/dl; 95% CI = −14.97, −6.37; p < 0.0001), (I^2 = 8% and p = 0.361)) Supplemental Tables 7 and 8. Sub-group analysis based on supplemental dosage showed that those with anthocyanin intake for more than 300 mg had 6.69 mg/dl significant reduction in TC level and 8.60 mg/dl significant reduction in LDL-C level. Participants who supplemented over than 12 week had a significant reduction in LDL-C (MD: −10.67 mg/dl; 95% CI: −14.97, −6.37). Moreover, a significant reduction was observed for TC, TG and LDL level among patients with hypercholesterolemia (Supplemental Tables 9 and 10).

Intake of anthocyanin had positive and significant effect on FBS in fix-effect model (MD: 2.98 mg/dl; 95% CI = 0.77, 5.19; p = 0.008), with high heterogeneity (I^2 = 83.5%, p < 0.0001). Intake of anthocyanin had no significant effect on serum insulin in fix-effect model (MD: −0.13 U/I; 95% CI = −0.71, 0.44; p = 0.645), with significant heterogeneity (I^2 = 52.4%, p = 0.098). In the analysis of random-effect model, intake of anthocyanin had no significant effects on FBS (MD: 0.25 mg/dl; 95% CI = −5.70, 6.21; p = 0.933) and serum insulin (MD: 0.09 U/I; 95% CI = −0.92, 1.11; p = 0.860). Between study heterogeneity was high for FBS (p = 0.000, and I^2 = 83.5%) and serum insulin (p = 0.098, and I^2 = 52.4%) (Supplemental Tables 11 and 12).

Intake of anthocyanin had no significant effects on HbA1c (MD: −0.32%; 95% CI = −0.64, 0.00; p = 0.050, (I^2 = 0.0%, p = 0.966)), and significant effect on HOMA-IR (MD: −0.21; 95% CI = −0.36, −0.07; p = 0.004, (I^2 = 37.9%, p = 0.200)), both in fixed-effect model.

6.3. Publication bias

Egger's tests indicated no significant evidence of small study effects for WC (P = 0.056), BMI (P = 0.171), FBS (P = 0.185), serum insulin (P = 0.524), HOMA-IR (P = 0.924), LDL (P = 0.332), TG (P = 0.296), TC (P = 0.951), SBP (P = 0.954) and DBP (P = 0.520). However, there was significant small study effects for weight (P = 0.029) and HDL-C (P = 0.031).

7. Discussion

Anthocyanin which is an important potential ingredient in fruits and vegetables may contribute to potentially positive effects on cardiovascular and chronic heart disease [23]. To the best of our knowledge, this study is the first meta-analysis that investigated the influence of anthocyanin on several cardio-metabolic factors in adults. The results in the current study showed a beneficial effect of taking anthocyanin supplements on HOMA-IR in adults, however there were no significant effects of anthocyanin supplementation on anthropometric indices, lipid profile, blood pressure and FBS and serum insulin. Also, there was a marginally significant effect on HbA1c. Based on subgroup analysis most important factors which were cause of heterogeneity were the dose and duration of supplementation. Twelve weeks supplementation significantly reduced weight, BMI, HDL and LDL. Also, SBP and DBP were higher in less than 12 week supplementation. Anthocyanin supplementation >300 mg had significant reducing effects on TC and LDL especially in patients with hypercholesterolemia. Also, HDL was significantly higher in patients with diabetes and hypercholesterolemia which indicate anthocyanin supplementation had more beneficial effects on these patients, not healthy individuals. Design of the studies was another source of heterogeneity.

Subgroup analysis revealed that anthocyanin supplementation in double-blind trials may reduce TC, TG, LDL and increase HDL levels.

According to our meta-analysis, HbA1c and HOMA-IR have shown improving results. Six weeks supplementation with sour cherry juices that contains high level of anthocyanin significantly reduced HbA1c in a pilot study [1]. These beneficial effects of anthocyanin supplementation on glycemic status could be due to stimulation of insulin release from pancreatic beta cells [21]. However we did not find any significant effect of anthocyanin on FBS which is in line with Alvarado et al. study [3]. Moreover, other researchers found increase in blood glucose after anthocyanin supplementation [18]. In our meta-analysis, HbA1c as a marker for long-term glycemic control, has shown an improvement in
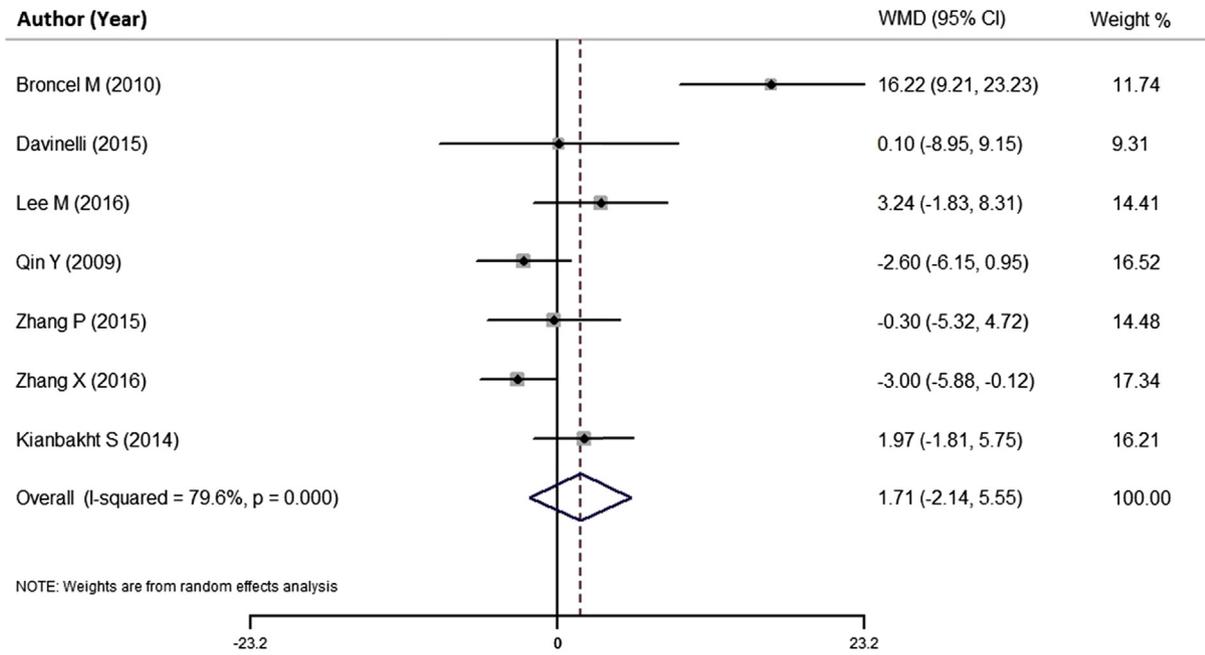
a. Weight
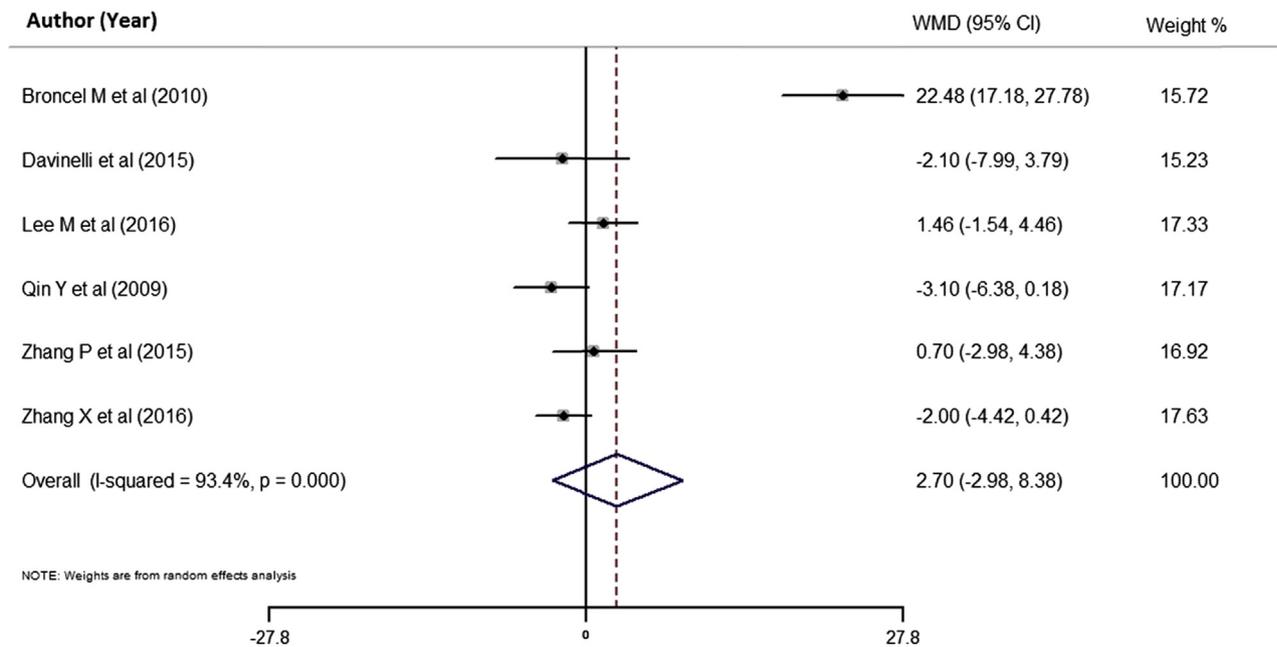
b. Waist circumference

Fig. 2. Effect of anthocyanin supplementation on anthropometric indices (a, b, c.) and blood pressure (d, e.).

Author (Year)	WMD (95% CI)	Weight %
Broncel M et al (2010)	6.77 (5.37, 8.17)	12.64
Davinelli et al (2015)	1.70 (-1.27, 4.67)	9.41
Lee M et al (2016)	0.78 (-0.16, 1.72)	13.35
Li D et al (2015)	-0.40 (-1.97, 1.17)	12.32
Qin Y et al (2009)	-1.30 (-2.53, -0.07)	12.92
Zhang P et al (2015)	-0.50 (-2.06, 1.06)	12.35
Zhang X et al (2016)	-0.70 (-1.38, -0.02)	13.65
Soltani R et al (2015)	-0.25 (-1.19, 0.69)	13.36
Overall (I-squared = 93.1%, p = 0.000)	0.71 (-0.88, 2.30)	100.00

NOTE: Weights are from random effects analysis

-8.17   0   8.17

c. BMI

Author (Year)	WMD (95% CI)	Weight %
Broncel M (2010)	16.51 (10.42, 22.60)	7.18
Cook M (2016)	3.21 (-6.23, 12.65)	4.77
Cook M (2016)	-0.90 (-9.46, 7.66)	5.31
Cook M (2016)	2.76 (-4.45, 9.97)	6.27
Curtis P (2009)	0.00 (-7.63, 7.63)	5.96
Davinelli (2015)	1.10 (-11.93, 14.13)	3.14
Lee M (2016)	3.26 (-2.64, 9.16)	7.34
Li D (2015)	-3.00 (-8.17, 2.17)	7.98
Ohguro H (2012)	1.47 (-6.68, 9.62)	5.59
Qin Y (2009)	0.50 (-6.14, 7.14)	6.73
Shim (2012)	2.78 (-0.37, 5.93)	9.75
Zhang P (2015)	-1.10 (-6.64, 4.44)	7.66
Zhang X (2016)	-1.30 (-5.81, 3.21)	8.58
Kent K (2015)	-6.50 (-13.27, 0.27)	6.62
CurrolaDiaz C (2010)	7.60 (1.42, 13.78)	7.10
Overall (I-squared = 64.3%, p = 0.000)	1.80 (-0.92, 4.52)	100.00

NOTE: Weights are from random effects analysis

-22.6   0   22.6

d. SBP

Fig. 2. (continued).

Author (Year)	WMD (95% CI)	Weight %
Broncel M (2010)	9.72 (3.75, 15.69)	4.68
Cook M (2016)	-1.23 (-7.13, 4.67)	4.76
Cook M (2016)	-2.38 (-8.99, 4.23)	3.99
Cook M (2016)	-0.30 (-6.03, 5.43)	4.97
Curtis P (2009)	-3.00 (-7.69, 1.69)	6.59
Davinelli (2015)	2.20 (-6.23, 10.63)	2.66
Lee M (2016)	2.52 (-1.90, 6.94)	7.14
Li D (2015)	-2.00 (-6.44, 2.44)	7.08
Ohguro H (2012)	5.36 (-0.71, 11.43)	4.55
Qin Y (2009)	1.10 (-2.78, 4.98)	8.33
Shim (2012)	-0.58 (-2.54, 1.38)	14.57
Zhang P (2015)	-0.60 (-4.31, 3.11)	8.77
Zhang X (2016)	1.50 (-1.60, 4.60)	10.53
Kent K (2015)	-4.30 (-11.63, 3.03)	3.38
CurrolaDiaz C (2010)	3.30 (-0.72, 7.32)	8.01
Overall (I-squared = 38.0%, p = 0.067)	0.66 (-0.82, 2.14)	100.00

NOTE: Weights are from random effects analysis
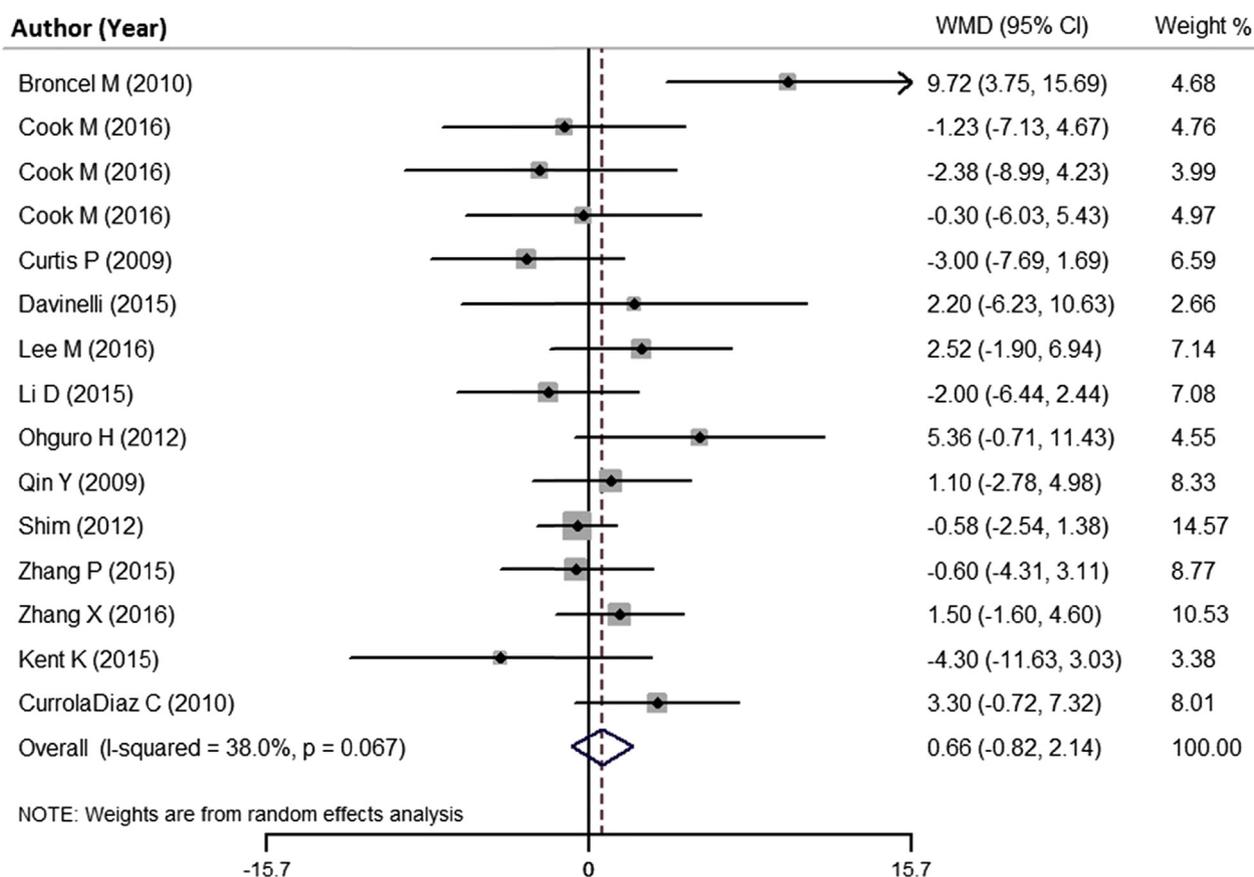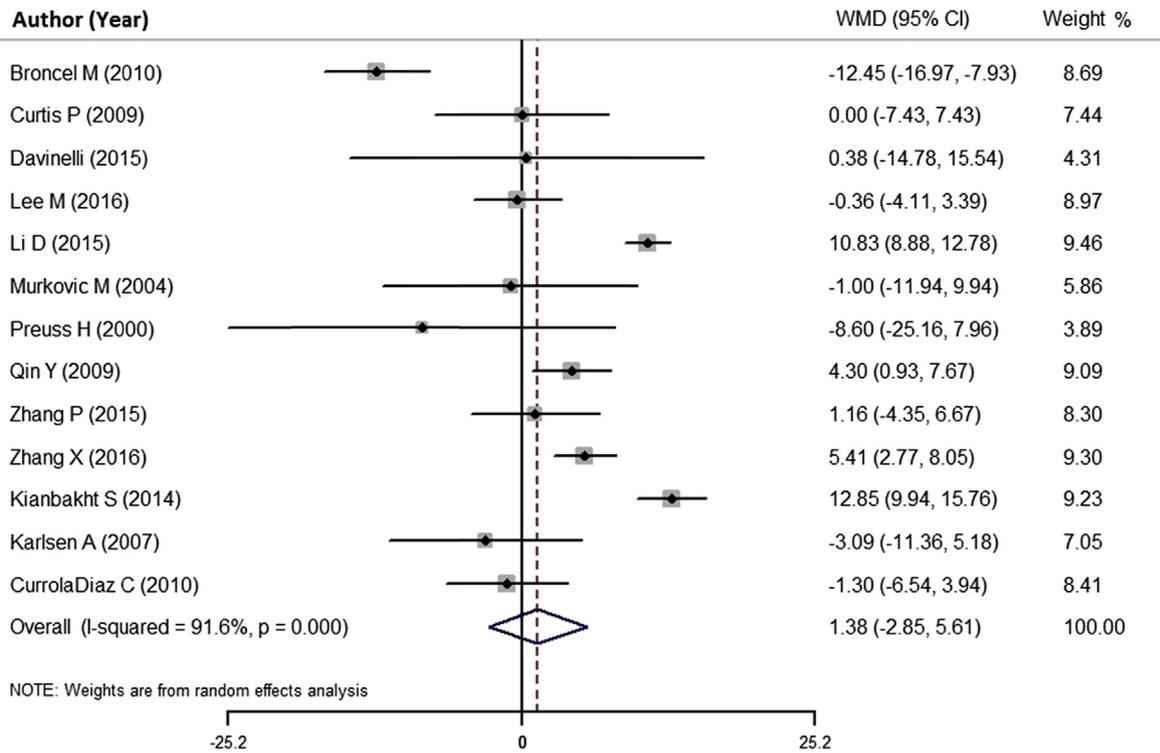
-15.7   0   15.7

e. DBP

Fig. 2. (*continued*).

response to anthocyanin supplementation. It is expected that weight reduction and controlling obesity are achieved by increasing insulin sensitivity with anthocyanin. Supplementation with anthocyanin showed a significant weight reduction in a rat model [38]. However, significant decreases in weight and BMI were only seen in studies with at least 12 weeks supplementation.
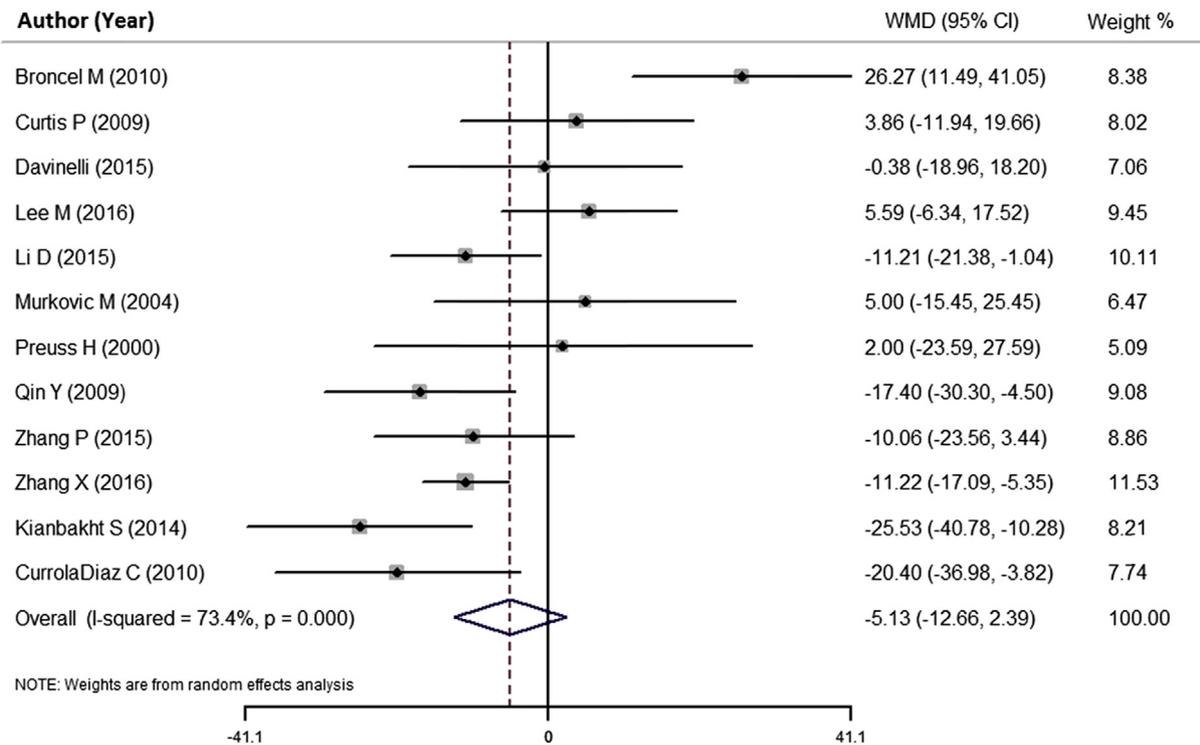
Although the pooled results of all included studies showed no significant effects of anthocyanin supplementation on LDL-C, HDL-C and weight, anthocyanin had beneficial effects on these variable in long-term exposure (>12 weeks anthocyanin intervention). Improving lipid profile has been considered as a potential strategy to prevent cardiovascular disease [39]. Accumulating evidence have shown that anthocyanin has a beneficial effect on increasing cholesterol efflux capacity by increasing HDL-Paraoxonase 1 activity [19]. Also, anthocyanin can decrease and inhibit the plasma cholesteryl-ester which subsequently could improve serum LDL and HDL levels [3]. Several studies have shown different effects of anthocyanin supplementation on lipid profile [18,27]. These different results depend on the duration of supplementation and the population studied. More than 12 weeks anthocyanin supplementation could decrease LDL-C and weight and increase HDL-C (MD:7.40 mg/dl; 95% CI: 6.04, 8.75). Hussellund et al., revealed that duration is more important than dose in interventional studies [18]. Zhu et al. indicated that 24-week supplementation with anthocyanin as a long-term intervention reduced LDL-C and increased HDL-C significantly [20]. Alvarado et al. also demonstrated that LDL-C had no significant decrease in 4 and 8 weeks

intervention, but there was a significant decrease after 12 week [3]. Moreover, a prospective epidemiological study demonstrated that anthocyanin can reduce the risk of cardiovascular disease, potentially in the long-term intervention [40]. Anthocyanin supplementation with more than 300 mg significantly decreased TC and LDL in this current study, which is in accordance with a previous study [28]. Usual daily intake of anthocyanin in different areas varies. In the United STATES, daily intake of anthocyanin was on average 12.5 mg/day [41], and in Europe daily intakes of anthocyanin ranged from 19.8 to 64.9 mg/day for men and 18.4−44.1 mg/day for women [42]. The most common dietary source of anthocyanin is fruits which contain low amounts of anthocyanin compare to supplements. Based on our results it seems that high amounts of anthocyanin (more than 300 mg) by daily supplementation reveal beneficial effects on cardio-metabolic factors such as LDL-C, and TC for more than 12 weeks intervention. While higher intakes vs. lower intakes of anthocyanin revealed 9−14% reduction in the risk of cardiovascular disease and mortality in two other studies [40,43].

Our results do not favor any significant clinical efficacy of anthocyanin supplementation on improving blood pressure and this result is in line with Zhu et al. study [44]. In contrast, some studies demonstrated a beneficial effect on blood pressure [45,46]. It is reasonable to expect that anthocyanin increases gene expression of endothelial nitric oxide synthase with vasoprotective properties and improves hypertension [1]. Inconclusive results between studies can be explained by different types of
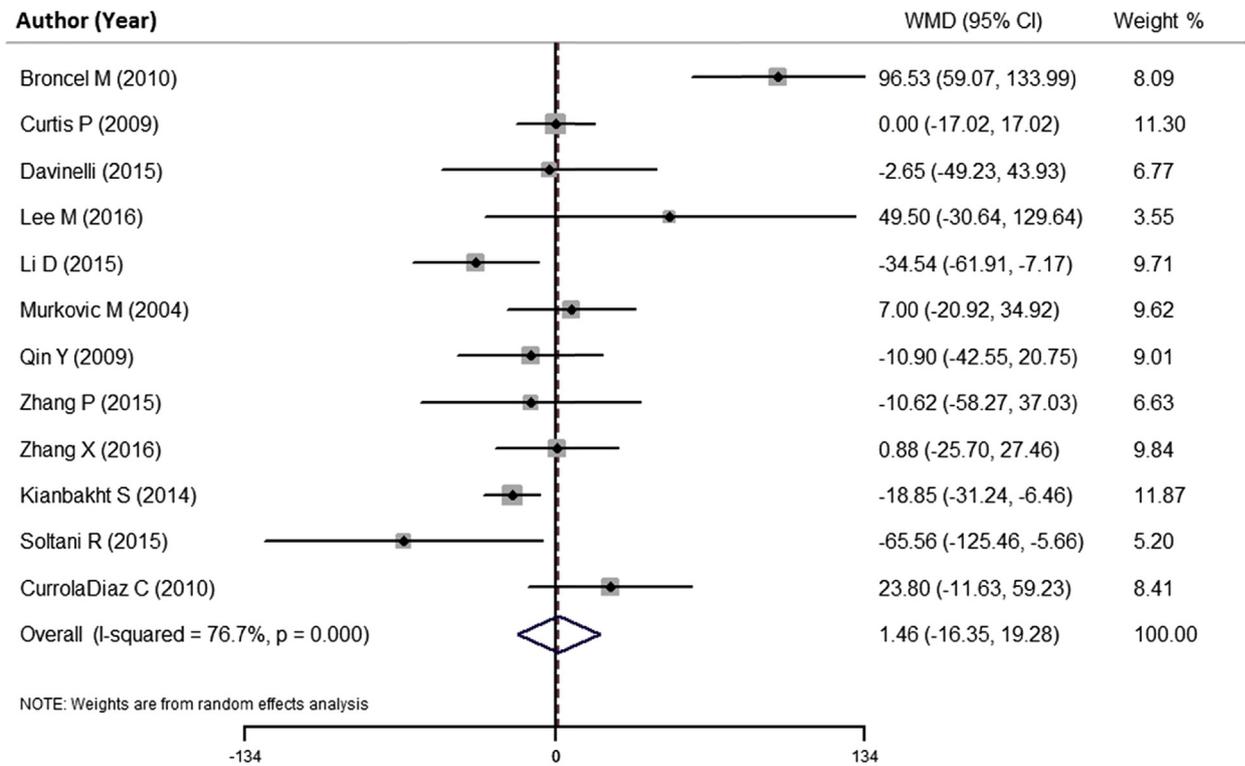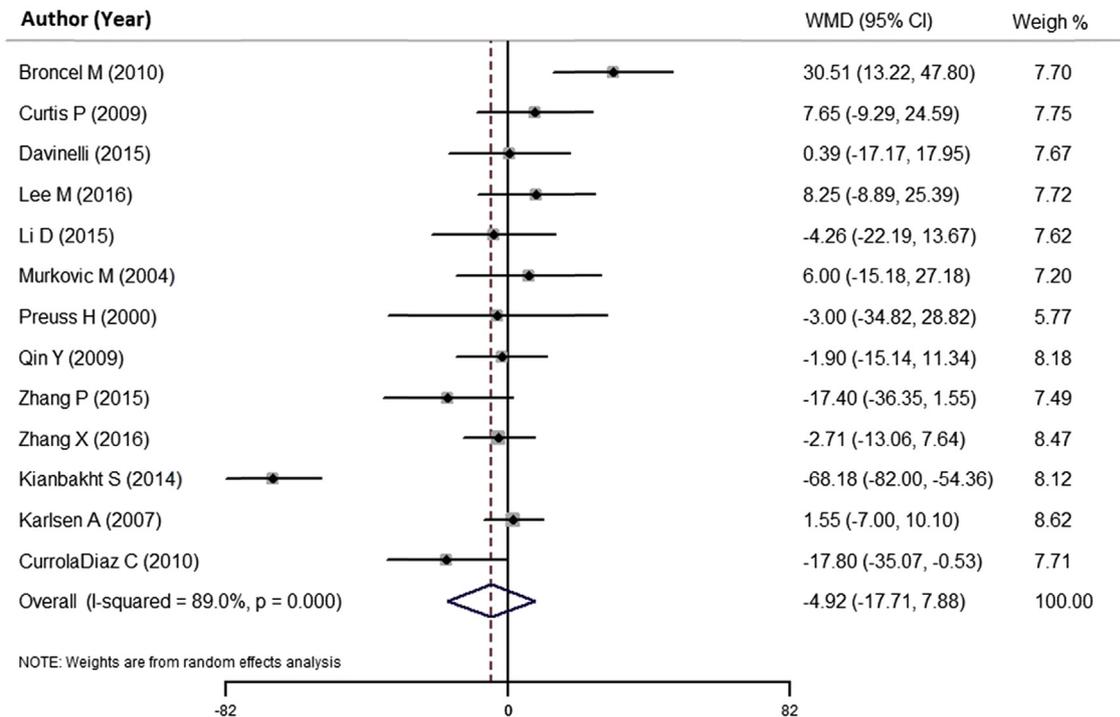
Author (Year)	WMD (95% CI)	Weight %
Broncel M (2010)	-12.45 (-16.97, -7.93)	8.69
Curtis P (2009)	0.00 (-7.43, 7.43)	7.44
Davinelli (2015)	0.38 (-14.78, 15.54)	4.31
Lee M (2016)	-0.36 (-4.11, 3.39)	8.97
Li D (2015)	10.83 (8.88, 12.78)	9.46
Murkovic M (2004)	-1.00 (-11.94, 9.94)	5.86
Preuss H (2000)	-8.60 (-25.16, 7.96)	3.89
Qin Y (2009)	4.30 (0.93, 7.67)	9.09
Zhang P (2015)	1.16 (-4.35, 6.67)	8.30
Zhang X (2016)	5.41 (2.77, 8.05)	9.30
Kianbakht S (2014)	12.85 (9.94, 15.76)	9.23
Karlsen A (2007)	-3.09 (-11.36, 5.18)	7.05
CurrolaDiaz C (2010)	-1.30 (-6.54, 3.94)	8.41
Overall (I-squared = 91.6%, p = 0.000)	1.38 (-2.85, 5.61)	100.00

NOTE: Weights are from random effects analysis

-25.2   0   25.2

a. HDL

Author (Year)	WMD (95% CI)	Weight %
Broncel M (2010)	26.27 (11.49, 41.05)	8.38
Curtis P (2009)	3.86 (-11.94, 19.66)	8.02
Davinelli (2015)	-0.38 (-18.96, 18.20)	7.06
Lee M (2016)	5.59 (-6.34, 17.52)	9.45
Li D (2015)	-11.21 (-21.38, -1.04)	10.11
Murkovic M (2004)	5.00 (-15.45, 25.45)	6.47
Preuss H (2000)	2.00 (-23.59, 27.59)	5.09
Qin Y (2009)	-17.40 (-30.30, -4.50)	9.08
Zhang P (2015)	-10.06 (-23.56, 3.44)	8.86
Zhang X (2016)	-11.22 (-17.09, -5.35)	11.53
Kianbakht S (2014)	-25.53 (-40.78, -10.28)	8.21
CurrolaDiaz C (2010)	-20.40 (-36.98, -3.82)	7.74
Overall (I-squared = 73.4%, p = 0.000)	-5.13 (-12.66, 2.39)	100.00

NOTE: Weights are from random effects analysis

-41.1   0   41.1

b. LDL

Fig. 3. Effect of anthocyanin supplementation on lipid profile (a, b, c, d.).

Author (Year)	WMD (95% CI)	Weight %
Broncel M (2010)	96.53 (59.07, 133.99)	8.09
Curtis P (2009)	0.00 (-17.02, 17.02)	11.30
Davinelli (2015)	-2.65 (-49.23, 43.93)	6.77
Lee M (2016)	49.50 (-30.64, 129.64)	3.55
Li D (2015)	-34.54 (-61.91, -7.17)	9.71
Murkovic M (2004)	7.00 (-20.92, 34.92)	9.62
Qin Y (2009)	-10.90 (-42.55, 20.75)	9.01
Zhang P (2015)	-10.62 (-58.27, 37.03)	6.63
Zhang X (2016)	0.88 (-25.70, 27.46)	9.84
Kianbakht S (2014)	-18.85 (-31.24, -6.46)	11.87
Soltani R (2015)	-65.56 (-125.46, -5.66)	5.20
CurrolaDiaz C (2010)	23.80 (-11.63, 59.23)	8.41
Overall (I-squared = 76.7%, p = 0.000)	1.46 (-16.35, 19.28)	100.00

NOTE: Weights are from random effects analysis

-134   0   134

c. TG

Author (Year)	WMD (95% CI)	Weigh %
Broncel M (2010)	30.51 (13.22, 47.80)	7.70
Curtis P (2009)	7.65 (-9.29, 24.59)	7.75
Davinelli (2015)	0.39 (-17.17, 17.95)	7.67
Lee M (2016)	8.25 (-8.89, 25.39)	7.72
Li D (2015)	-4.26 (-22.19, 13.67)	7.62
Murkovic M (2004)	6.00 (-15.18, 27.18)	7.20
Preuss H (2000)	-3.00 (-34.82, 28.82)	5.77
Qin Y (2009)	-1.90 (-15.14, 11.34)	8.18
Zhang P (2015)	-17.40 (-36.35, 1.55)	7.49
Zhang X (2016)	-2.71 (-13.06, 7.64)	8.47
Kianbakht S (2014)	-68.18 (-82.00, -54.36)	8.12
Karlsen A (2007)	1.55 (-7.00, 10.10)	8.62
CurrolaDiaz C (2010)	-17.80 (-35.07, -0.53)	7.71
Overall (I-squared = 89.0%, p = 0.000)	-4.92 (-17.71, 7.88)	100.00

NOTE: Weights are from random effects analysis

-82   0   82

d. TC

Fig. 3. (continued).

Author (Year)		WMD (95% CI)	Weight %
Broncel M (2010)		15.97 (10.84, 21.10)	12.24
Curtis P (2009)		-1.79 (-6.78, 3.20)	12.30
Lee M (2016)		1.73 (-3.18, 6.64)	12.33
Li D (2015)		-10.80 (-26.15, 4.55)	7.10
Qin Y (2009)		-3.60 (-16.89, 9.69)	8.05
Shim (2012)		6.90 (0.75, 13.05)	11.77
Zhang P (2015)		-3.60 (-9.71, 2.51)	11.79
Zhu Y (2011)		-0.20 (-9.43, 9.03)	10.17
Soltani R (2015)		-35.43 (-55.42, -15.44)	5.34
CurrolaDiaz C (2010)		10.00 (-1.61, 21.61)	8.90
Overall (I-squared = 83.5%, p = 0.000)		0.25 (-5.70, 6.21)	100.00

NOTE: Weights are from random effects analysis

-55.4   0   55.4

a. FBS

Author (Year)		WMD (95% CI)	Weight %
Li D (2015)		-0.30 (-1.16, 0.56)	13.69
Soltani R (2015)		-0.32 (-0.66, 0.02)	86.31
Overall (I-squared = 0.0%, p = 0.966)		-0.32 (-0.64, 0.00)	100.00

-1.16   0   1.16

b. HbA1c (Fix-effect model)

Fig. 4. Effect of anthocyanin supplementation on blood sugar factors (a, b, c, d.).

c. HOMA-IR (Fix-effect model)

d. Serum insulin

Fig. 4. (continued).

supplements. Different ingredients such as stilbenes, catechins, phenolic acids and flavonols can show various effects compared to purified anthocyanin. Moreover, various health conditions of participants and study populations and their baseline conditions might account for these inconsistent results.

8. Limitations

This study has some limitations. Most analyses had high levels of heterogeneity, but this is expected because the RCT's that were included had various population groups or doses and duration for supplementation forms. It seems that longer intervention with anthocyanin supplementation, result in positive effects on cardio-metabolic factors. In addition, some studies did not have enough data to perform subgroup analysis for certain variables such as serum insulin or being normotensive or hypertensive in various populations. Moreover, our search was limited to the published English studies. Some studies did not report data for dietary intake of anthocyanin; therefore we could not adjust the effect of dietary anthocyanin intake on considered variables.

9. Conclusion

Although this meta-analysis had some limitations, it demonstrates some interesting evidences, suggesting that anthocyanin supplementation might be effective on reducing some blood sugar factors such as HOMA-IR in adults. Moreover, supplementation for more than 12 weeks had significant effects on weight and HDL-C. Due to variation in sample size and population of the included studies, further high-quality and well-designed RCTs are needed, particularly with a homogeneous population.

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Conflict of interest

The authors declare no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.06.979.

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