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Effect of dietary anthocyanins on biomarkers of oxidative stress and antioxidative capacity: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

In this study, the efficacy of dietary anthocyanins (ACs) on indices of oxidative stress and antioxidative capacity was evaluated through a meta-analytical approach. meta-analysis of 23 trials indicated that ACs significantly reduced the levels of malondialdehyde (MDA; −0.41, 95% CI: −0.62 to −0.21, $P < 0.001$), oxidized low-density lipoprotein (Ox-LDL; −0.27, 95% CI: −0.55 to 0.02, $P = 0.064$), and isoprostane (−0.57, 95% CI: −0.78 to −0.36, $P < 0.001$) while significantly increased the level of total antioxidative capacity (TAC; 0.32, 95% CI: 0.08 to 0.55, $P = 0.008$) and activity of superoxide dismutase (SOD; 0.29, 95% CI: 0.07 to 0.51, $P = 0.010$) and glutathione peroxidase (GPx; 0.59, 95% CI: 0.19 to 1.0, $P = 0.004$). Compared to healthy subjects, ACs were more useful for unhealthy subjects because of the significant decrease in MDA, Ox-LDL, and isoprostane levels; and significant increase in TAC level and SOD activity. The overall results indicate that dietary ACs alleviate oxidative stress and enhance antioxidative capacity in the subjects.

1. Introduction

Oxidative stress indicates a condition in which the production of reactive oxygen species (ROS) is beyond the capability of the anti-oxidative defense system to destroy them. Elevated levels of ROS damage to main cellular components such as lipids, proteins, and DNA, can lead to cytotoxic, genotoxic, and carcinogenic effects (Pisoschi & Pop, 2015; Sies, 1991). On the other hand, ROS activate nuclear factor κB pathways and cause inflammation via increasing the gene expression of inflammatory factors (Serasanambati & Chilakapati, 2016). Evidence from previous surveys demonstrates that oxidative stress is associated with the pathogenesis of several human degenerative diseases such as diabetes, cancers, and cardiovascular diseases (Rani, Deep, Singh, Palle, & Yadav, 2016).

The enzymes such as catalase, glutathione peroxidase (GPx), and superoxide dismutase (SOD), and the molecules like reduced glutathione are considered as natural endogenous antioxidative defense system against oxidative stress. In addition, entrance of natural antioxidants, like some vitamins and polyphenols, into the body through consumption of fruits and vegetables can be effective in preventing the harmful effects of oxidative stress (Jafari, 2016; Pisoschi & Pop, 2015). Previous studies showed that intake of dietary natural antioxidants improved the activity of endogenous enzymes involved in antioxidative defense system against oxidative stress (Jafari, 2016; Mathew, Tiwari, & Jatawa, 2011; Pisoschi & Pop, 2015).

Anthocyanins (ACs), a subgroup of polyphenolic compounds, are natural pigments that contribute to formation of red to blue color in various vegetables and fruits such as berries, black currant, and purple sweet potato. The *in vitro* and *in vivo* studies identified ACs as powerful antioxidative compounds to prevent the progression of several chronic degenerative diseases (Kirakosyan et al., 2018; Norberto et al., 2013; Pojer, Mattivi, Johnson, & Stockley, 2013).

Human clinical trials demonstrated that intake of dietary ACs or anthocyanin-rich foodstuffs have several health benefits such as protection against cardiovascular diseases (Alvarez-Suarez et al., 2014), alleviation of inflammation in subjects with metabolic syndrome (Nair, Mariappan, Stull, & Francis, 2017), weight reduction in overweight/obese subjects (Cardile, Graziano, & Venditti, 2015), improvement of glycemic status in diabetics (Gorji et al., 2014), protection against bone loss in postmenopausal smokers (Kaume, Gbur, DiBrezzo, Howard, &

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Devareddy, 2014), alleviation of lipid profile in subjects with polygenic dyslipidemia (Hajifaraji et al., 2018), and prevention of obesity in healthy subjects (Tucakovic et al., 2018).

The efficacy of dietary ACs on indices of oxidative stress and antioxidative capacity is investigated in several human clinical trials, but different results have been reported. In this research, we evaluated the effect of pure ACs or ACs-rich extract/powder on levels of malondialdehyde (MDA), oxidized low-density lipoprotein (Ox-LDL), isoprostane, total antioxidative capacity (TAC), and activities of SOD and GPx through a meta-analytical approach.

2. Methods

2.1. Search strategy

Four biomedical literature databases including PubMed, Scopus, ISI Web of Science, and MagIran were searched for published trials up to 10 February 2020. The used keywords were: anthocyanin, anthocyanins, anthocyanin-rich, oxidative stress, antioxidant capacity, antioxidative capacity, antioxidant defense, antioxidative defense, lipid oxidation, lipid peroxidation, malondialdehyde, MDA, oxidized low-density lipoprotein, Ox-LDL, isoprostane, superoxide dismutase, SOD, glutathione peroxidase, and GPx.

Manual searching was carried out on the reference list of selected trials and published reviews to avoid losing the studies. The search was limited to clinical trials of human subjects and performed by 2 authors (ES and AAF).

2.2. Study eligibility

The studies were selected for this meta-analysis if they met the following criteria: (*i*) the parallel or crossover randomized controlled trials (RCTs) on adult subjects (age ≥ 18 y) in which dietary ACs were provided for the intervention group; (*ii*) RCTs used placebo in control group or the difference between the groups was only intake of ACs; (*iii*) the duration of intervention was at least 2 weeks; (*iv*) the anthocyanin intake was reported or could be calculated for the intervention group; (*v*) the outcomes provided adequate statistics on baseline and endpoint values of oxidative stress or antioxidative capacity markers including MDA, Ox-LDL, isoprostane, TAC, SOD, or GPx.

2.3. Data extraction

The following data were extracted from the selected trials: (*i*) study characteristics including first author's last name, publication year, daily dose and form of ACs, study design, duration of intervention, and sample size of control and intervention group; (*ii*) participant information including country of origin, average age, and health status; (*iii*) study outcomes including levels of MDA, Ox-LDL, isoprostane, TAC, SOD, or GPx. The GetData Graph Digitizer software version 2.24 was employed to extract data from the plots.

2.4. Quality evaluation of trials and overall estimates

The quality of each eligible trial was evaluated by Cochrane Collaboration tool including the risk of bias domains such as random sequence generation (RSG), allocation concealment (AC), blinding of participants and personnel (BPP), blinding of outcome assessment (BOA), incomplete outcome data (IOD), selective outcome reporting (SOR), and other sources of bias including bias of study design, trial stopped early, extreme baseline imbalance, and fraudulent trial. Each mentioned domain was graded as low, unclear, or high risk of bias (Higgins et al., 2019). The RCTs quality were categorized as "Good", "Fair", or "Low" as described in our previous study (Fallah, Sarmast, Fatehi, & Jafari, 2020).

The NutriGrade scoring system was used to evaluate the overall estimate quality of each marker (Schwingshackl et al., 2016). This scoring system comprises several items such as risk of bias, precision, heterogeneity, directness, publication bias, funding bias, and study design. The overall estimate of each marker ranked from 0 to 10. The ranks of 0–3.99, 4–5.99, 6–7.99, and 8–10 were regarded as very low, low, moderate, and high quality, respectively.

2.5. Statistical analyses

The effect size for MDA, Ox-LDL, isoprostane, TAC, SOD, or GPx in each trial was calculated as bias corrected standardized mean difference (Hedges' g method) and its 95% confidence interval (CI) (Askari, Iraj, Salehi-Abargouei, Fallah, & Jafari, 2015). Because the selected trials were performed in various settings, random effects model was used to compute the summary effect for the effect sizes (DerSimonian & Laird, 1986; Fallah et al., 2018). The variables including duration of trials, dosages of ACs, and health status of participants were used to conduct subgroup analyses. The inter-study heterogeneity was explored by Cochrane Q test at $P \leq 0.050$ (Higgins et al., 2019). The degree of inter-study heterogeneity was quantified by *I*-squared (I^2) index; and I^2 values of 25, 50, and 75 were considered as low, moderate, and high estimates, respectively (Higgins, Thompson, Deeks, & Altman, 2003). The sources of inter-study heterogeneity were assessed by conducting influence analysis (Jafari, Rostampour, Fallah, & Hesami, 2017). The publication bias was analyzed by Begg and Mazumdar adjusted rank correlation test (Begg & Mazumdar, 1994; Jafari, Feizi, Askari, & Fallah, 2015) and Egger's regression asymmetry test (Egger, Smith, Schneider, & Minder, 1997; Jafari, Fallah, & Barani, 2016). The analyses were carried out using Stata software version 14.2 (Stata Corporation, College Station, TX) and $P \leq 0.050$ was regarded as significant value.

3. Results

3.1. Search results

The literature search yielded 2533 records, of which 1231 were duplicate. After excluding duplicates, the remaining records were assessed and 1174 records were removed because of their irrelevancy to the topic. After further screening, 23 studies (Arevström et al., 2019; Basu et al., 2010, 2014; Broncel et al., 2010; Chew et al., 2019; Davinelli, Bertoglio, Zarrelli, Pina, & Scapagnini, 2015; Espinosa-Moncada et al., 2018; Guo et al., 2020; Johnson et al., 2017; Kim et al., 2018; Li, Zhang, Liu, Sun, & Xia, 2015; Maeda-Yamamoto et al., 2018; Moazen et al., 2013; Naruszewicz, Łaniewska, Millo, & Dłużniewski, 2007; Nilsson, Salo, Plaza, & Björck, 2017; Park et al., 2015; Puupponen-Pimiä et al., 2013; Riso et al., 2013; Riva et al., 2017; Soltani, Hakimi, Asgary, Ghanadian, Keshvari, & Sarrafzadegan, 2014; Terrazas et al., 2020; Vidlar et al., 2010; Xie et al., 2017) comparing intervention group (administered dietary ACs) with control group were selected to conduct meta-analyses. The process is presented in Fig. 1.

3.2. Study specifications

The specifications of 23 trials, enrolling 1044 subjects, performed in Iran, USA, Poland, Italy, China, Korea, Japan, Czech Republic, Finland, Brazil, Colombia, and Sweden are summarized in Table 1. The administrated dose of ACs was from 1.7 to 1230 mg/day; and the dietary intervention lasted from 2 to 26 weeks. The participants were healthy in 8 trials (Chew et al., 2019; Guo et al., 2020; Maeda-Yamamoto et al., 2018; Nilsson et al., 2017; Park et al., 2015; Riso et al., 2013; Riva et al., 2017; Terrazas et al., 2020), individuals with metabolic syndrome in 5 trials (Basu et al., 2010; Broncel et al., 2010; Espinosa-Moncada et al., 2018; Kim et al., 2018; Puupponen-Pimiä et al., 2013), diabetic in 2 trials (Li et al., 2015; Moazen et al., 2013), obese/overweight in 2 trials (Basu et al., 2014; Davinelli et al., 2015), individuals with post myocardial infarction in 2 trials (Arevström et al., 2019;

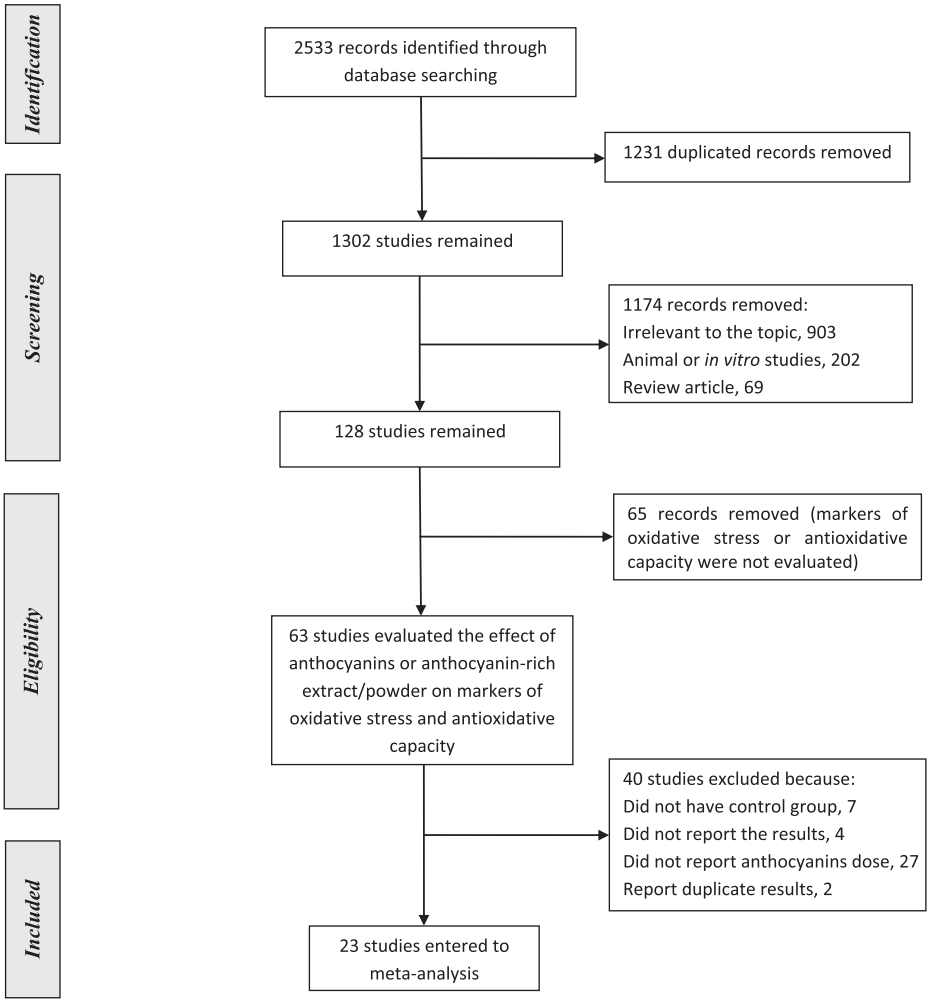

Fig. 1. PRISMA flow diagram of study identification, inclusion, and exclusion.

Naruszewicz et al., 2007), individuals with lower urinary tract symptoms in 1 trial (Vidlar et al., 2010), former smokers in 1 trial (Xie et al., 2017), hypertensives in 1 trial (Johnson et al., 2017), and hyperlipidemic in 1 trial (Soltani et al., 2014).

3.3. Quality evaluation of trials and overall estimates

Quality appraisal of trials based on Cochrane criteria are shown in Table 2. Despite the fact that all the eligible trials were randomised, explanation for RSG and AC were missing in 9 (Basu et al., 2010, 2014; Broncel et al., 2010; Davinelli et al., 2015; Li et al., 2015; Naruszewicz et al., 2007; Nilsson et al., 2017; Park et al., 2015; Riva et al., 2017) and 13 (Arevström et al., 2019; Basu et al., 2010, 2014; Espinosa-Moncada et al., 2018; Johnson et al., 2017; Li et al., 2015; Moazen et al., 2013; Naruszewicz et al., 2007; Nilsson et al., 2017; Park et al., 2015; Puupponen-Pimiä et al., 2013; Riva et al., 2017; Vidlar et al., 2010) trials, respectively. In addition, 1 trial (Xie et al., 2017) for RSG and 2 trials (Broncel et al., 2010; Xie et al., 2017) for AC had high risk of bias. Four trials (Basu et al., 2010; Broncel et al., 2010; Naruszewicz et al., 2007; Xie et al., 2017) had high risk of bias for BPP, whereas no trial was high risk of bias based on BOA. None of the trials was high risk of bias for IOD, SOR, and other sources of bias including bias of study design, extreme baseline imbalance, trial stopped early, and fraudulent trial. From 23 eligible trials, 20 trials (Arevström et al., 2019; Basu et al., 2014; Chew et al., 2019; Davinelli et al., 2015; Espinosa-Moncada et al., 2018; Guo et al., 2020; Johnson et al., 2017; Kim et al., 2018; Li et al., 2015; Maeda-Yamamoto et al., 2018; Moazen et al., 2013; Nilsson et al., 2017; Park et al., 2015; Puupponen-Pimiä et al., 2013; Riso et al., 2013; Riva et al., 2017; Soltani et al., 2014; Terrazas et al., 2020; Vidlar et al., 2010; Xie et al., 2017) were classified as "Good", 1 trial (Naruszewicz et al., 2007) as "Fair", and 2 trials (Basu et al., 2010; Broncel et al., 2010) as "Low".

The meta-analysis quality was high for MDA. This fact points out that further survey presumably will not affect the confidence in the estimation of overall effect. Also, the meta-analysis quality was moderate for Ox-LDL, isoprostane, TAC, SOD, and GPx (Table 3), indicating that further survey might change the confidence in the estimation of overall effects.

3.4. Effect of ACs on MDA

The overall effect from 18 trials, with 635 subjects, indicated significant reduction in MDA level following administration of dietary ACs (Supplementary Data, Fig. S1: −0.32, 95% CI: −0.54 to −0.11, $P = 0.003$); however, inter-trial heterogeneity was high based on I^2 statistic (46.7%) and Cochrane Q test ($P = 0.015$). The influence analysis showed that studies of Maeda-Yamamoto et al. (2018) and Guo et al. (2020; anthocyanin dose of 20 mg/day) were the source of heterogeneity. After omission of the mentioned studies, the inter-trial heterogeneity was reduced ($I^2 = 28.8\%$, Cochrane Q test $P = 0.134$); and the overall estimate showed significant reduction in MDA level following ACs supplementation (Fig. 2: −0.41, 95% CI: −0.62 to −0.21, $P < 0.001$).

Table 1
Characteristics of randomised 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
Naruszewicz et al. (2007)	Poland	Parallel	44	Post myocardial infarction	6 weeks	Chokeberry extract capsule	63.75	Placebo capsule (maltodextrin)	Ox-LDL, isoprostane
Basu et al. (2010)	USA	Parallel	48	Metabolic syndrome	8 weeks	Freeze-dried blueberry powder reconstituted in water	742	Water	MDA, Ox-LDL
Broncel et al. (2010)	Poland	Parallel	47	Metabolic syndrome	2 months	Aronia extract capsule	300	Placebo capsule (maltodextrin)	MDA, SOD, GPx
Vidlar et al. (2010)	Czech Republic	Parallel	42	Lower urinary tract symptoms	6 months	Capsule of cranberry fruit powder + dietary instruction	1.65	Received dietary instruction	MDA, SOD, GPx, TAC
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	MDA, TAC
Puupponen-Pimiä et al. (2013)	Finland	Parallel	32	Metabolic syndrome	12 weeks	Strawberry purée, frozen raspberries, and frozen cloudberries	70.7	Restriction of berry consumption	Isoprostane
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	SOD, GPx
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	MDA
Soltani et al. (2014)	Iran	Parallel	50	Hyperlipidemic	4 weeks	Caucasian whortleberry extract capsule	90	Placebo capsule(tribasic calcium phosphate)	MDA
Davinelli et al. (2015)	Italy	Parallel	42	Overweight and smokers	4 weeks	Maqui berry extract capsule	162	Placebo capsule (maltodextrin)	Ox-LDL, isoprostane
Li et al. (2015)	China	Parallel	58	Diabetic	24 weeks	Capsule of purified anthocyanins from bilberry and black currant	320	Placebo capsule (pullulan + maltodextrin)	Isoprostane, TAC
Park et al. (2015)	Korea	Parallel	39	Healthy male smokers	4 weeks	Freeze-dried black raspberry powder reconstituted in water	1230	Placebo powder (carboxymethyl cellulose + Methyl-ρ-hydroxybenzoate + sucrose + sweet rice flour + red No. 40 + blue No. 1) reconstituted in water	MDA, Ox-LDL, SOD, GPx
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)	MDA, Ox-LDL, isoprostane, SOD, GPx
Nilsson et al. (2017)	Sweden	Cross over	20	Healthy older subjects	5 weeks	Mixed berry powder consumed as a beverage	248.5	Placebo beverage	MDA, Ox-LDL
Riva et al. (2017)	Italy	Parallel	21	Healthy subjects with dry eye symptoms	4 weeks	Bilberry extract tablet	57.6	Placebo tablet	TAC
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)	Ox-LDL, isoprostane, SOD, GPx, TAC
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	MDA, isoprostane
Kim et al. (2018)	USA	Parallel	37	Metabolic syndrome	12 weeks	Açaí berry powder consumed as a beverage	199.6	Placebo beverage	Isoprostane
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)	MDA, SOD

(*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
Arevström et al. (2019)	Sweden	Parallel	50	Post myocardial infarction	8 weeks	Freeze-dried bilberry powder reconstituted in water	900	No dietary intervention	Ox-LDL
Chew et al. (2019)	USA	Parallel	78	Healthy overweight	8 weeks	Cranberry extract consumed as low-calorie beverage	6.22	Low-calorie placebo beverage	SOD, GPx
Guo et al. (2020)	China	Parallel	107	Healthy	2 weeks	Capsule of purified anthocyanins from berries	20, 40, 80, 160, 320	Placebo capsule (maltodextrin + pullulan + citric acid)	MDA, isoprostane, TAC
Terrazas et al. (2020)	Brazil	Cross-over	10	Healthy male cyclists	2 weeks	Pasteurized açai pulp	284.4	Placebo (water + xanthan gum + citric acid + sucralose + artificial açai flavor + artificial food dyes)	MDA, TAC

Abbreviations: GPx, glutathione peroxidase; MDA, malondialdehyde; Ox-LDL, oxidized low-density lipoprotein; SOD, superoxide dismutase; TAC, total antioxidative capacity.

3.5. Effect of ACs on Ox-LDL

Seven studies, with 352 participants, explored the efficacy of ACs supplementation on level of Ox-LDL. The overall estimate showed marginally significant reduction in Ox-LDL level (Supplementary Data, Fig. S2: −0.50, 95% CI: −1.0 to 0.01, $P = 0.054$). Heterogeneity among the studies was high according to the results of I^2 statistic (79.4%) and Cochrane Q test ($P < 0.01$). Influence analysis revealed that the study of Davinelli et al. (2015) was the source of heterogeneity. After exclusion of this study, the heterogeneity was reduced ($I^2 = 29.7\%$, Cochrane Q test $P = 0.201$), and random-effects analysis showed a marginal significant reduction of Ox-LDL after consuming ACs (Fig. 2: −0.27, 95% CI: −0.55 to 0.02, $P = 0.064$).

3.6. Effect of ACs on isoprostane

There were 449 participants in 13 trials in which the efficacy of ACs supplementation on isoprostane level was assessed. The overall analysis demonstrated significant reduction of isoprostane level following ACs administration (Fig. 2: −0.57, 95% CI: −0.78 to −0.36, $P < 0.001$). No evidence of inter-trial heterogeneity was found by I^2 statistic (0%) and Cochrane Q test ($P = 0.604$).

3.7. Effect of ACs on TAC

Effect of ACs supplementation on TAC was examined in 11 studies with 325 subjects; and the results showed significant increase in TAC level (Fig. 3: 0.32, 95% CI: 0.08 to 0.55, $P = 0.008$). Heterogeneity among the studies was low according to I^2 statistic (18.8%) and Cochrane Q test ($P = 0.264$).

3.8. Effect of ACs on SOD

Eight studies with 407 participants involved in the meta-analysis had data on the effect of ACs on SOD activity; and the overall estimate demonstrated significant increase in SOD activity (Supplementary Data, Fig. S3: 0.37, 95% CI: 0.12 to 0.62, $P = 0.004$). Heterogeneity among the studies was moderate according to I^2 statistic (30.4%) and Cochrane Q test ($P = 0.185$). Influence analysis revealed that study of Broncel et al. (2010) was the source of heterogeneity. After omitting the mentioned study, the heterogeneity was clearly reduced ($I^2 = 0.0\%$, Cochrane Q test $P = 0.630$), and significant increase in SOD activity was obtained (Fig. 4: 0.29, 95% CI: 0.07 to 0.51, $P = 0.010$).

3.9. Effect of ACs on GPx

Seven trials, with 331 subjects, evaluated the effect of dietary ACs on GPx activity, and the overall estimate showed significant increase in GPx activity (Supplementary Data, Fig. S4: 0.45, 95% CI: 0.0 to 0.89, $P = 0.048$). According to the I^2 statistic (55%) and Cochrane Q test ($P = 0.038$), inter-trial heterogeneity was high. Influence analysis showed that the study of Riso et al. (2013) was the source of heterogeneity. After exclusion of this study, the inter-trial heterogeneity was reduced ($I^2 = 37\%$, Cochrane Q test $P = 0.160$); and overall estimate showed significant increase in GPx activity following ACs administration (Fig. 4: 0.59, 95% CI: 0.19 to 1.0, $P = 0.004$).

3.10. Subgroup analyses

Subgroup analysis based on intervention duration showed that ACs supplementation for less than 8 weeks decreased the serum levels of MDA and isoprostane and increased TCA level and GPx activity, while intervention duration ≥8 weeks increased activities of SOD and GPx. It was found that ACs doses less than 300 mg/day decreased levels of MDA and isoprostane and increased SOD activity; however, significant increase in GPx activity was determined by consuming ACs doses equal

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

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomeassessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias[a]	Overall quality[b]
Naruszewicz et al. (2007)	U	U	H	U	L	L	L	Fair
Basu et al. (2010)	U	U	H	U	L	L	U	Low
Broncel et al. (2010)	U	H	H	U	U	L	U	Low
Vidlar et al. (2010)	L	U	U	L	L	L	L	Good
Moazen et al. (2013)	L	U	L	L	L	L	L	Good
Puupponen-Pimiä et al. (2013)	L	U	U	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
Davinelli et al. (2015)	U	L	L	U	L	L	L	Good
Li et al. (2015)	U	U	L	L	L	L	L	Good
Park et al. (2015)	U	U	L	L	L	L	L	Good
Johnson et al. (2017)	L	U	L	L	L	L	L	Good
Riva et al. (2017)	U	U	U	L	L	L	L	Good
Nilsson et al. (2017)	U	U	L	L	L	L	L	Good
Xie et al. (2017)	H	H	H	U	L	L	U	Low
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
Arevström et al. (2019)	L	U	U	L	L	L	L	Good
Chew et al. (2019)	L	L	L	L	L	U	L	Good
Guo et al. (2020)	L	L	U	U	L	L	L	Good
Terrazas et al. (2020)	L	L	U	U	L	L	L	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.

or more than 300 mg/day in participants. Administration of dietary ACs reduced the levels of MDA, Ox-LDL, and isoprostane while increased TAC level and SOD activity in unhealthy Subjects (Table 4).

3.11. Publication bias

On the basis of Begg and Mazumdar adjusted rank correlation test, no evidence of publication bias was found for MDA ($P = 0.103$), Ox-LDL ($P = 0.805$), isoprostane ($P = 0.126$), TAC ($P = 0.392$), SOD ($P = 0.063$), and GPx ($P = 0.881$). In addition, Egger regression asymmetry test showed no publication bias for MDA ($P = 0.091$), Ox-LDL ($P = 0.387$), isoprostane ($P = 0.501$), TAC ($P = 0.922$), SOD ($P = 0.227$), and GPx ($P = 0.930$).

4. Discussion

It has been determined that ACs have favorable antioxidative activity, but it is varied from one anthocyanin compound to another. This activity depends on the position and number of hydroxyl groups, degree of glycosylation, and presence of donor electrons in their structure (Miguel, 2011; Reis, Monteiro, de Souza Gomes, & do Carmo, M.M., da Costa, G.V., Ribera, P.C., & Monteiro, M.C. , 2016).

Human interventional studies, in overall, have failed to confirm the antioxidative effects of ACs. We conducted this meta-analysis in order to find documental results on the effects of ACs administration on markers of oxidative stress and antioxidative capacity. Our study represented that lipid peroxidation decreased after consumption of ACs. Researchers showed that there is an ATP-dependent process called "*revers cholesterol transport*" in which cholesterol return from macrophages to the liver. It inhibits the production of Ox-LDL and therefore, prevents the transformation of foam cell from macrophage. ACs are able to act as electron receptors in complex I of mitochondrial respiratory chain and promote ATP production (Skemiene, Liobikas, & Borutaite, 2015). They also activate AMP-activated protein kinases resulting in the phosphorylation of acetyl COA carboxylase, which lead to increased fatty acid metabolism (Forbes-Hernández et al., 2017; Yan & Zheng, 2017). These mechanisms warrant the reverse flow of cholesterol to the liver.

ACs also inhibit the production of Ox-LDL by increasing the levels of nuclear peroxisome proliferator-activator receptor γ (PPARγ) and

Table 3
Summary of findings with the NutriGrade scoring system.

Outcome	Effect size (95% CI)	No. of participants (studies)	Score	Outcome quality
MDA	−0.32 (−0.53, −0.11)	635 (18 RCTs)	8.5	High
Ox-LDL	−0.50 (−1.00, 0.01)	352 (8 RCTs)	6	Moderate
Isoprostane	−0.57 (−0.78, −0.36)	449 (13 RCTs)	7.25	Moderate
TAC	0.32 (0.08, 0.55)	325 (11 RCTs)	7	Moderate
SOD	0.37 (0.12, 0.62)	407 (8 RCTs)	7	Moderate
GPx	0.45 (0.0, 0.89)	331 (7 RCTs)	6	Moderate

Abbreviations: CI, confidence interval; GPx, glutathione peroxidase; MDA, malondialdehyde; Ox-LDL, oxidized low-density lipoprotein; RCTs, randomized controlled trials; SOD, superoxide dismutase; TAC, total antioxidative capacity.

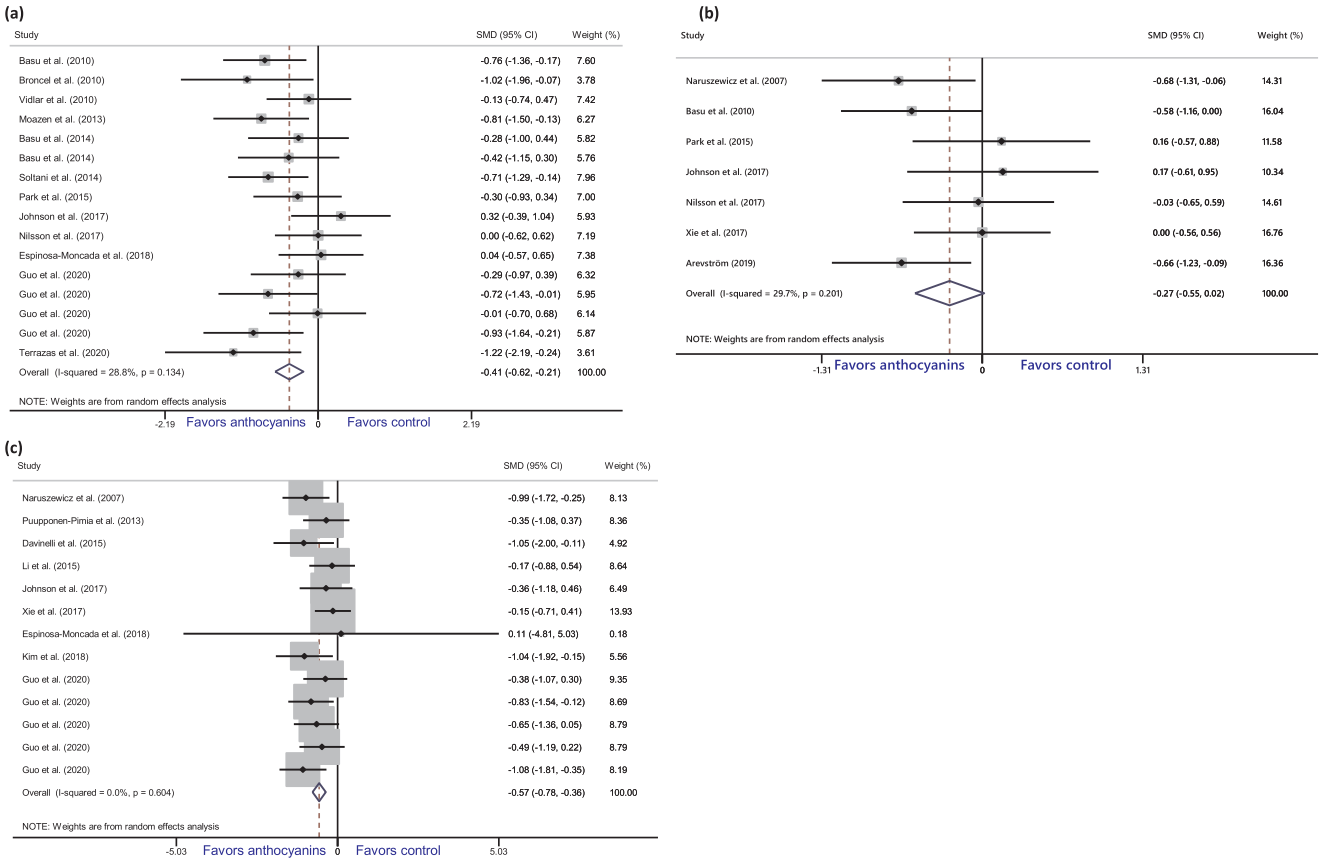

Fig. 2. Forest plots of the effect of dietary anthocyanins on MDA (a), Ox-LDL (b), and isoprostane (c). For MDA meta-analysis performed without studies of Maeda-Yamamoto et al. (2018) and Guo et al. (2020; anthocyanins dosage of 20 mg/day) and for Ox-LDL meta-analysis performed without study of Davinelli et al. (2015).

downregulating the expression of CD36 gene in macrophages (Li, Wang, Luo, Zhao, & Chen, 2017; Wang et al., 2012). Aviram et al. (2004) showed that consumption of ACs increase serum paroxonase 1 activity, the major anti-atherosclerotic component of high-density lipoprotein cholesterol (HDL-C), and support the blood cholesterol cleaning property of these lipoproteins. By such aforementioned mechanisms, ACs reduce the production of cholesterol, low-density lipoprotein cholesterol (LDL-C), and Ox-LDL hence reduce the levels of lipid peroxidation markers like MDA and isoprostane (Arevström et al., 2019; Skemiene et al., 2015; Takikawa, Inoue, Horio, & Tsuda, 2010). It can be concluded that consumption of ACs-rich extracts reduces the risk of atherosclerosis in human. Some studies reported that ACs inhibit the production of antibodies against LDL-C, and prevent its degradation to Ox-LDL (Takikawa et al., 2010; Weseler & Bast, 2012).

Inflammatory processes induce oxidative stress and reduce antioxidative capacity. The nuclear factor κB (NF-κB) pathways play

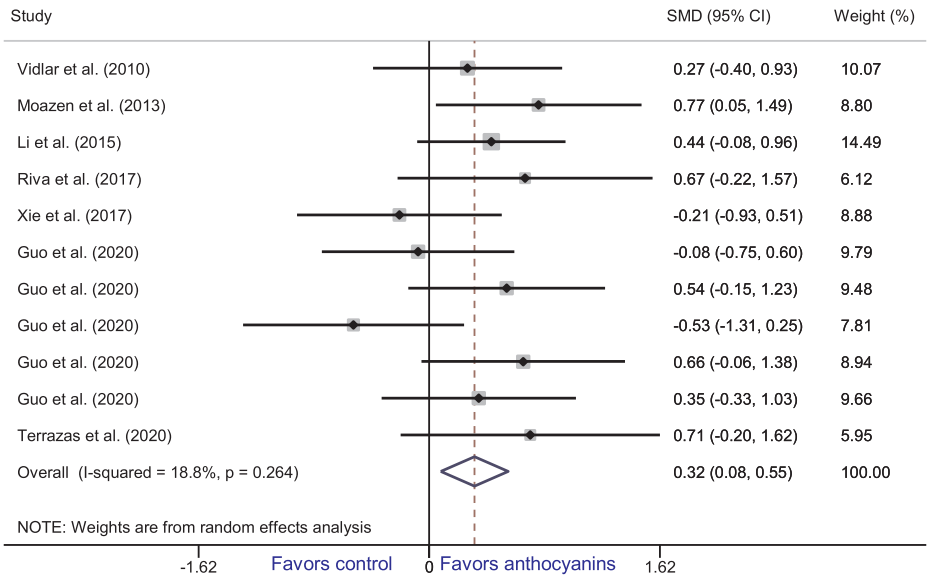

Fig. 3. Forest plot of the effect of dietary anthocyanins on total antioxidative capacity.

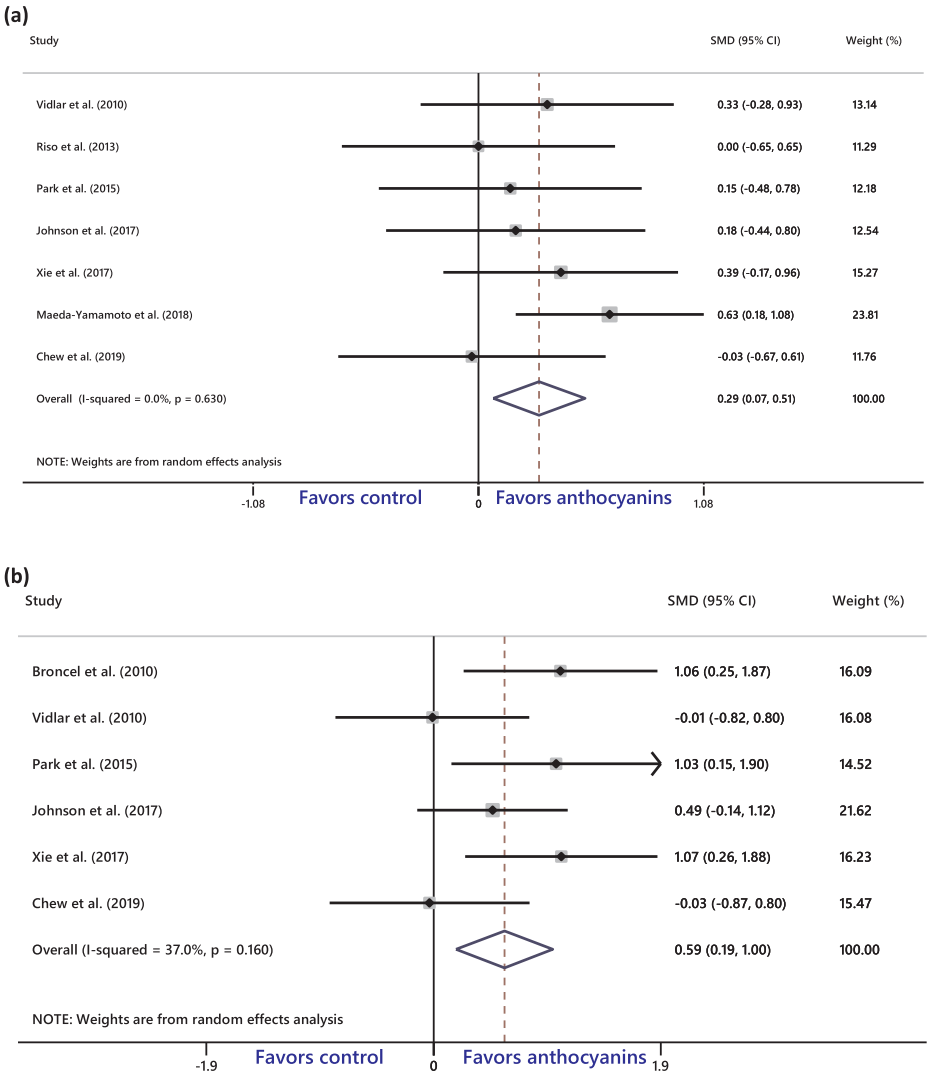

Fig. 4. Forest plots of the effect of dietary anthocyanins on SOD (a) and GPx (b). For SOD and GPx meta-analyses performed without studies of Broncel et al. (2010) and Riso et al. (2013), respectively.

important role in regulating inflammatory processes. These pathways, activated by ROS, induce inflammation by increasing the gene expression of inflammatory markers. ACs can block NF-κB pathways by trapping ROS, hence reducing inflammation and oxidative stress (Fallah et al., 2020; Li et al., 2017; Miguel, 2011).

Plasminogen activator inhibitor-1 (PAI-1) is an adipocytokine associated with vascular inflammation and development of cardiovascular and metabolic disorders. The ACs downregulated PAI-1 gene expression level, hence controled inflammation and oxidative stress (Gomes et al., 2019).

ACs regulate the nitric-oxide synthase activity and inhibit the activity of some oxidase enzymes that produce reactive oxygen molecules. The hydroxyl groups in the structure of ACs reinforce the activity of antioxidative enzymes like SOD (Ruel, Pomerleau, Couture, Lamarche, & Couillard, 2005). ACs can be direct substrates for peroxidases, which result in H_2O_2 deactivation, hence increase GPx activity (Broncel et al., 2010). The mentioned mechanisms justify the enhancement of total antioxidative capacity after consumption of ACs. It should be noted that such effects are expected to be more pronounced in subjects with higher levels of oxidative stress conditions. This was prominently observed in our subgroup analysis on health status that ACs consumption have more benefits for unhealthy subjects compared to healthy ones.

The *in vitro* and animal model studies demonstrated that the biological effects of ACs are mostly related to their antioxidative activities; therefore, ACs can alleviate oxidative stress and enhance antioxidative defense (Li et al., 2017; Miguel, 2011). Results of this meta-analysis did not indicate dose-dependent effects of dietary ACs on markers of oxidative stress and antioxidative capacity. In contrast, the dose-dependent effects of ACs to ameliorate oxidative stress and enhance antioxidative defense have been demonstrated in some *in vitro* and animal model studies (Chen et al., 2019; Chen, Wang, Pan, Guo, & Chen, 2018; Long, Gao, Sun, Liu, & Zhao-Wilson, 2009; Setiawan & Nadhil, 2019; Yan & Zheng, 2017).

Results of this meta-analysis revealed that dietary ACs decreased the levels of oxidative stress markers (MDA, isoprostane, and Ox-LDL) and enhanced the markers of antioxidative capacity (TAC and SOD) only in unhealthy subjects. But animal model studies demonstrated the beneficial effects of ACs on markers of oxidative stress and antioxidative defense in both healthy animals and animals with impaired health (Bilanda et al., 2020; Li et al., 2019; Mahmoud, 2013; Noratto, Chew, & Atienza, 2017; Sozański et al., 2019; Żary-Sikorska, Fotschki, Fotschki, Wiczkowski, & Juśkiewicz, 2019).

It appears that administration of pure ACs or ACs-rich supplements, as powerful antioxidants, are safe for most heathy and unhealthy individuals. Although occurrence of ACs adverse effects are uncommon, minor cases of nausea, vomiting, constipation, diarrhea, or skin rash was found following the administration of ACs (Basu et al., 2010; Moazen et al., 2013; Yang et al., 2017).

Table 4
Results of the effect of dietary anthocyanins on biomarkers of oxidative stress and antioxidative capacity based on subgroup analyses.

Outcome	Variable	No. of trials	Effect size (95% CI)	*P* value	I^2 (%)	Q-statistics (*P*)
MDA	*Intervention duration*					
	< 8 weeks[a]	10	−0.45 (−0.70, −0.19)	0.001	31.1	0.160
	≥8 weeks[b]	6	−0.35 (−0.71, 0.003)	0.052	35.8	0.168
	Anthocyanins dosage					
	< 300 mg/day[a,b]	11	−0.37 (−0.59, −0.15)	0.001	14.6	0.305
	≥300 mg/day	5	−0.51 (−0.98, −0.04)	0.032	54.7	0.065
	Health status					
	Healthy[a,b]	7	−0.43 (−0.84, 0.05)	0.061	30	0.199
	Unhealthy	9	−0.40 (−0.68, −0.12)	0.005	36	0.130
Ox-LDL	*Intervention duration*					
	< 8 weeks[c]	3	−0.20 (−0.70, 0.30)	0.422	42.5	0.176
	≥8 weeks	4	−0.30 (−0.70, 0.09)	0.126	38.6	0.181
	Anthocyanins dosage					
	< 300 mg/day[c]	3	−0.23 (−0.65, 0.20)	0.302	34.3	0.218
	≥300 mg/day	4	−0.29 (−0.72, 0.15)	0.192	43.1	0.153
	Health status					
	Healthy	3	0.03 (−0.33, 0.39)	0.881	0.0	0.920
	Unhealthy[c]	4	−0.50 (−0.84, −0.16)	0.004	14.4	0.320
Isoprostane	*Intervention duration*					
	< 8 weeks	8	−0.75 (−1.02, −0.47)	< 0.001	0.0	0.839
	≥8 weeks	5	−0.34 (−0.66, 0.01)	0.057	0.0	0.553
	Anthocyanins dosage					
	< 300 mg/day	10	−0.58 (−0.82, −0.34)	< 0.001	0.0	0.657
	≥300 mg/day	3	−0.54 (−1.10, 0.02)	0.058	39.6	0.191
	Health status					
	Healthy	6	−0.35 (−0.62, 0.10)	0.094	0.0	0.423
	Unhealthy	7	−0.60 (−0.93, −0.28)	< 0.001	0.0	0.528
TAC	*Intervention duration*					
	< 8 weeks	8	0.37 (0.06, 0.68)	0.021	29.2	0.195
	≥8 weeks	3	0.23 (−0.13, 0.56)	0.216	2.7	0.358
	Anthocyanins dosage					
	< 300 mg/day	9	0.29 (0.01, 0.60)	0.058	33.6	0.149
	≥300 mg/day	2	0.40 (−0.01, 0.81)	0.056	0.0	0.841
	Health status					
	Healthy	8	0.24 (−0.08, 0.56)	0.136	31.6	0.176
	Unhealthy	3	0.47 (0.11, 0.82)	0.010	0.0	0.599
SOD	*Intervention duration*					
	< 8 weeks	2	0.08 (−0.37, 0.53)	0.732	0.0	0.742
	≥8 weeks[d]	5	0.35 (0.10, 0.61)	0.006	0.0	0.534
	Anthocyanins dosage					
	< 300 mg/day	4	0.39 (0.11, 0.66)	0.005	0.0	0.428
	≥300 mg/day[d]	3	0.11 (−0.25, 0.48)	0.543	0.0	0.917
	Health status					
	Healthy	3	0.18 (−0.18, 0.54)	0.335	0.0	0.770
	Unhealthy[d]	4	0.35 (0.06, 0.64)	0.017	7	0.358
GPx	*Intervention duration*					
	< 8 weeks[e]	1	1.03 (0.15, 1.90)	0.022	–	–
	≥8 weeks	5	0.52 (0.07, 0.97)	0.024	41.5	0.145
	Anthocyanins dosage					
	< 300 mg/day	3	0.35 (−0.37, 1.06)	0.344	56.7	0.099
	≥300 mg/day[e]	3	0.79 (0.35, 1.22)	< 0.001	0.0	0.458
	Health status					
	Healthy	3	0.69 (−0.02, 1.40)	0.058	53.4	0.117
	Unhealthy[e]	3	0.51 (−0.04, 1.07)	0.072	40.6	0.186

Abbreviations: CI, confidence interval; GPx, glutathione peroxidase; MDA, malondialdehyde; Ox-LDL, oxidized low-density lipoprotein; SOD, superoxide dismutase; TAC, total antioxidative capacity.

[a] Analyses performed without study of Maeda-Yamamoto et al. (2018).
[b] Analyses performed without study of Guo et al. (2020; anthocyanins dosage of 20 mg/day).
[c] Analyses performed without study of Davinelli et al. (2015).
[d] Analyses performed without study of Broncel et al. (2010).
[e] Analyses performed without study of Riso et al. (2013).

The limitations of current meta-analysis are as follows: (*a*) the used trials administered various sources of ACs with different composition and amount of other compounds; (*b*) the participants of used trials varied in health status; (*c*) various methods were applied to determine the levels of oxidative stress markers and activity of enzymes, which may affect the results.

5. Conclusions

The results of current meta-analysis indicate that the administration of dietary ACs reduced the levels of MDA, Ox-LDL, and isoprostane while increased the level of TAC and activity of SOD and GPx. Compared to healthy subjects, dietary ACs were more useful for unhealthy subjects because of the significant decrease in levels of MDA, Ox-LDL, and isoprostane and significant increase in TAC level and SOD activity. We Suggest more clinical trials with various durations and

dosages in subjects with different health status to clarify the efficacy of dietary ACs on markers of oxidative stress and antioxidative capacity.

6. Author's contribution

Elham Sarmast and Aziz A. Fallah were involved in literature search, data extraction, and quality assessment of the trials. Tina Jafari, Elham Sarmast, and Aziz A. Fallah contributed to data synthesis, statistical analyses, and writing the manuscript. Elham Sarmast supervised the study team. All authors read and approved final manuscript for submission.

Ethical statement

The authors declare the followings:

- This research did not include any human subjects and animal experiments.
- The present study is the original work of the authors. The used methods are standard; and the reported data are represented accurately in the paper.
- The authors have written the paper entirely and the work and/or words of the other authors have been appropriately cited.
- The present study has not been published, accepted for publication, or under editorial review for publication elsewhere.
- All the authors have made a significant contribution to the conception, design, execution and data interpretation of the present study. Also, all of them will hold themselves jointly and individually responsible for its content.
- All the authors approve submission of the manuscript in *Journal of Functional Foods*.

Declaration of Competing Interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2020.103912.

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