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Review

# Impact of dietary anthocyanins on systemic and vascular inflammation: Systematic review and meta-analysis on randomised clinical trials

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ABSTRACT

Anthocyanins are natural bioactive compounds that have several health benefits. This systematic review and meta-analysis assessed the impact of dietary anthocyanins on markers of systemic and vascular inflammation. Meta-analysis of 32 randomised controlled trials indicated that dietary anthocyanins significantly decreased levels of C-reactive protein (CRP; −0.33 mg/l, 95% CI: −0.55 to −0.11, $P = 0.003$), interleukin-6 (IL-6; −0.41 ρg/ml, 95% CI: −0.70 to −0.13, $P = 0.004$), tumor necrosis factor-alpha (TNF-α; −0.64 ρg/ml, 95% CI: −1.18 to −0.09, $P = 0.023$), intercellular adhesion molecule-1 (−52.4 ng/ml, 95% CI: −85.7 to −19.1, $P = 0.002$), and vascular adhesion molecule-1 (VCAM-1; −49.6 ng/ml, 95% CI: −72.7 to −26.5, $P < 0.001$) while adiponectin level was significantly increased (0.75 μg/ml, 95% CI: 0.23 to 1.26, $P = 0.004$). The levels of interleukin-1β (IL-1β; −0.45 ρg/ml, 95% CI: −3.77 to 2.88, $P = 0.793$) and P-selectin (−6.98 ng/ml, 95% CI: −18.1 to 4.15, $P = 0.219$) did not significantly change. Subgroup analyses showed that administration of higher doses of anthocyanins (> 300 mg/day) significantly decreased levels of CRP, IL-6, TNF-α, and VCAM-1. The results indicate that dietary anthocyanins reduce the levels of systemic and vascular inflammation in the subjects.

## 1. Introduction

Results of previous surveys have indicated the contribution of low-grade chronic inflammation on the development and progression of various non-communicable chronic diseases like diabetes mellitus type 2, chronic kidney disease, stroke, atherosclerosis, cardiovascular diseases, and malignancies (Nathan, 2002; Tabas and Glass, 2013). The inflammatory response is characterized by the activation of various signaling pathways that increase expression and levels of pro-inflammatory mediators such as C-reactive protein (CRP), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and other cytokines. Higher concentrations of pro-inflammatory mediators not only predict future development of chronic diseases, but also mediate pathogenesis of the diseases (Dinarello, 2000; Tabas and Glass, 2013). Therefore, reduction of the levels of pro-inflammatory mediators is one way to decrease the risk of such chronic diseases.

Anthocyanins, a member of the flavonoids family, are water-soluble vacuolar pigments responsible for red-orange to blue-violet colors in many fruits, vegetables, and flowers. At first, anthocyanins were only famous for their coloring attributes influencing the sensory characteristics of food products. But now the focus is on the health benefits of these compounds due to their biological activities (Stintzing and Carle, 2004; Norberto et al., 2013). The *in vivo* and *in vitro* studies indicated that biological activities of anthocyanins are mainly related to their antioxidative characteristics (Shih et al., 2010; Rugină et al., 2012; Maciel et al., 2018; Prokop et al., 2018). Considering the fact that free radical damage is the etiology of many chronic diseases, potential antioxidative activity of anthocyanins can slow down the progression of such diseases (Li et al., 2017).

In human clinical trials, the beneficial effects of dietary administration of anthocyanins or anthocyanin-rich foodstuffs are reported as follows: Prevention of cardiovascular diseases (Novotny et al., 2015), reduction of blood pressure in hypertensive subjects (Johnson et al., 2015), enhancement of oxidative status in healthy smokers (Park et al., 2015), reduction of thrombogenesis in overweight and obese subjects (Thompson et al., 2017b), bone loss protection in postmenopausal smokers (Kaume et al., 2014), prevention of type 2 diabetes in pre-diabetics (An et al., 2016), reduction of serum lipids in patients with metabolic syndrome (Basu et al., 2010a), enhancement of liver function in non-alcoholic fatty liver disease (Zhang et al., 2015), and reduction

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of fasting blood sugar and glycosylated hemoglobin in patients with type 2 diabetes (Gorji et al., 2014).

Several human clinical trials have investigated the effect of dietary anthocyanins on inflammatory markers of subjects with different health status; however, different results have been reported. Some studies reported that consumption of anthocyanins reduced the levels of some inflammatory markers (Curtis et al., 2009; Hassellund et al., 2013; Asgary et al., 2016; Johnson et al., 2017). On the other hand, the other studies found no significant changes in the levels of inflammatory markers following anthocyanins administration (Kolehmainen et al., 2012; Li et al., 2015; Jeong et al., 2016; Chew et al., 2019). Therefore, this study aimed to evaluate and elucidate the impact of pure anthocyanins or anthocyanin-rich extract/powder on serum levels of CRP, IL-6, TNF-α, IL-1β, adiponectin, ICAM-1, VCAM-1, and P-selectin.

## 2. Methods

### 2.1. Strategy of searching

This research was conducted and the results were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) instructions (Moher et al., 2015). The protocol of this research was recorded in PROSPERO, the international database of prospectively registered systematic review in health and social care (registry code: CRD42017068611).

Five electronic databases including PubMed, ISI Web of Science, Scopus, MagIran, and Scientific Information Database (SID) were searched up to 1 April 2019. The detail of search strategy is described in Supplementary Data, Appendix A.

The search was carried out by 2 authors (AAF and TJ) independently, and the obtained articles were assessed. For screening, 3 authors (AAF, ES, and PF) separately assessed the articles through the review of titles and abstracts; and if necessary, the full texts. After screening, the full texts of remained articles were evaluated based on inclusion criteria (section 2.2) to identify the studies eligible for systematic review and meta-analysis. At each stage, doubtful cases were discussed within the research team.

### 2.2. Selection of studies

The inclusion criteria to choose the articles were: (*a*) parallel or cross-over randomised controlled trials (RCTs) in adults (age ≥ 18 years old) in which the intervention group consumed pure anthocyanins or anthocyanin-rich extract/powder; (*b*) RCTs administrated placebo in control group and pure anthocyanins or anthocyanin-rich extract/powder in intervention group; (*c*) RCTs that did not prescribe placebo in control group, but the difference of this group with intervention group was only administration of anthocyanins; (*d*) intervention duration was not less than 3 weeks; (*e*) a quantitative or quantifiable anthocyanin content was reported for the intervention group; (*f*) RCTs provided sufficient information on baseline and end-trial circulating and vascular markers comprising CRP, IL-6, TNF-α, IL-1β, adiponectin, ICAM-1, VCAM-1, or P-selectin.

### 2.3. Data extraction

Two authors (AAF and ES) independently assessed the eligible RCTs, and following items were abstracted: last name of first author, year of publication, country of origin, number of subjects in each group, design and duration of RCT, daily dosage and form of anthocyanins, health condition of participants, and concentrations of CRP, IL-6, TNF-α, IL-1β, adiponectin, ICAM-1, VCAM-1, and P-selectin.

### 2.4. Quality assessment of studies and outcomes

The quality of selected RCTs was assessed by Cochrane Collaboration's risk of bias tool that includes the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. For each domain, RCTs were classified into low, unclear, or high risk of bias (Higgins and Green, 2008).

The quality of meta-analysis for each outcome was assessed by NutriGrade scoring system that consists of the following criteria for meta-analysis of RCTs: risk of bias, precision, heterogeneity, directness, publication bias, funding bias, and study design. In this scoring system, each outcome scored from 0 to 10. The scores ≥8, 6–7.99, 4–5.99, and 0–3.99 were judged as high, moderate, low, and very low quality, respectively (Schwingshackl et al., 2016).

### 2.5. Statistical methods

For each eligible RCT, the effect size for CRP (mg/l), IL-6 (ρg/ml), TNF-α (ρg/ml), IL-1β (ρg/ml), adiponectin (μg/ml), ICAM-1 (ng/ml), VCAM-1 (ng/ml), or P-selectin (ng/ml) was computed as unstandardized mean difference and 95% confidence interval (CI). The net mean difference in intervention or control group was calculated by the following formula: (measure at baseline – measure at end-trial). Standard deviation (SD) of the mean difference in intervention or control group was calculated as follow: $SD = sqrt[(SD_{baseline})^2 + (SD_{end\text{-}trial})^2 - (2R \times SD_{baseline} \times SD_{end\text{-}trial})]$, supposing a correlation coefficient ($R$) = 0.50 (Fallah et al., 2018; Jafari et al., 2018). In RCTs reporting standard error of the mean (SEM), SD was calculated as follow: SD = SEM × sqrt ($n$), where $n$ is the number of participants. For outcomes presented as median and interquartile range, mean and SD values were calculated according to the procedure of Wan et al. (2014). Since the eligible RCTs were conducted in various settings, random effects were employed to account for anticipated heterogeneity between contributing studies (DerSimonian and Laird, 1986). Study-level characteristics including duration of RCTs, anthocyanins doses, baseline inflammatory markers, and health status of the subjects were pre-specified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random effects meta-regression. Cochrane's Q tests were employed to test the hypothesis of inter-trial heterogeneity (Higgins and Green, 2008). *I*-squared ($I^2$) index, has a range of 0–100%, was used to quantify inter-trial heterogeneity. $I^2$ values of 25, 50 and 75% are referred to low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). Publication bias was evaluated by Begg and Mazumdar adjusted rank correlation test (Begg and Mazumdar, 1994; Jafari et al., 2015) and Egger's regression asymmetry test (Egger et al., 1997; Jafari et al., 2017). Sensitivity analysis was performed to examine the extent to which inferences might depend on a particular RCT or number of RCTs. In order to conduct statistical analyses, data from selected RCTs were entered into an Excel sheet and then imported into a Stata database (Stata software version 11.2; Stata Corporation, College Station, TX). Level of significance was set at $P \leq 0.050$.

## 3. Results

### 3.1. Search results

We detected 3369 records in our initial systematic search, and then excluded 1571 duplicates. After assessing the remaining records, 1673 were removed since the records were irrelevant to the topic, animal trials, or review articles. Finally, 125 records were assessed carefully and 32 studies (Karlsen et al., 2007; Naruszewicz et al., 2007; Curtis et al., 2009; Basu et al., 2010a, 2014, 2018, 2010b; Stull et al., 2010; Vidlar et al., 2010; Zhu et al., 2011; Kolehmainen et al., 2012; Hassellund et al., 2013; Moazen et al., 2013; Riso et al., 2013; Soltani et al., 2014; Li et al., 2015; Asgary et al., 2016; Jeong et al., 2016; Lee et al., 2016; Loo et al., 2016; Zhang et al., 2016; Johnson et al., 2017;

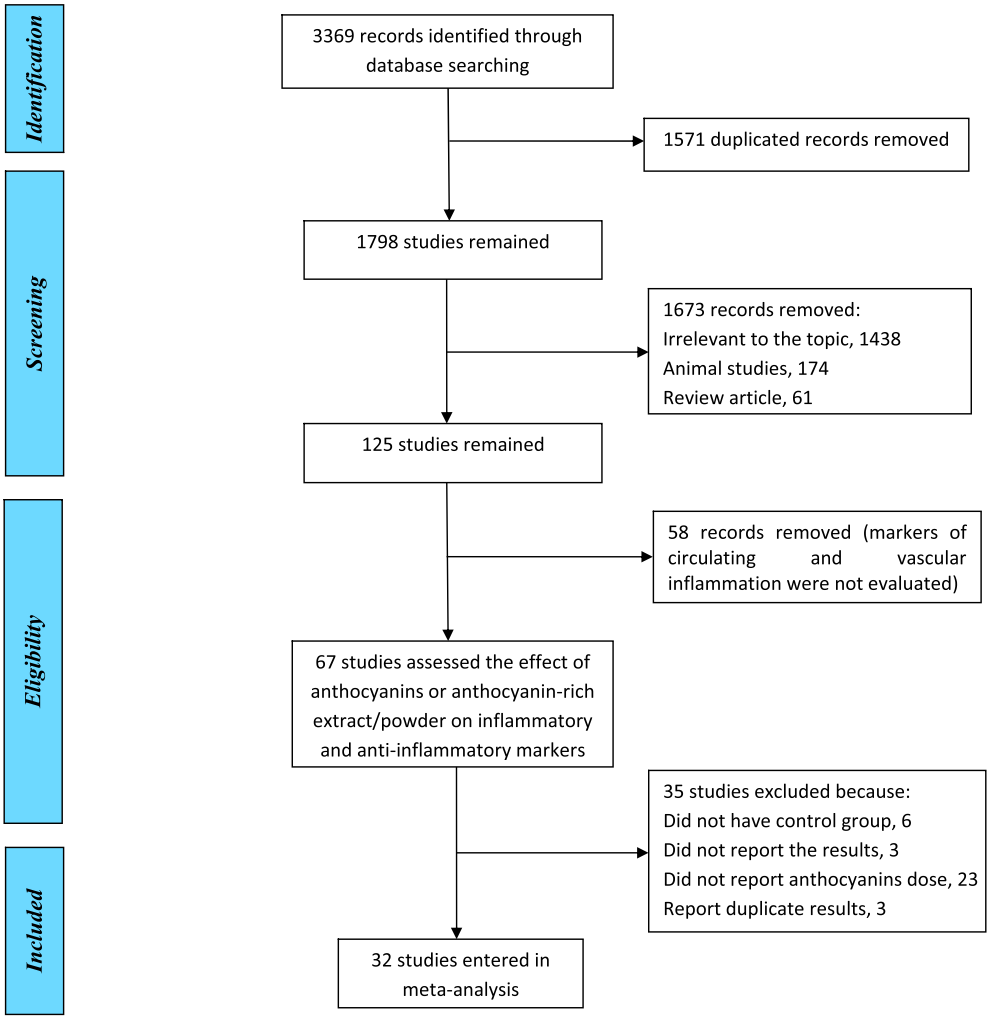


**Fig. 1.** PRISMA flow diagram of study identification, inclusion, and exclusion.

Thompson et al., 2017a; Xie et al., 2017; Yang et al., 2017; Espinosa-Moncada et al., 2018; Kim et al., 2018; Maeda-Yamamoto et al., 2018; Marín-Echeverri et al., 2018; Arevström et al., 2019; Chew et al., 2019; Schell et al., 2019) comparing an intervention group (received dietary pure anthocyanins or anthocyanins-rich extract/powder) with a control group entered meta-analysis (Fig. 1).

### 3.2. Study characteristics

The main characteristics of 32 RCTs, with 1744 subjects, carried out in Norway, Poland, United Kingdom, United States of America, Iran, Italy, Czech Republic, China, Korea, Japan, Colombia, Sweden, Australia, and Finland are outlined in Table 1. The dosage of anthocyanins was between 1.60 and 1323 mg/day; and the trial duration was between 3 and 24 weeks. The subjects were healthy in 6 RCTs (Karlsen et al., 2007; Curtis et al., 2009; Riso et al., 2013; Thompsonet al., 2017a; Maeda-Yamamoto et al., 2018; Chew et al., 2019), individuals with metabolic syndrome in 7 RCTs (Basu et al., 2010a, 2010b; Kolehmainen et al., 2012; Jeong et al., 2016; Espinosa-Moncada et al., 2018; Kim et al., 2018; Marín-Echeverri et al., 2018), individuals with diabetes mellitus type 2 in 4 RCTs (Moazen et al., 2013; Li et al., 2015; Yang et al., 2017; Schell et al., 2019), overweight/obese in 4 RCTs (Stull et al., 2010; Basu et al., 2014, 2018; Lee et al., 2016), pre-hypertensive in 3 RCTs (Hassellund et al., 2013; Loo et al., 2016; Johnson et al., 2017), hyperlipidemic in 2 RCTs (Soltani et al., 2014; Asgary et al., 2016), hypercholesterolemic in 2 RCTs (Zhu et al., 2011; Zhang et al., 2016), individuals with myocardial infarction in 2 RCTs (Naruszewicz et al., 2007; Arevström et al., 2019), former smokers in 1 RCT (Xie et al., 2017), and individuals with lower urinary tract symptoms in 1 RCT (Vidlar et al., 2010).

### 3.3. Quality assessment of RCTs and outcomes

The results of risk of bias assessment are presented in Table 2. Although all of the selected studies were randomized, the random sequence generation and allocation concealment were unclear in 10 (Karlsen et al., 2007; Naruszewicz et al., 2007; Curtis et al., 2009; Basu et al., 2010a, 2014, 2010b; Stull et al., 2010; Kolehmainen et al., 2012; Li et al., 2015; Zhang et al., 2016) and 15 (Karlsen et al., 2007; Naruszewicz et al., 2007; Basu et al., 2010a, 2014, 2010b; Vidlar et al., 2010; Zhu et al., 2011; Moazen et al., 2013; Li et al., 2015; Zhang et al., 2016; Johnson et al., 2017; Thompson et al., 2017a; Espinosa-Moncada et al., 2018; Arevström et al., 2019; Schell et al., 2019) studies, respectively. Moreover, 3 studies (Loo et al., 2016; Thompson et al., 2017a; Xie et al., 2017) for random sequence generation and 6 studies (Curtis et al., 2009; Basu et al., 2010b; Stull et al., 2010; Kolehmainen et al., 2012; Loo et al., 2016; Xie et al., 2017) for allocation concealment had high risk of bias. Seven RCTs (Karlsen et al., 2007; Basu et al., 2010a, 2010b; Kolehmainen et al., 2012; Loo et al., 2016; Thompson et al., 2017a; Xie et al., 2017) had high risk of bias based on blinding of participants and personnel, while only 1 RCT (Loo et al., 2016) had high risk of bias for blinding of outcome assessment. Incomplete

**Table 1**
Characteristics of randomized controlled trials (RCTs) included in the meta-analyses.

| Reference | Country | RCT design | No. of subjects | Health status | Intervention duration | Intervention group | Anthocyanins dose (mg/day) | Control group | Outcomes studied |
|---|---|---|---|---|---|---|---|---|---|
| Karlsen et al. (2007) | Norway | Parallel | 118 | Healthy | 3 weeks | Capsule of purified anthocyanins from bilberry and black currant | 300 | Placebo capsule (maltodextrin + blue color) | CRP, IL-6, TNF-α, IL-1β |
| Naruszewicz et al. (2007) | Poland | Parallel | 44 | Post myocardial infarction | 6 weeks | Chokeberry extract capsule | 63.75 | Placebo capsule (maltodextrin) | CRP, IL-6, adiponectin, ICM-1, VCAM-1 |
| Curtis et al. (2009) | UK | Parallel | 52 | Healthy | 12 weeks | Elderberry extract capsule | 500 | Placebo capsule | CRP, IL-6, TNF-α |
| Basu et al. (2010a) | USA | Parallel | 48 | Metabolic syndrome | 8 weeks | Freeze-dried blueberry powder reconstituted in water | 742 | Water | CRP, IL-6, adiponectin, ICM-1, VCAM-1 |
| Basu et al. (2010b) | USA | Parallel | 27 | Metabolic syndrome | 8 weeks | Freeze-dried strawberry powder reconstituted in water | 154 | Water | ICAM-1, VCAM-1 |
| Stull et al. (2010) | USA | Parallel | 32 | Obese and insulin resistant | 6 weeks | Smoothie contained freeze-dried blueberry powder | 668 | Smoothie without freeze-dried blueberry powder | CRP, TNF-α |
| Vidlar et al. (2010) | Czech Republic | Parallel | 42 | Lower urinary tract syndrome | 6 months | Capsule of cranberry fruit powder + dietary instruction | 1.65 | Received dietary instruction | CRP |
| Zhu et al. (2011) | China | Parallel | 146 | Hypercholesterolemic | 12 weeks | Capsule of purified anthocyanins from bilberry and black currant | 320 | Placebo capsule | VCAM-1 |
| Kolehmainen et al. (2012) | Finland | Parallel | 24 | Metabolic syndrome | 8 weeks | Dried bilberries powder + bilberry purée | 1323 | Habitual diet | CRP, IL-6, adiponectin |
| Hassellund et al. (2013) | Norway | Cross-over | 27 | Prehypertensive | 4 weeks | Capsule of purified anthocyanins from bilberry and black currant | 640 | Placebo capsule (maltodextrin + blue color) | CRP, IL-6, TNF-α, ICM-1, VCAM-1, P-selectin |
| Moazen et al. (2013) | Iran | Parallel | 36 | Diabetic | 6 weeks | Freeze-dried strawberry powder reconstituted in water | 154 | Placebo powder (lactose + pectin + strawberry flavor) reconstituted in water | CRP |
| Riso et al. (2013) | Italy | Cross-over | 18 | Healthy | 6 weeks | Freeze-dried blueberry powder reconstituted in water | 375 | Placebo powder (fructose + glucose + citric acid + blueberry flavor) reconstituted in water | CRP, IL-6, TNF-α, VCAM-1 |
| Basu et al. (2014) | USA | Parallel | 60 | Abdominal adiposity and elevated serum lipids | 12 weeks | Freeze-dried strawberry powder reconstituted in water | 78, 155 | fiber and cane sugar powder reconstituted in water | CRP, ICM-1, VCAM-1 |
| Soltani et al. (2014) | Iran | Parallel | 50 | Hyperlipidemic | 4 weeks | Caucasian whortleberry extract capsule | 90 | Placebo capsule (tribasic calcium phosphate) | CRP |
| Li et al. (2015) | China | Parallel | 58 | Diabetic | 24 weeks | Capsule of purified anthocyanins from bilberry and black currant | 320 | Placebo capsule (pullulan + maltodextrin) | IL-6, TNF-α, adiponectin |
| Asgary et al. (2016) | Iran | Parallel | 40 | Hyperlipidemic | 4 weeks | Caucasian whortleberry extract capsule | 1.60 | Placebo capsule (tribasic calcium phosphate) | IL-6, TNF-α, ICM-1, VCAM-1 |
| Jeong et al. (2016) | Korea | Parallel | 51 | Metabolic syndrome | 12 weeks | Black raspberry extract capsule | 100 | Placebo capsule (isomaltose + magnesium stearate + silica) | CRP, IL-6, TNF-α, adiponectin, ICM-1, VCAM-1 |
| Lee et al. (2016) | Korea | Parallel | 63 | Overweight/obese | 8 weeks | Black soybean testa extract capsule | 32 | Placebo capsule (starch + natural dark purple pigment) | IL-6, TNF-α |
| Loo et al. (2016) | Finland | Cross-over | 37 | Mildly hypertensive | 8 weeks | Dried chokeberry powder mixed with chokeberry juice | 1024 | Placebo powder (wheat flour + rice powder + cane sugar) mixed with placebo juice (Sugar syrup + water) | CRP, IL-6, TNF-α |
| Zhang et al. (2016) | China | Parallel | 146 | Hypercholesterolemic | 24 weeks | Capsule of purified anthocyanins from bilberry and black currant | 320 | Placebo capsule | CRP, TNF-α, IL-1β, P-selectin |

(*continued on next page*)

**Table 1** (*continued*)

| Reference | Country | RCT design | No. of subjects | Health status | Intervention duration | Intervention group | Anthocyanins dose (mg/day) | Control group | Outcomes studied |
|---|---|---|---|---|---|---|---|---|---|
| Johnson et al. (2017) | USA | Parallel | 40 | Stage 1- and pre-hypertensive | 8 weeks | freeze-dried highbush blueberry powder | 469 | Placebo powder (maltodextrin + fructose + citric acid + silica + purple and red color) | CRP, TNF-α |
| Thompson et al. (2017a) | Australia | Cross-over | 16 | Healthy | 4 weeks | Capsule of purified anthocyanins from Norwegian bilberries | 320 | Placebo capsule (maltodextrin + blue color) | CRP |
| Xie et al. (2017) | USA | Parallel | 49 | Former smokers without inflammation and oxidative stress | 12 weeks | Aronia berry extract capsule | 45.1 | Placebo capsule (rice powder + beet juice concentrate) | CRP, IL-6, TNF-α, adiponectin, IL-1β, ICM-1, VCAM-1, P-selectin |
| Yang et al. (2017) | China | Parallel | 160 | Prediabetes or early untreated diabetes | 12 weeks | Capsule of purified anthocyanins from bilberry and black currant | 320 | Placebo capsule (Pullulan + maltodextrin) | CRP |
| Basu et al. (2018) | USA | Cross-over | 17 | Obese with knee osteoarthritis | 12 weeks | Freeze-dried strawberry powder reconstituted in water | 154 | Placebo powder reconstituted in water | TNF-α |
| Espinosa-Moncada et al. (2018) | Colombia | Cross-over | 40 | Metabolic syndrome | 4 weeks | Freeze-dried *Vaccinium meridionale* powder reconstituted in water | 75.7 | Placebo powder reconstituted in water | CRP, adiponectin |
| Kim et al. (2018) | Korea | Parallel | 37 | Metabolic syndrome | 12 weeks | Solids of açaí pulp berries consumed as beverage | 199.6 | Placebo beverage (artificial color + water + sugar + citric acid + artificial flavor) | CRP, IL-6, TNF-α |
| Maeda-Yamamoto et al. (2018) | Japan | Parallel | 76 | Healthy | 12 weeks | Powder of Sunrouge tea extract reconstituted in water | 11.2 | Placebo powder (barley tea extract reconstituted in water) | Adiponectin |
| Marín-Echeverri et al. (2018) | Colombia | Cross-over | 40 | Metabolic syndrome | 4 weeks | Freeze-dried *Vaccinium meridionale* powder reconstituted in water | 75.7 | Placebo powder reconstituted in water | IL-6, TNF-α, IL-1β |
| Arevström et al. (2019) | Sweden | Parallel | 50 | Post myocardial infarction | 8 weeks | Freeze-dried bilberry powder reconstituted in water | 900 | No dietary intervention | CRP |
| Chew et al. (2019) | USA | Parallel | 78 | Healthy overweight | 8 weeks | Cranberry extract consumed as low-calorie beverage | 6.22 | Low-calorie placebo beverage | CRP, IL-6, TNF-α |
| Schell et al. (2019) | USA | Cross-over | 22 | Diabetic | 4 weeks | Frozen red raspberries blended with water to form a puree | 225 | Ripe banana blended with water to form a puree | CRP, IL-6, TNF-α, IL-1β, |

*Abbreviations:* CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular adhesion molecule-1.

**Table 2**
Risk of bias assessment of included randomized controlled trials according to the Cochrane guidelines.

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other sources of bias[a] | Overall quality[b] |
|---|---|---|---|---|---|---|---|---|
| Karlsen et al. (2007) | U | U | H | U | L | L | L | Fair |
| Naruszewicz et al. (2007) | U | U | L | L | L | L | L | Good |
| Curtis et al. (2009) | U | H | L | L | H | L | U | Fair |
| Basu et al. (2010a) | U | U | H | U | L | L | U | Low |
| Basu et al. (2010b) | U | H | H | U | U | L | U | Low |
| Stull et al. (2010) | U | H | L | L | U | H | L | Low |
| Vidlar et al. (2010) | L | U | U | L | L | L | L | Good |
| Zhu et al. (2011) | L | U | L | L | L | L | L | Good |
| Kolehmainen et al. (2012) | U | H | H | U | L | L | U | Low |
| Hassellund et al. (2013) | L | L | L | L | L | L | U | Good |
| Moazen et al. (2013) | L | U | L | L | L | L | L | Good |
| Riso et al. (2013) | L | L | U | U | L | L | L | Good |
| Basu et al. (2014) | U | U | L | L | L | L | U | Good |
| Soltani et al. (2014) | L | L | L | L | L | L | L | Good |
| Li et al. (2015) | U | U | L | L | L | L | L | Good |
| Asgary et al. (2016) | L | L | L | L | L | L | L | Good |
| Jeong et al. (2016) | L | L | L | L | U | L | L | Good |
| Lee et al. (2016) | L | L | L | L | L | L | U | Good |
| Loo et al. (2016) | H | H | H | H | L | L | U | Low |
| Zhang et al. (2016) | U | U | L | L | L | L | L | Good |
| Johnson et al. (2017) | L | U | L | L | L | L | L | Good |
| Thompson et al. (2017a) | H | U | H | L | U | H | U | Low |
| Xie et al. (2017) | H | H | H | U | L | L | U | Low |
| Yang et al. (2017) | L | L | L | L | L | L | L | Good |
| Basu et al. (2018) | L | L | L | L | L | L | L | Good |
| Espinosa-Moncada et al. (2018) | L | U | L | L | L | L | L | Good |
| Kim et al. (2018) | L | L | L | L | L | L | U | Good |
| Maeda-Yamamoto et al. (2018) | L | L | L | L | L | L | L | Good |
| Marín-Echeverri et al. (2018) | L | U | L | L | L | L | L | Good |
| Arevström et al. (2019) | L | U | U | L | L | L | L | Good |
| Chew et al. (2019) | L | L | L | L | L | U | L | Good |
| Schell et al. (2019) | L | U | L | L | L | L | U | Good |

*Abbreviations:* L, low risk of bias; H, high risk of bias; U, unclear risk of bias.
[a] Bias of study design, trial stopped early, extreme baseline imbalance, and fraudulent trial.
[b] "Good" if at least 4 domains were low risk of bias, "Fair" if 3 domains were low risk of bias, "Low" if less than 3 domains were low risk of bias.

outcome data and selective outcome reporting were sources of bias in 1 (Curtis et al., 2009) and 2 (Stull et al., 2010; Thompson et al., 2017a) RCTs, respectively. None of the RCTs was high risk for other sources of bias such as bias of study design, trial stopped early, extreme baseline imbalance, and fraudulent trial. From 32 RCTs selected for meta-analysis, 23 RCTs (Naruszewicz et al., 2007; Vidlar et al., 2010; Zhu et al., 2011; Hassellund et al., 2013; Moazen et al., 2013; Riso et al., 2013; Basu et al., 2014, 2018; Soltani et al., 2014; Li et al., 2015; Asgary et al., 2016; Jeong et al., 2016; Lee et al., 2016; Zhang et al., 2016; Johnson et al., 2017; Yang et al., 2017; Espinosa-Moncada et al., 2018; Kim et al., 2018; Maeda-Yamamoto et al., 2018; Marín-Echeverri et al., 2018; Arevström et al., 2019; Chew et al., 2019; Schell et al., 2019) were categorized as "Good", 2 RCTs (Karlsen et al., 2007; Curtis et al., 2009) as "Fair", and 7 RCTs (Basu et al., 2010a, 2010b; Stull et al., 2010; Kolehmainen et al., 2012; Loo et al., 2016; Thompson et al., 2017a; Xie et al., 2017) as "Low". The RCTs classified as "Good" had no domain with high risk of bias, while "Fair" and "Low" classified RCTs had at least one domain with high risk of bias (Table 2).

The quality of meta-analysis for CRP, IL-6, TNF-α, adiponectin, and VCAM-1 was high (Table 3), which implies that further research likely will not change the confidence in the effect estimates. Meta-analysis quality was low for IL-1β, ICAM-1, and P-selectin (Table 3), which implies that further research will provide important evidence and probably change the effect estimates.

### 3.4. Effect of anthocyanins on CRP

There were 25 RCTs, with 1341 participants, in which the effect of dietary anthocyanins on serum CRP level was evaluated. The pooled estimate revealed that dietary anthocyanins significantly decreased serum CRP level (Fig. 2: −0.33 mg/l, 95% CI: −0.55 to −0.11, $P = 0.003$). Considering $I^2$ index (0.0%) and Cochrane Q test ($P = 0.912$), a very low inter-trial heterogeneity was detected.

### 3.5. Effect of anthocyanins on IL-6

The effect of dietary anthocyanins on serum level of IL-6 was assessed in 17 RCTs with 870 subjects. The pooled estimate demonstrated a significant decrease in serum IL-6 level following anthocyanins administration (Fig. 3: −0.41 ρg/ml, 95% CI: −0.70 to −0.13, $P = 0.004$). The $I^2$ index (10.4%) and Cochrane Q test ($P = 0.333$) revealed a low inter-trial heterogeneity.

### 3.6. Effect of anthocyanins on TNF-α

Eighteen RCTs with 925 participants had data about the impact of dietary anthocyanins on serum TNF-α level. The overall estimate showed that intake of anthocyanins significantly reduced serum TNF-α level (Fig. 4: −0.64 ρg/ml, 95% CI: −1.18 to −0.09, $P = 0.023$). The

**Table 3**
Summary of findings with the NutriGrade scoring system.

| Outcome | Effect size (95% CI) | No. of participants (studies) | Score | Outcome quality |
|---|---|---|---|---|
| CRP | −0.33 mg/l (−0.55 to −0.11) | 1341 (25 RCTs) | 8.5 | High |
| IL-6 | −0.41 ρg/ml (−0.70 to −0.13) | 870 (17 RCTs) | 8.25 | High |
| TNF-α | −0.64 ρg/ml (−1.18 to −0.09) | 925 (18 RCTs) | 8.25 | High |
| IL-1β | −0.45 ρg/ml (−3.77 to 2.88) | 375 (5 RCTs) | 5.75 | Low |
| Adiponectin | 0.75 μg/ml (0.23–1.26) | 390 (8 RCTs) | 8 | High |
| ICAM-1 | −52.4 ng/ml (−85.7 to −19.1) | 346 (9 RCTs) | 5.75 | Low |
| VCAM-1 | −49.6 ng/ml (−72.7 to −26.5) | 510 (11 RCTs) | 8 | High |
| P-selectin | −6.98 ng/ml (−18.1 to 4.15) | 222 (3 RCTs) | 5.5 | Low |

*Abbreviations:* CI, confidence interval; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; IL-6, interleukin-6; RCTs, randomized controlled trials; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular adhesion molecule-1.

$I^2$ index (20.4%) and Cochrane Q test ($P = 0.211$) indicated a low inter-trial heterogeneity.

### 3.7. Effect of anthocyanins on adiponectin

There were 8 RCTs, with 390 participants, in which the effect of dietary anthocyanins on serum adiponectin level was assessed. The pooled estimate revealed a significant increase in serum adiponectin level following administration of anthocyanins (Fig. 5: 0.75 μg/ml, 95% CI: 0.23 to 1.26, $P = 0.004$). Considering $I^2$ index (0.0%) and Cochrane Q test ($P = 0.631$), a very low inter-trial heterogeneity was detected.

### 3.8. Effect of anthocyanins on IL-1β

The effect of dietary anthocyanins on serum IL-1β level was assessed in 5 RCTs with 375 subjects. The overall estimate demonstrated no significant change in serum IL-1β level following intake of anthocyanins (Supplementary Data, Appendix B, Fig. S1: −0.45 ρg/ml, 95% CI: −3.77 to 2.88, $P = 0.793$). Based on $I^2$ index (0.0%) and Cochrane Q test ($P = 0.969$), a very low inter-trial heterogeneity was found.

### 3.9. Effect of anthocyanins on ICAM-1

There were 9 RCTs, with 346 participants, in which the effect of dietary anthocyanins on serum ICAM-1 level was assessed. The pooled estimate revealed a significant decrease in serum ICAM-1 level following administration of anthocyanins (Fig. 6: −52.4 ng/ml, 95% CI: −85.7 to −19.1, $P = 0.002$). Considering $I^2$ index (27.3%) and Cochrane Q test ($P = 0.201$), a moderate inter-trial heterogeneity was detected.

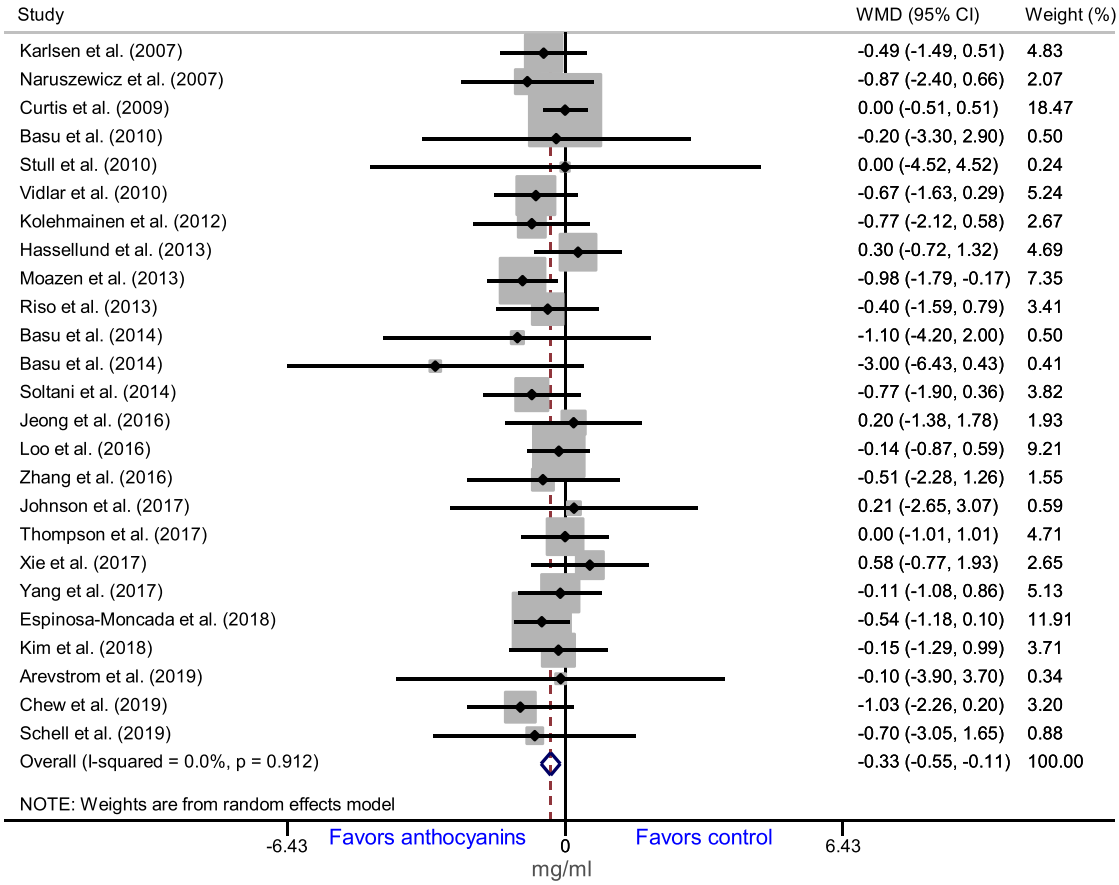


**Fig. 2.** Forest plot of the effect of dietary anthocyanins on C-reactive protein.

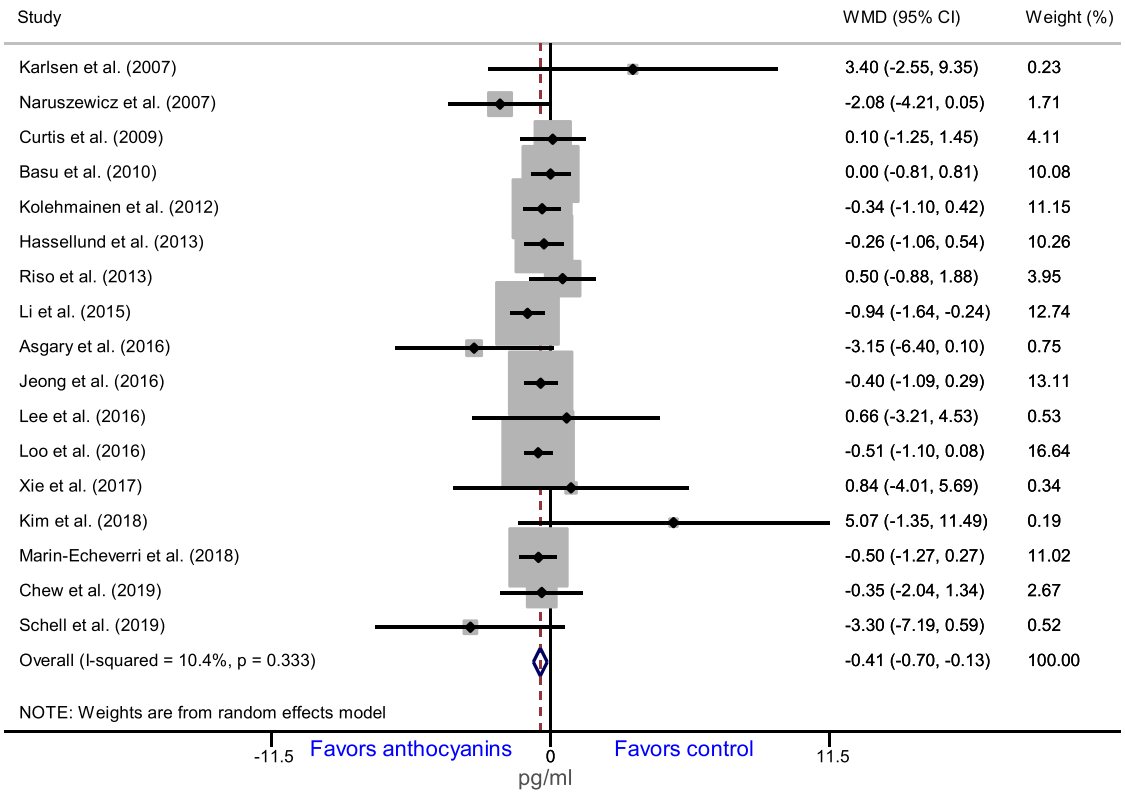


**Fig. 3.** Forest plot of the effect of dietary anthocyanins on interleukin-6.

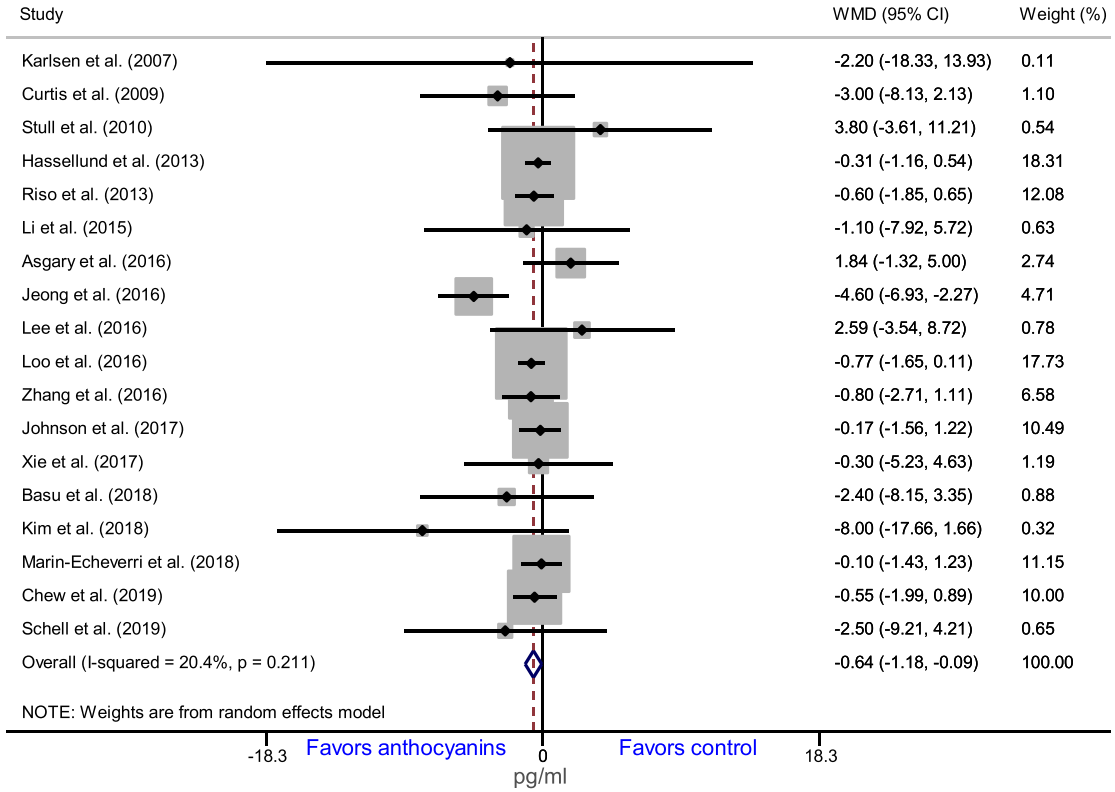


**Fig. 4.** Forest plot of the effect of dietary anthocyanins on tumor necrosis factor-alpha.

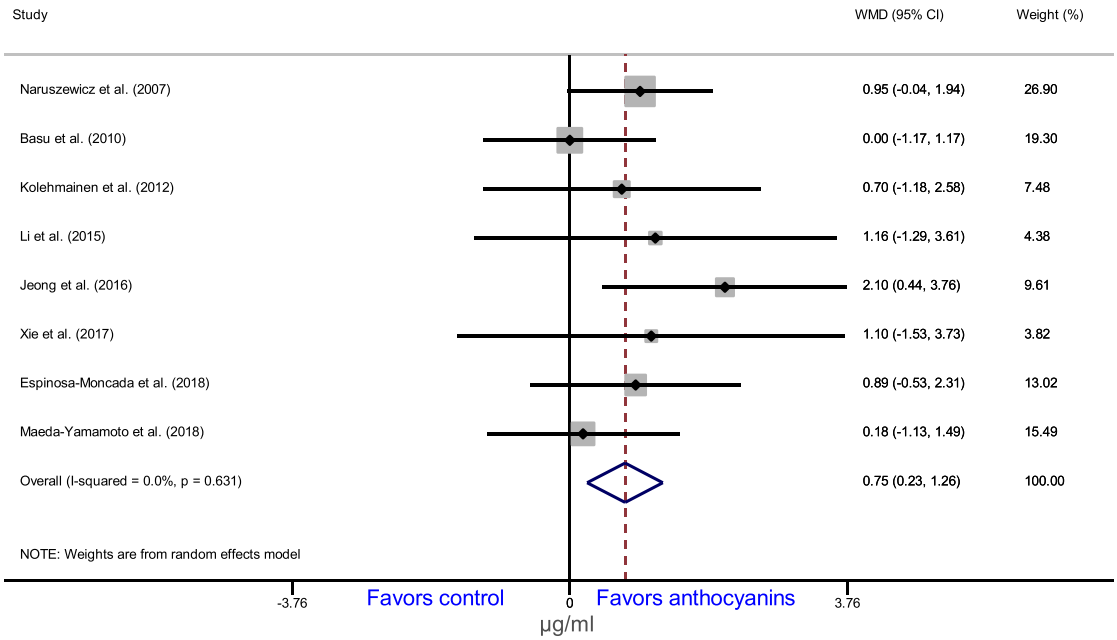


**Fig. 5.** Forest plot of the effect of dietary anthocyanins on adiponectin.

### 3.10. Effect of anthocyanins on VCAM-1

The effect of dietary anthocyanins on serum level of VCAM-1 was assessed in 11 RCTs with 510 subjects. The pooled estimate demonstrated a significant decrease in serum VCAM-1 level following anthocyanins administration (Fig. 7: −49.6 ng/ml, 95% CI: −72.7 to −26.5, $P < 0.001$). The $I^2$ index (0.0%) and Cochrane Q test ($P = 0.630$) revealed a very low inter-trial heterogeneity.

### 3.11. Effect of anthocyanins on P-selectin

The effect of dietary anthocyanins on serum P-selectin level was assessed in 3 RCTs with 222 subjects. The overall estimate demonstrated no significant change in serum P-selectin level following intake of anthocyanins (Supplementary Data, Appendix B, Fig. S2: −6.98 ng/ml, 95% CI: −18.1 to 4.15, $P = 0.219$). Based on $I^2$ index (0.0%) and Cochrane Q test ($P = 0.755$), a very low inter-trial heterogeneity was found.

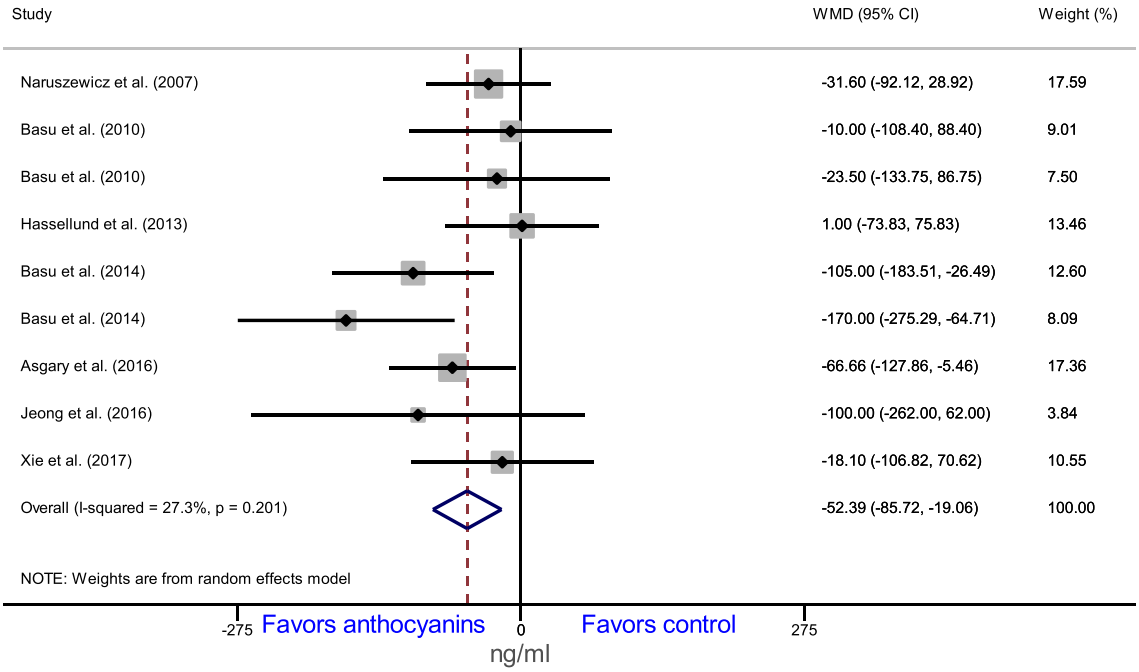


**Fig. 6.** Forest plot of the effect of dietary anthocyanins on intercellular adhesion molecule-1.

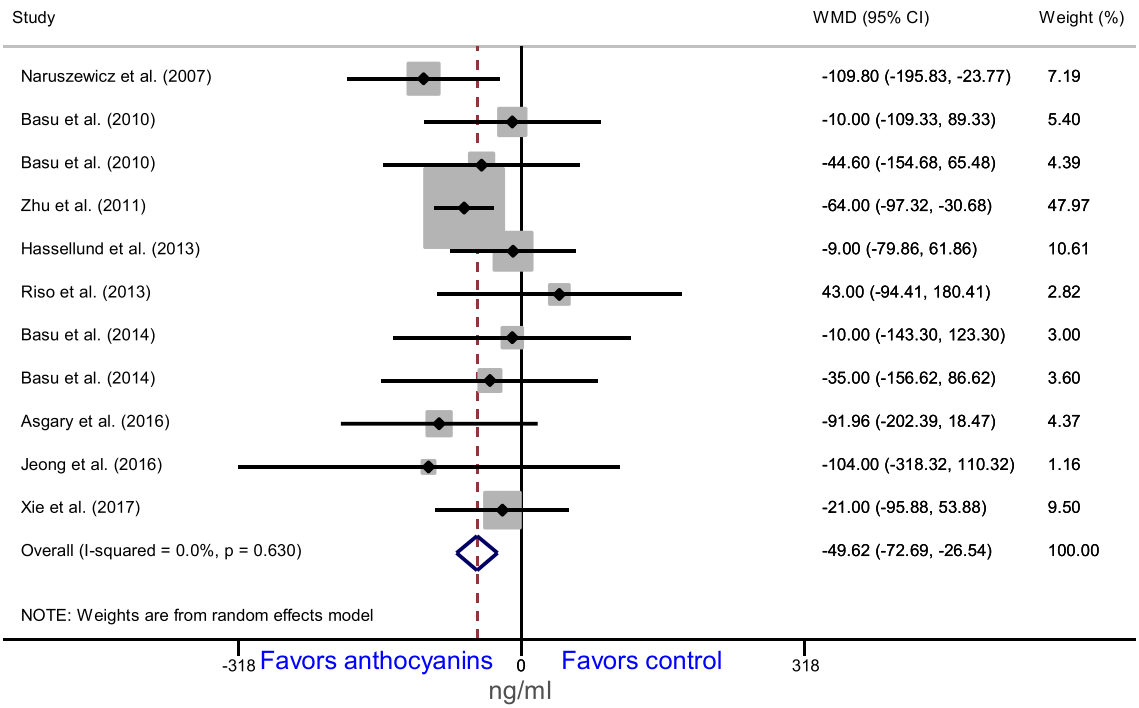


**Fig. 7.** Forest plot of the effect of dietary anthocyanins on vascular adhesion molecule-1.

### *3.12. Meta-regression, subgroup and sensitivity analyses*

Considering the fact that intervention duration, anthocyanins dose, baseline levels of studied markers, and health status of subjects might influence the net changes of the markers, we performed meta-regression and subgroup analyses based on these probable confounders. Meta-regression analysis revealed inverse association between the effect sizes of CRP ($P$ for interaction = 0.041), IL-6 ($P$ for interaction = 0.036), TNF-α ($P$ for interaction = 0.038), and VCAM-1 ($P$ for interaction = 0.035) and anthocyanins doses. No relation was found for other probable confounders. Subgroup analyses revealed that intake of higher doses of anthocyanins (> 300 mg/day) significantly decreased levels of CRP, IL-6, TNF-α, and VCAM-1 (Table 4).

Sensitivity analyses showed that the elimination of each RCT at one time or the simultaneous elimination of fair and low quality RCTs (studies with high risk of bias) did not significantly change the overall estimates of CRP, IL-6, TNF-α, adiponectin, IL-1β, ICAM-1, VCAM-1, and P-selectin (data not shown).

### *3.13. Publication bias*

Based on results of Begg and Mazumdar adjusted rank correlation test, no sign of publication bias was detected for CRP ($P$ = 0.815), IL-6 ($P$ = 0.099), TNF-α ($P$ = 0.472), adiponectin ($P$ = 0.458), IL-1β ($P$ = 0.327), ICAM-1 ($P$ = 0.404), VCAM-1 ($P$ = 0.697), and P-selectin ($P$ = 0.117). Moreover, results of Egger's regression asymmetry test revealed no publication bias for CRP ($P$ = 0.316), IL-6 ($P$ = 0.607), TNF-α ($P$ = 0.489), adiponectin ($P$ = 0.415), IL-1β ($P$ = 0.263), ICAM-1 ($P$ = 0.564), VCAM-1 ($P$ = 0.360), and P-selectin ($P$ = 0.187).

## 4. Discussion

Chronic non-communicable diseases like cardiovascular events, obesity, diabetes, and other metabolic diseases are introduced as current phenomena of 21st century. In such diseases, a systemic and vascular low-grade inflammation and increased activity of inflammatory mediators are recognized as background. Considering the promotion in controlling the infectious diseases, people have chance for living longer. Along with increased longevity, the production and activity of pro-inflammatory markers and free radicals increase. The anti-inflammatory and antioxidative capacity of body decreases with aging, hence taking anti-inflammatory or antioxidant supplements seems necessary.

CRP, an acute phase reactive protein, is produced by hepatocytes as a result of stimulation of IL-6 that is secreted by macrophages and T-cells. Recent evidences suggest that higher levels of CRP were associated with increased risk of cardiovascular diseases, diabetes, and other metabolic disorders (Windgassen et al., 2011). TNF-α, as a cytokine, is produced by monocytes and adipose tissue, and induces the inflammatory processes via the regulation of inflammatory cytokines especially IL-6 (Liu et al., 2006). IL-1β is also recognized as a pro-inflammatory cytokine released in response to the infection or tissue injuries (Lopez-Castejon and Brough, 2011). Adhesion molecules including ICAM-1, VCAM-1, and P-selectin are mainly expressed on surface of leukocytes and endothelial cells and mediate cell-matrix or cell-cell interactions. These molecules have been considered as vascular inflammatory markers because their levels are increased in patients with systematic vascular inflammation and cardiovascular diseases (Demerath et al., 2001; Savoia and Schiffrin, 2007).

Chronic low-grade inflammation can induce the infiltration of immune cells into the adipose tissue and increase the production of inflammatory mediators. The elevated levels of inflammatory markers in the blood circulation may disrupt the normal metabolic functions of cells and result in accumulation of harmful agents like free-radicals and reactive oxygen species (ROS). Therefore, a cyclic process of inflammation and oxidative stress is produced, which promote the risk of cardiovascular and metabolic disorders like diabetes (Rani et al., 2016). The nuclear factor κB (NF-κB) pathways are activated by ROS and

**Table 4**
Results of the effect of dietary anthocyanins on circulating and vascular inflammation based on meta-regression and subgroup analyses.

| Outcome | Variable | No. of trials | Effect size (95% CI) | $I^2$ (%) | Q-statistics (*P*) | *P* for interaction[a] |
|---|---|---|---|---|---|---|
| **CRP** | *Intervention duration* | | | | | 0.128 |
| | ≤ 8 weeks | 16 | −0.13 mg/l (−0.48, 0.22) | 0.0 | 0.655 | |
| | > 8 weeks | 9 | −0.46 mg/l (−0.75, −0.18) | 0.0 | 0.949 | |
| | *Anthocyanins dosage* | | | | | 0.041 |
| | ≤ 300 mg/day | 13 | −0.09 mg/l (−0.40, 0.22) | 0.0 | 0.997 | |
| | > 300 mg/day | 12 | −0.59 mg/l (−0.91, −0.27) | 0.0 | 0.777 | |
| | *Baseline CRP* | | | | | 0.135 |
| | ≤ 3 mg/l | 14 | −0.14 mg/l (−0.41, 0.13) | 0.0 | 0.947 | |
| | > 3 mg/l | 11 | −0.73 mg/l (−1.12, −0.35) | 0.0 | 0.975 | |
| | *Health status* | | | | | 0.234 |
| | Healthy individuals | 5 | −0.17 mg/l (−0.56, 0.22) | 0.5 | 0.404 | |
| | Individuals with impaired health | 20 | −0.41 mg/l (−0.68, −0.14) | 0.0 | 0.947 | |
| **IL-6** | *Intervention duration* | | | | | 0.213 |
| | ≤ 8 weeks | 11 | −0.35 ρg/ml (−0.75, 0.05) | 15.8 | 0.293 | |
| | > 8 weeks | 6 | −0.51 ρg/ml (−0.94, −0.08) | 9.5 | 0.355 | |
| | *Anthocyanins dosage* | | | | | 0.036 |
| | ≤ 300 mg/day | 10 | −0.60 ρg/ml (−1.29, 0.09) | 24.5 | 0.218 | |
| | > 300 mg/day | 7 | −0.38 ρg/ml (−0.68, −0.07) | 0.0 | 0.466 | |
| | *Baseline IL-6* | | | | | 0.099 |
| | ≤ 2 pg/ml | 4 | −0.21 ρg/ml (−0.63, 0.21) | 0.0 | 0.857 | |
| | > 2 pg/ml | 13 | −0.54 ρg/ml (−0.96, −0.11) | 22.5 | 0.216 | |
| | *Health status* | | | | | 0.415 |
| | Healthy individuals | 5 | 0.22 ρg/ml (−0.60, 1.04) | 0.0 | 0.775 | |
| | Individuals with impaired health | 12 | −0.50 ρg/ml (−0.81, −0.18) | 18.1 | 0.266 | |
| **TNF-α** | *Intervention duration* | | | | | 0.188 |
| | ≤ 8 weeks | 10 | −0.42 ρg/ml (−0.90, 0.05) | 0.0 | 0.793 | |
| | > 8 weeks | 8 | −1.81 ρg/ml (−3.46, −0.16) | 48.5 | 0.059 | |
| | *Anthocyanins dosage* | | | | | 0.038 |
| | ≤ 300 mg/day | 10 | −1.02 pg/ml (−2.65, 0.51) | 49.8 | 0.036 | |
| | > 300 mg/day | 8 | −0.52 pg/ml (−1.01, −0.03) | 0.0 | 0.875 | |
| | *Baseline TNF-α* | | | | | 0.487 |
| | ≤ 8 pg/ml | 9 | −0.45 ρg/ml (−0.92, 0.02) | 0.0 | 0.924 | |
| | > 8 pg/ml | 9 | −1.27 pg/ml (−2.97, 0.44) | 51.5 | 0.036 | |
| | *Health status* | | | | | 0.512 |
| | Healthy individuals | 5 | −0.65 ρg/ml (−1.56, 0.26) | 0.0 | 0.927 | |
| | Individuals with impaired health | 13 | −0.67 ρg/ml (−1.46, 0.12) | 41.3 | 0.059 | |
| **Adiponectin** | *Intervention duration* | | | | | 0.313 |
| | ≤ 8 weeks | 4 | 0.64 μg/ml (−0.01, 1.26) | 0.0 | 0.648 | |
| | > 8 weeks | 4 | 0.99 μg/ml (0.05, 1.93) | 7.0 | 0.358 | |
| | *Anthocyanins dosage* | | | | | 0.088 |
| | ≤ 300 mg/day | 5 | 0.93 μg/ml (0.32, 1.55) | 0.0 | 0.524 | |
| | > 300 mg/day | 3 | 0.33 μg/ml (−0.59, 1.25) | 0.0 | 0.639 | |
| | *Baseline adiponectin* | | | | | 0.246 |
| | ≤ 5 μg/ml | 4 | 0.96 μg/ml (0.24, 1.68) | 6.7 | 0.360 | |
| | > 5 μg/ml | 4 | 0.48 μg/ml (−0.36, 1.26) | 0.0 | 0.745 | |
| | *Health status* | | | | | 0.503 |
| | Healthy individuals | 2 | 0.36 μg/ml (−0.81, 1.53) | 0.0 | 0.539 | |
| | Individuals with impaired health | 6 | 0.84 μg/ml (0.27, 1.41) | 0 | 0.501 | |
| **ICAM-1** | *Intervention duration* | | | | | 0.142 |
| | ≤ 8 weeks | 5 | −32.3 ng/ml (−65.6, 0.95) | 0.0 | 0.700 | |
| | > 8 weeks | 4 | −94.4 ng/ml (−159.4, −29.4) | 38.6 | 0.180 | |
| | *Anthocyanins dosage* | | | | | 0.093 |
| | ≤ 300 mg/day | 7 | −3.03 ng/ml (−62.6, 56.5) | 22.9 | 0.254 | |
| | > 300 mg/day | 2 | −66.2 ng/ml (−102.9, −29.6) | 0.0 | 0.862 | |
| | *Health status* | | | | | 0.327 |
| | Healthy individuals | 1 | −18.1 ng/ml (−106.8, 70.6) | – | – | |
| | Individuals with impaired health | 8 | −56.8 ng/ml (−93.6, 20.0) | 32.8 | 0.166 | |
| **VCAM-1** | *Intervention duration* | | | | | 0.364 |
| | ≤ 8 weeks | 6 | −40.9 ng/ml (−83.9, 2.10) | 14.8 | 0.319 | |
| | > 8 weeks | 5 | −54.4 ng/ml (−82.9, −25.8) | 0.0 | 0.770 | |
| | *Anthocyanins dosage* | | | | | 0.035 |
| | ≤ 300 mg/day | 7 | −33.7 ng/ml (−75.9, 8.47) | 0.0 | 0.737 | |
| | > 300 mg/day | 4 | −56.1 ng/ml (−96.2, −16.1) | 30.0 | 0.232 | |
| | *Health status* | | | | | 0.621 |
| | Healthy individuals | 2 | −6.35 ng/ml (−72.1, 59.4) | 0.0 | 0.423 | |
| | Individuals with impaired health | 9 | −55.7 ng/ml (−80.3, −31.1) | 0.0 | 0.709 | |

*Abbreviations:* CI, confidence interval; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular adhesion molecule-1.

[a] *P* value obtained from meta-regression analysis.

support the inflammation by increasing the gene expression of inflammatory markers. Anthocyanins (as potent antioxidants) trap ROS, hence the activation of NF-κB pathways is blocked and the gene expression of inflammatory markers is inhibited (Chen et al., 2006; Dembinska-Kiec et al., 2008; Rani et al., 2016).

Previous studies have demonstrated the anti-inflammatory effects of anthocyanins in animal models and cell cultures following induction of inflammation (Atalay et al., 2003; Herath et al., 2003; Cimino et al., 2006; Gasparrini et al., 2017, 2018; Joo et al., 2018; Sun et al., 2018). However, the results of anthocyanins administration in human clinical trials are controversial. Our meta-analysis revealed for the first time that dietary anthocyanins reduced the serum levels of CRP, IL-6, TNF-α, ICAM-1, and VCAM-1 but not IL-1β and P-selectin in the subjects. Takikawa et al. (2010) reported the amelioration in insulin sensitivity and hyperglycemia in diabetic mice after administration of anthocyanins. They found that anthocyanins reduced gene expression of retinol binding protein 4 (RBP4) and activated the AMP-activated protein kinase (AMPK). Serum level of RBP4 increased in inflammatory conditions and is known to be associated with obesity and insulin resistance. AMPK, the most regulatory component of energy balance in the cells, increased the gene expression of glucose transporter 4 (Glut4) in the cell membrane; therefore, enhanced the glucose uptake and ameliorated the hyperglycemia.

Adiponectin is known as an anti-inflammatory marker derived from adipose tissue. Adiponectin has some insulin-sensitizing characteristics and decreased in the serum of insulin resistant, diabetic, and obese subjects. Chronic inflammation and oxidative stress reduced the production of adiponectin from adipocytes (Lu et al., 2008). Results of our meta-analysis showed that dietary anthocyanins increased the serum level of adiponectin in the participants. It has been demonstrated that anthocyanins induced adiponectin gene expression and secretion in adipocytes via regulation of transcriptional factor forkhead box O1 and nuclear receptor PPAR-γ (Liu et al., 2014).

Results of this study indicate that higher doses of dietary anthocyanins (> 300 mg/day) can affect serum levels of CRP, IL-6, TNF-α, and VCAM-1 in the participants. The dose-dependent effects of dietary anthocyanins on inflammatory markers are still unknown in human clinical trials. In contrast, the anthocyanins effects on inflammatory markers in a dose-dependent manner are proved in some *in vitro* and animal model studies (Lau et al., 2007; Ahmet et al., 2009; Liu et al., 2014).

It has been demonstrated that anthocyanins or anthocyanins-rich foodstuffs are safe and well tolerated in humans (Corcoran et al., 2012). Side effects of dietary anthocyanins are uncommon; however, 5 included RCTs in our meta-analysis reported limited side effects. Asgary et al. (2016) found that 4 out of 20 individuals consuming whortleberry extract capsules complained of gastrointestinal upset due to consumption of capsules with empty stomach. Basu et al. (2010a) reported that 9 out of 25 participants consuming freeze-dried blueberries were withdrawn during the first week of study due to adverse effects like nausea, vomiting, constipation, and diarrhea. Hassellund et al. (2013) found that from 27 individuals who consumed anthocyanins capsules, 3 cases of minor headache, 2 cases of darker stools, and 1 case of nausea were observed. Moazen et al. (2013) found only one case of nausea among 20 participants following the administration of freeze-dried strawberries. Yang et al. (2017) found that from 80 individuals who consumed pure anthocyanins capsules, 4 cases of dark stools, 1 case of diarrhea, 1 case of dizziness, and 1 case of skin rash were observed. The other 27 RCTs used in this study did not report adverse effects in participants either in intervention or in control groups.

This study had some limitations: (*i*) the eligible studies used different sources of dietary anthocyanins that vary in composition as well as the contents of other bioactive compounds. This may confound the effects of anthocyanins on inflammatory markers; (*ii*) the subjects of eligible studies had different health status; (*iii*) the design of 6 studies (Hassellund et al., 2013; Loo et al., 2016; Basu et al., 2018; Espinosa-Moncada et al., 2018; Marín-Echeverri et al., 2018; Schell et al., 2019) were cross-over, which differs from the other studies; moreover, one of them (Loo et al., 2016) had no wash out period for treatment effects; (*iv*) different methods and instruments were used to measure the inflammatory and anti-inflammatory markers, which may affect the results.

These are some strengths of this meta-analysis: (*i*) this is the first study assessing the efficacy of dietary anthocyanins on inflammatory and anti-inflammatory markers following a comprehensive systematic search; (*ii*) since the quality of pooled estimates for CRP, IL-6, TNF-α, VCAM-1, and adiponectin was high, the obtained results are reliable.

## 5. Conclusions

Results of this study demonstrate that dietary anthocyanins significantly decreased CRP, IL-6, TNF-α, ICAM-1, and VCAM-1 levels, while adiponectin level was significantly increased. Dietary anthocyanins did not significantly change IL-1β and P-selectin levels in the subjects. Our results also demonstrated that administration of higher doses of anthocyanins (> 300 mg/day) are more effective to reduce the levels of CRP, IL-6, TNF-α, and VCAM-1. We recommend more clinical trials with different durations and doses in patients with various levels of inflammation to elucidate the effects of dietary anthocyanins on inflammatory and anti-inflammatory markers.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110922.

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