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The Postprandial Effect of Anthocyanins on Cardiovascular Disease Risk Factors: a Systematic Literature Review of High-Fat Meal Challenge Studies

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Abstract

© 2020, Springer Science+Business Media, LLC, part of Springer Nature. Purpose of review: Recurrent post-prandial metabolic imbalances are important contributing factors to the development of cardiovascular disease (CVD). This study evaluated whether anthocyanin consumption attenuates the deleterious postprandial response of high-fat meals on CVD risk factors including blood pressure, vascular endothelial function, lipid profile and biomarkers related to oxidative stress, antioxidant status and immune response. Recent findings: Five electronic databases were searched up to the period of 1 February 2020, yielding 13 eligible studies, including randomised or cross-over clinical trials (18–59 years of age), using PRISMA guidelines (PROSPERO registration: CRD42019126265). Potential bias was assessed using the revised Cochrane risk-of-bias tool for randomised trials. Beneficial effects of anthocyanins were reported in biomarkers of oxidative stress and antioxidant status in 6 out of 9 studies, and in 3 out of 6 studies for inflammatory response. Two positive results were found concerning attenuation of post-prandial endothelial dysfunction, increased triacylglycerol and total cholesterol exerted by the high fat meal. Blood pressure and lipoproteins were the parameters with least beneficial results. Summary: Our systematic literature review revealed beneficial effects of dietary anthocyanin interventions on CVD risk factors following a HFM challenge; however, heterogeneity in results exists. The most promising results were for the attenuation of deleterious postprandial effects on oxidative stress and antioxidant status, triacylglycerol and total cholesterol concentrations, vascular endothelial function and inflammatory biomarkers. Post-prandial changes in blood pressure and lipoproteins were least affected by anthocyanins. Further studies are required in order to better elucidate the post-prandial effects of anthocyanins and CVD risk factors.

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Title: The postprandial effect of anthocyanins on cardiovascular disease risk factors: A systematic literature review of high-fat meal challenge studies

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Abstract

Background & aim: Recurrent post-prandial metabolic imbalances are important contributing factors to development of cardiovascular disease (CVD). The aim of this study is to evaluate whether anthocyanin consumption attenuates the deleterious postprandial response of high-fat meals on CVD risk factors including blood pressure, vascular endothelial function, lipid profile and biomarkers related to oxidative stress, antioxidant status and immune response.

Methods: Five electronic databases were searched up to the period of 1st February 2020, yielding 13 eligible studies, including randomised or cross-over clinical trials (18-59 years of age), undertaken using the procedures outlined in the PRISMA statement (PROSPERO registration: CRD42019126265). Studies were assessed for potential bias using the revised Cochrane risk-of-bias tool for randomised trials

Results: Beneficial effects of anthocyanins were reported, in one or more biomarkers, for oxidative stress and antioxidant status in 6 out of 9 studies, and in 3 out of 6 studies for inflammatory response. Two positive results were found concerning attenuation of the post-prandial endothelial dysfunction, increased triacylglycerol and total cholesterol exerted by the high fat meal. Blood pressure and lipoproteins were the parameters with least beneficial results.

Conclusion: Despite some positive findings, there was heterogeneity for changes in some CVD risk factors between studies. The most promising results were for the attenuation of deleterious postprandial effects on oxidative stress and antioxidant status, triacylglycerol and total cholesterol concentrations, as well as for vascular endothelial function and inflammatory biomarkers. The post-prandial changes in blood pressure and lipoproteins were the parameters least affected by anthocyanin treatment. Further studies are required in order to advance in the knowledge of how post-prandial changes are associated with CVD incidence and progress, and to investigate how these imbalances can be attenuated by bioactive compounds such anthocyanins.

Keywords: anthocyanins, cardiovascular disease, postprandial, inflammation, oxidative stress

Declarations

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data used in this systematic review are presented in the referenced papers.

Code availability

Not applicable

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Introduction

Cardiovascular diseases (CVD) are still the number one cause of death globally, representing 31% of deaths in 2016. Most CVDs can be prevented by addressing and managing behavioural risk factors such as diet [1]. Several CVD risk factors are associated to the atherosclerotic process and other vascular dysfunctions closely linked to nutrition [2].

There is an emerging evidence that metabolic imbalances at the postprandial state, particularly after a high-energy meal rich in fat, are important contributing factors to development of CVD [3,4]. Overall, the underlying mechanism involves a sharp increase in triacylglycerol along with an aberrant production of pro-oxidant molecules leading to an oxidative stress state, which may impair vascular and endothelial functions, as well as mediate the onset of an inflammatory response, which further contributes to the generation of more free radicals, thus creating a deleterious vicious cycle [3–5]. Dietary fats comprise heterogeneous molecules with diverse structures, which affect diverse cell processes such as transcription regulation, cellular and organelle membrane structure and function, ion channel activity and electrophysiology. Responses vary depending on both the fatty acid composition of the food source, as well interactions with accompanying nutrients, the food matrix, and how it has been processed[6]. Modification of the type of dietary fat in a food or overall meal has been shown to result in postprandial effects on appetite [7], lipaemia and markers for inflammation and endothelial activity[8].

The high-fat meal (HFM) challenge is one way to investigate these imbalances promoted in a daily basis in Western diets [3]. Thus, this type of studies allows dietetic therapeutic opportunities to attenuate the harmful effects of aberrant production of pro-oxidant molecules. Nutrition plays a major role in enhancing endogenous antioxidant defences and

regulating the inflammatory state [9] and dietary components consumed alongside a high fat meal may be beneficial in blunting a harmful postprandial response [10].

Anthocyanins, a subclass of flavonoids, are emerging as a potential therapeutic option for CVD risk factors[11]. Anthocyanins are the largest class of water-soluble plant pigments, that are responsible for the blue, purple and red colour of many fruits and vegetables, such as blueberries, blackberries, red grapes, plums and eggplants [12]. The positive results of anthocyanins on CVD risk factors are related to its antioxidant and immunomodulatory effects, thereby attenuating the cooperative and synergistic deleterious effects of oxidative stress and inflammation in this condition [11,12]. In humans, anthocyanins intake has been associated with a lower risk of cardiovascular events [13,14], as well as studies using anthocyanins as a diet intervention have shown improvements in vascular function [15] and in biomarkers related to oxidative stress [16–19], antioxidant status [17,19–21], lipid profile [22–24] and inflammatory response [25,26] in both long-term and acute designs.

To date, there has been no review of the effect of such compounds in studies using a HFM challenge. In order to address this question, a systematic literature review was undertaken using the procedures outlined in the PRISMA statement [27] aiming to evaluate if concomitant consumption of anthocyanins with a HFM attenuates the deleterious postprandial response of parameters known to be CVD risk factors, including blood pressure, vascular endothelial function, lipid profile and biomarkers related to oxidative stress, antioxidant status and immune response.

Methods

Search strategy

A systematic literature review was undertaken using the procedures outlined in the PRISMA statement [27]. Five electronic databases were searched up to the period of 1st February 2020; Medline, Scopus, CINAHL, Web of Science and PubMed. Two researchers were responsible for studies selection, data extraction, quality assessment and synthesis. The search strategy was carried out in accordance with the database orientations using Boolean operators (OR and AND), parenthesis, quotation marks and asterisk. Quotation marks were used to search for exact terms or expressions; parenthesis were used to indicate a group of search terms or combine two groups of search terms enabling all possible combinations of sentences; asterisks were used to search all words derived of the precedent inflected part. The groups of search terms used were: "endothelium function" or "endothelium dysfunction" or "laser speckle" or "laser doppler" or "flow-mediated dilatation" or FMD or LSCI or "arterial stiffness" or "pulse wave velocity" or PWV or "lipid profile" or LDL or VLDL or ox-LDL or "oxidative stress" or "lipid peroxidation" or "blood pressure" or cytokines or inflammation or immune or inflammatory or chemokine or adhesion or malondialdehyde or isoprostanes or nitrite or nitrate or ENO* "nitric oxide") AND ("postprandial" or "postprandial" or "post prandial" or "meal challenge" or "challenge meal" or "test meal") AND anthocyanins. The study selection, quality assessment, data extraction and synthesis were conducted by two researchers independently and then reviewed by all authors. The review was registered with PROSPERO (CRD42019126265).

Selection criteria

Selection criteria were formed using the Population Intervention Comparison Outcome Study design **(PICOS)** format [27]. The criteria used to screen the titles and abstracts of literature returned through database searching (Table 1).

158 **Table 1. PICOS (participants, interventions, comparisons, outcomes, and study design)**
159 **criteria to define the research question**

Parameter	Inclusion criteria
Participants	Young adults (18-59 years of age)
Interventions	Dietary intervention with anthocyanins in whole food or purified extract
Comparators	A comparison group receiving a control intervention
Outcomes	CVD risk factors including blood pressure, lipid profile, vascular and endothelial function, biomarkers related to inflammation, oxidative stress and antioxidant status
Study design	Randomised or cross-over clinical trials with high fat meal challenge for all groups.

160

161 Only articles published in English were included. Exclusion criteria: mean age of
162 participants <18 or >59 years; no nutritional information of the HFM, placebo or dietary
163 intervention; other conditions besides the HFM challenge. Reference lists of included articles
164 were screened for further studies that may have been missed in initial database search.

165

166 ***Data extraction***

167 Two independent reviewers extracted data and cross checked results to ensure
168 consistency. The following data were extracted from each study and reported in a summary
169 table; year of publication, author(s), participant demographics, sample size, anthocyanin source
170 and dose, control used, test meal and study outcomes (Table 2). Authors were contacted if
171 further information was required.

172

173 ***Risk of bias assessment***

174 Studies included in this review were assessed for potential bias using the revised
175 Cochrane risk-of-bias tool for randomised trials [28]. Two researchers independently reviewed
176 each study, performing evaluation across five risk-of-bias domains, with each domain rated

either low risk, high risk or some concern of bias. The prescribed algorithm was used to determine domain ratings and overall risk-of-bias judgement for each study [28].

Results

Study selection

A total of 9135 articles returned through database searching. 1464 duplicates were removed and 7671 articles were excluded during title and abstract screening (Figure 1). The full-text of the remaining 29 articles were accessed and evaluated according the study selection criteria. Sixteen articles were excluded as they did not meet all criteria and the remaining 13 studies were eligible for the review.

C*haracteristics of studies included in review*

The characteristics of the 13 studies reviewed are summarised in Table 2. All studies included had a cross-over design with a wash-out period ranging from 4 to 28 days, of which four were double-blinded [29–32], seven were single-blinded [26,33–38] and two did not present blind strategies [39,40]. The mean age of subjects involved in included studies ranged from 20.2 to 50.9 years and five studies were conducted only in male subjects [29,32,33,37,40], while all other recruited men and women. The majority of studies were conducted on healthy individuals, except for one study on subjects with an atherosclerosis-prone phenotype [33], one on subjects with obesity and insulin resistance phenotype [35] and another one with participants with at least one CVD risk factor [39]. In relation to the dose of anthocyanins used in the intervention, six studies used a dose <100mg [26,30,31,33,36,39] and four studies used doses >100mg [29,32,37,38], while two studies used three different doses [35,40] and one study used two different doses [34] within both ranges. Overall, the dose ranged from 11.2 to 1530mg of

anthocyanins. The fat content within meal challenges were <40g in four studies [26,30,34,35] and >40g in nine studies [29,31–33,36–40]. Concerning fat content as % of energy, the meal challenges in six studies provided >50% of energy from fats[29,30,32,33,39,40], while seven studies provided <50% energy from fats[26,31,34–38]. The main type of fats within the challenge meals were derived from animal products with high content of saturated fats such as cream, sausages, cheese, fried potatoes, bacon, eggs and butter. There were no relevant source of omega-3 fatty acids included in any of the challenge meals. All studies used a macronutrient matched placebo in the control arm. In eleven studies [26,29–37,39], either a beverage, yoghurt

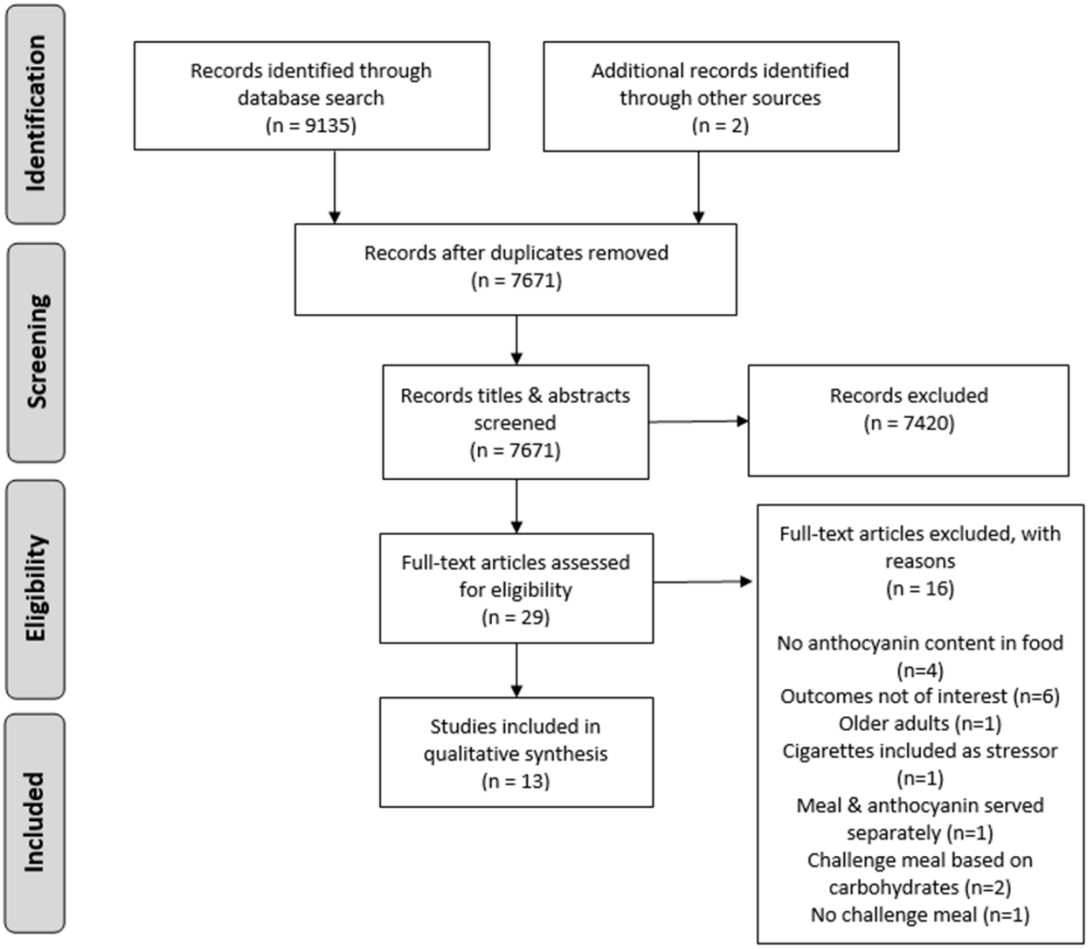

Figure 1: Flow diagram of the search and selection strategy.

213 or smoothie was used, while two studies[38,40] provided meals without incorporating
214 the freeze-dried source of anthocyanins. One study used water as an additional control
215 treatment[39], while another also matched the content of vitamin C in the placebo[32].
216
217 ***Risk of bias***
218 The overall risk of bias was judged as "low risk" for ten studies [26,29,30,32,34–36,38–
219 40], while three studies [31,33,37] were judged as having "some concern" due to ranking as
220 such in one or more risk domains (Table 3). Among the studies that were identified as having
221 "some concern" regarding risk of bias, two studies [33,37] had missing information on domain
222 1 (risk of bias arising from the randomization process) and one study [31] had missing
223 information on domain 3 (risk of bias due to missing outcome data) [28].
224
225 ***Outcomes***
226 The outcomes analysed in the included studies were blood pressure, lipid profile,
227 vascular and endothelial function, as well as biomarkers related to inflammation, oxidative
228 stress and antioxidant status (Table 2). The postprandial response of such outcomes were
229 analysed after the intake of the high-fat meal challenge, which means that a significant decrease
230 may actually mean an attenuation of an increase pattern. Three studies measured blood pressure
231 [29,38,39] before and after the HFMC, none of which found significant changes in systolic
232 blood pressure. One study found a reduction in diastolic blood pressure in the anthocyanins
233 intervention group ($p=0.0045$), while an absence of effect was observed in the other two arms
234 administering water or a matched anthocyanins-free placebo [39]. Vascular and endothelial
235 function were evaluated by three studies [29,38,39]. Alqurashi et al. [29] assessed endothelial
236 function in the brachial artery by flow-mediated dilatation (FMD) with a postprandial increase
237 of 1.4% versus 0.4% at 2h ($p=0.001$) and an increase of 0.8% versus a decrease of -0.3% at 6h

238 **Table 2**. **High-fat meal challenge studies analysing cardiovascular risk factors**

Reference	Population sample size	Diet intervention(s)	Control arm(s)	Test meal	Outcomes
Alqurashi et al. 2015, UK[29]	Healthy male adults (n=23), mean age 46yr ± 1.9, BMI 27.6kg/m2 ± 0.4	Açai smoothie: 150g frozen açai pulp, 50g banana, 155.1Kcal, 8.5g fat, 2.4g PTN, 17.2g CHO, 7.2g fibre, **493mg anthocyanins**	Colour and macronutrient matched smoothie	Meal+beverage: 869.7 Kcal (60.6% from fat), 58.5g fat, 74.4g CHO, 11.4g PTN	**Blood pressure:** ↔ **FMD**: ↑ 1.4%, p=0.001 at 2h and ↑ 0.8%, p<0.001 at 4h. **Plasma total oxidant capacity** (peroxide concentrations): ↓ area under the curve over 7h, p=0.02
Cerletti et al. 2014, Italy[39]	Adults (n=18: 9 females, 9 males), 36.9 ± 10.5yr, BMI 26.8 ±4.0. At least one CVD risk factor (overweight, hypertension, smoking, high serum cholesterol or TG levels	Red orange juice: **53.1mg anthocyanins**	a)Blonde orange juice; b) water	890 Kcal (52.6% from fat), 52g fat, 25g PTN, 81g CHO	**Augmentation index (vascular stiffness):** ↓ 2.18 ± 19.26 to -6.11 ± 11.90, p=0.0030 **Reactive hyperemia index (vascular reactivity):** ↔ **Blood pressure**: ↔ (diastolic blood pressure within group:↓ p=0.0045) **TAG:** ↔ (↓ within the intervention group, p=0.0131)
Edirisinghe et al. 2010, USA[26]	Healthy adults (n=24, 14 females, 10males) BMI 29.2 ±2.3, 50.9yrs ± 15	Milk based beverage + strawberry powder, **39.04mg anthocyanins**	Macronutrient matched placebo beverage	962.3 Kcal (28.1% from fat), 30g fat, 36g PTN, 135g CHO	**hsCRP:** ↓ 3.1 (SEM 0.1) vs 2.7 (SEM 0.5) mg/L, P=0.02 at 6h **IL-6:** ↓ 3.4 (SEM 0.5) vs 4.5 (SEM 0.5) pg/ml, P<0.05 at 6h. **TNF-α:** ↔ **IL-1β:** ↔
Miglio et al. 2012, Italy[30]	Healhy adults (n=14), 45yr ± 9, BMI 26.8kg/m^2 ± 2.2	a) Fruit juice (86% mix apple, grape, blueberry, pomegranate juices), **6.5mg anthocyanins** b) Fruit juice (63% mix of pineapple, blackcurrant and plum	Energy and sugar matched placebo, 66g CHO	1344 Kcal (54.2% from fat), 81g fat, 104g CHO, 52g PTN, 3.1g fibre	**Urinary FRAP**: ↑ 35%, p<0.01 **Plasma TRAP**: ↑ p<0.05 at 1h, ↑ 8%, p<0.001 at 2h, ↑ p<0.01 at 4h. **Plasma FRAP:** ↔ **Plasma uric acid**: ↓ p<0.05 at 8h **Plasma Thiols:** ↓ p<0.05 at 0.5, 1, 4 and 8h, ↓ p<0.01 **Ascorbic acid:** ↔

		juices), **16mg anthocyanins**			
Ono-Moore et al. 2016, USA[34]	Healthy adults (n=23, 18 females, 5 males), 30yr ± 3yr, BMI 21.9kg/m2 ± 0.4	Yoghurt + freeze dried blueberry powder: a) **87.9mg anthocyanins**; b) **154.5mg anthocyanins**	Macronutrient matched control yoghurt: 191 Kcal, 0.6g fat, 45.1g CHO, 1.2g PTN, 10g fibre	653 Kcal (40.0% from fat), 29g fat, 73.6g CHO, 24g PTN	**TAG:** ↔ **LDL-c:** ↔ **HDL-c:** ↔ **IL-8:** ↔ **IL-1β:** ↔ **TNF-α:** ↔
Park et al. 2016, USA[35]	Adults with obesity and insulin resistance phenotype (n=21, 16 females, 5 males), 39.8yr ± 13.8, BMI 40.2 ± 7.2	Freeze dried whole strawberry powder: a) **42.2mg anthocyanins**; b) **87.9mg**; c) **154.5mg**	Milk based colour and macronutrient matched beverage	967 Kcal (23.6% from fat), 25.4g fat, 146.2g CHO, 36.9g PTN, 12.3g fibre	**TAG:** ↔ **ORAC:** ↔ **IL-6:** ↔ **OxLDL-c**: ↓ –3.0 ± 0.8 U/L, $p<0.05$
Richter et al. 2017, USA[38]	Healthy adults (n=30, 13 females, 17 males), BMI 31 kg/m^2 ± 0.5, 28yr ± 2.0	Freeze dried strawberry powder: **163.41mg** anthocyanins (added to meal)	Strawberry flavoured powder (added to meal)	1004Kcal (44.8% from fat), 50g fat, 105g CHO, 32g PTN, 7g fibre	**Blood pressure:** ↔ **TAG:** ↔ **OxLDL-c:** ↔ **MDA:** ↔ **Augmentation index:** ↔ **Aortic stiffness (PWV):** ↔
Urquiaga et al. 2016, Chile[40]	Healthy adult males (n=9), 20.2yr (18.7-27.3), BMI 24.6 kg/m^2 (20.7-29.4)	Berry concentrate: a) added on beverage, **90mg anthocyanins**; b) added on burger and on beverage, **174.3mg anthocyanins**	Plain burger and water	527 Kcal (58.9% from fat), 48.7g PTN, 34.33g fat, 4.6g CHO	**TAG:** ↔ **MDA**: ↓ $p<0.05$ at all time points for intervention "b" and ↓ $p<0.05$ at 5 and 6h for intervention "a" **PTNcarbonyls:** ↓ $p<0.05$ at 2, 3, 4, 5 and 6h for intervention "b" and ↓ $p<0.05$ at 4 and 6h for intervention "a" **Plasma FRAP:** ↔ **Ascorbic acid:** ↔

Huang 2016, USA[36]	Healthy adults (n= 14, 9 males and 5 females), 25yrs ± 4, BMI 26kg/m^2 ± 2	Freeze dried strawberry added to a beverage, **49.02mg anthocyanins**	Macronutrients matched beverage: 41Kcal, 0.8g PTN, 0.1g fat, 9.1g CHO	841 Kcal (43.9% from fat), 41g fat, 96g CHO	**TAG:** ↔ **OxLDL-c:** ↔ **IL-6:** ↓ p=0.048 (intervention consumed before the meal) over 10h; ↔ (intervention consumed within and after the meal, trend p<0.1) over 10h
Kay & Holub 2002, Canada[37]	Healhy males(n=8), mean age 46.9 ±1.9), BMI 23.8kg/m^2 ± 0.8	Freeze dried wild-blueberry supplement: **1160mg anthocyanins**	Control supplement matched in CHO and energy	853 Kcal (49.3% from fat), 46.7 g fat, 75.2g CHO, 32.4g PTN, 4.5g fibre	**ORAC:** ↑ p<0.05 **Total antioxidant status**: ↑ 4.5%, p=0.05. **TAG:** ↔ **TC:** ↔ **LDL-c:** ↔ **HDL-c:** ↔
Peluso et al. 2011, Italy[31]	Healthy adults, (n=14, 12 males and 2 females), 45.1yrs ± 8.6, BMI 26.8 kg/m^2 ± 2.2	Blackcurrant, plum and pineapple beverage: **16mg anthocyanins**	Placebo beverage devoid of antioxidant activity	Meal+beverage: 1344 Kcal (30.0% from fat), 184g CHO, 44.8g fat, 49g PTN	**TAG:** ↔ **TC:** ↔ [prevented a significant increase (p<0.001) observed only at the control group over 8h] **IL-17:** ↓ p<0.05 at 4 and p<0.01 at 8h **IL-6:** ↓ 0.5h (p<0.01), 1h (P<0.05) and 2h (p<0.001) **TNF-a:** ↓ at multiple time points (p<0.01 at 1h, p<0.05 at 2 and 6h, p<0.001 at 4 and 8h)
Huebbe et al. 2011, Germany[33]	Adult with atherosclerosis prone phenotype (n=11), 37.4 yrs ±1.9, BMI 32.1 ±1.2	Blackcurrant based beverage (15% blackcurrant puree, 9% raspberry puree, 7% cherry puree, 39% red grape juice + banana puree): **11.2mg anthocyanins** (7.5mg delphinidin-3-glucoside, 7.5mg cyanidin-3-glucoside,	Macronutrient matched beverage: 1029Kcal, 63.8g fat, 6.0g PTN, 107.6g CHO, 1.8g fibre	Blackcurrant based beverage (added cream and sugar): 1029 Kcal (55.8% from fat), 63.8g fat, 6.0g PTN, 107.6g CHO, 1.8g fibre	**TAG:** ↔ (↓ trend, p=0.059) **LDL-c:** ↔ **HDL-c:** ↔ **TC:** ↔ **OxLDL-c:** ↔ **IL-1β:** ↔ **TNF-α:** ↔ **ORAC:** ↑ p<0.040 at 90min and p<0.02 at 120 min **Ascorbic acid:** ↑ 14 mmol/l, p<0.004

		0.8mg malvidin-3-glucoside)			
Polley et al. 2019, USA[32]	Healthy adults (22 yrs ± 3.0), BMI 25.5 ±3.4	Montmorency tart cherry concentrate: 1513.8mg anthocyanins	Macronutrient matched beverage +11mg of vitamin C: 166.5Kcal, CHO 39.4g; PTN 2.24g	Biscuit, sausage patty and butter: 920 Kcal (58.7% from fat), 60.0g fat, 22.2g PTN, 72g CHO,	**ORAC:** ↔ **FRAP:** ↔ **TG:** ↔

Abbreviations and symbols: CHO, carbohydrate; PTN, protein; FMD, flow-mediated dilatation; Kcal, kilocalories; TAG, triacylglycerol; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; OxLDL-c, oxidized low-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; FRAP, ferric reducing ability of plasma; TRAP, total radical-trapping antioxidant parameter; ORAC: oxygen radical absorbance capacity; ↔, no significant changes; ↑, significant increase; ↓, significant decrease

($p<0.001$), comparing the intervention with the placebo group, respectively. Cerletti et al. [39] assessed vascular stiffness through the augmentation index (AI) and vascular reactivity through the reactive hyperemia index (RHI). The latter did not present significant changes, but there was a significant decrease (2.18 ± 19.26 to -6.11 ± 11.90, $p=0.0030$) in the AI 3h after the meal only in the anthocyanins intervention arm [39]. Richter et al. [38] investigated AI and augmentation pressure through pulse wave analysis and the aortic stiffness assessed by carotid-femoral pulse wave velocity (PWV). None of the parameters were significantly different between intervention and control arms [38].

Regarding the lipid profile, ten studies evaluated triacylglycerol (TAG) [31–40], of which one study found a higher decrease ($p=0.0131$) in the intervention group [39] and other study found a trend($p=0.059$) of a decrease 60 minutes after ingestion of the HFMC [33]. Total cholesterol (TC) was evaluated by five studies [31,33,34,37,39] and two studies found significant changes. Cerltetti et al. [39] found a reduction ($p=0.0339$) only in the anthocyanin intervention arm [39], while Peluso et al. [31] found that the anthocyanins prevented an increase in the intervention group, therefore a significant increase was only observed in the control group over 8h ($p<0.001$) [31]. The studies that measured HDL-c [33,34,37] and LDL-c [33,34,37] did not find any significant changes.

Among inflammatory markers, six studies evaluated IL-6 [26,31,33–36] concentrations, of which three [26,31,36] reported significant changes. In one study [26] the anthocyanin intervention was able to attenuate an increase in IL-6 response six hours after the HFMC compared to the placebo group [3.4 (SEM 0.5) versus 4.5 (SEM 0.5) pg/ml, $P<0.05$]. Similarly, Peluso et al. [31] found a significant attenuation in postprandial IL-6 concentration at 0.5 ($p<0.01$), 1 ($P<0.05$) and 2h ($p<0.001$) time points [31]. Another study [36] found a trend to attenuate such response in two groups (consuming the anthocyanins intervention within or after the HFMC) and a significant decrease in the group consuming the anthocyanins

275 **Table 3 – Overall risk of bias of included studies**

	Alqurashi et al, 2016	Cerletti et al., 2016	Edirisinghe et al., 2011	Miglio et al., 2014	Ono-Moore et al., 2016	Park et al., 2016	Richter et al., 2017	Urquiaga et al, 2017	Huang et al., 2016	Kay & Holub, 2002	Peluso et al. 2011	Huebbe et al., 2016	Polley et al., 2019
Domain 1: Risk of bias arising from the randomisation process	+	+	+	+	+	+	+	+	+	?	+	?	+
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	+	+	+	+	+	+	+	+	+	+	+	+	+
Domain 3: Risk of bias due to missing outcome data	+	+	+	+	+	+	+	+	+	+	?	+	+
Domain 4: Risk of bias in measurement of the outcome	+	+	+	+	+	+	+	+	+	+	+	+	+
Domain 5: Risk of bias in selection of the reported result	+	+	+	+	+	+	+	+	+	+	+	+	+
Overall risk of bias	+	+	+	+	+	+	+	+	+	?	?	?	+

276 Symbols: + low risk; ? some concern

intervention before the meal (p=0.048). The cytokine TNF-α was evaluated by four studies [26,31,33,34] and with one study [31] finding a significant result preventing a postprandial rise of TNF-α concentrations at multiple time points ($p<0.01$ at 1h, $p<0.05$ at 2 and 6h, $p<0.001$ at 4 and 8h).

There were no significant changes in IL-1β concentrations between treatments cross the three studies evaluated this cytokine [26,33,34]. Only one study [26] evaluated hsCRP concentrations before and after the HFMC presenting a significant lower concentration compared to placebo [3.1 (SEM 0.1) versus 2.7 (SEM 0.5) mg/L, P=0.02]. Still, there was one study that measured IL-8 concentration finding not significant results [34] and one study that evaluate Il-17 which found a significant postprandial reduction at 4($p<0.05$) and 8h($p<0.001$) time points [31].

A large variety of oxidative stress and antioxidant status biomarkers were measured by nine studies [29,30,32,33,35–38,40] included in this review. Four studies [33,35,36,38] evaluated OxLDL-c concentrations; however, only one study [35] found a significant reduction (–3.0 ± 0.8 U/L, $p<0.05$) in the intervention arm compared to placebo. Plasma malondialdehyde (MDA) concentration was measured in two studies [38,40] in which one found that the anthocyanins interventions arms were able to prevent postprandial MDA accumulation ($p<0.05$ at multiple time points), and the mean value of the area under the curve of was reduced compared to placebo [40]. This same study also found a reduction ($p<0.05$ at multiple time points for both anthocyanins interventions) in plasma protein carbonyls and an increase in the DPPH (2,2-diphenyl-1-picrylhydrazyl) plasma antioxidant capacity [40]. The ferric reducing ability of plasma (FRAP) assay was used to examine antioxidant capacity in was evaluated by three studies [30,32,40], but no significant effects of anthocyanin intervention were detected. However, Miglio et al. [30] found a 35% increase in the urinary excretion of antioxidants as indicated by raised urinary FRAP ($P<0.01$). This same study found an increase ($p<0.05$ at 1h,

$p<0.001$ at 2h and $p<0.01$ at 4h) in plasma total radical-trapping antioxidant parameter (TRAP), as well as a significant attenuation in the increase of endogenous antioxidants thiols and uric acid (UA) ($p<0.05$ at 8h). Plasma ascorbic acid (vitamin C) was measured in four studies [30,33,37,40], of which one study [33] found an increase in the anthocyanin intervention arm (+14 mmol/l, $p<0.004$) compared to the placebo. The oxygen radical absorbance capacity (ORAC) of plasma/serum was evaluated, before and after the HFMC, in five studies [32,33,35,37,40], of which two found significant changes. In one study [33], the intervention was able to prevent the postprandial decrease in the ORAC of plasma at 90 and 120 min following the HFM challenge ($p<0.040$ and $p<0.02$, respectively), while another study [37] found a significant increase in serum ORAC 1h after the HFMC in intervention group when compared to the control ($p<0.05$). Furthermore, this same study found a significant increase in the total antioxidant status (TAS) assay (+4.5%, $p=0.05$). Lastly, one study [29] measured the total oxidant capacity in plasma by assessing the total peroxide concentrations, and found a significantly lower incremental area under the curve in the intervention group($p = 0.02$).

Discussion

The results of studies included in this systematic literature review indicate that the postprandial state, after exposure to a high fat meal, may provide a useful context to investigate acute metabolic changes, from well known lipid responses to complex phenolic compound signalling pathways, that contribute to the development of CVD. A wide range of risk factors such as blood pressure, lipid profile, vascular and endothelial function, as well as biomarkers related to inflammation, oxidative stress and antioxidant status were included as outcomes in the acute studies in the review.

Despite the lack of positive results in blood pressure, of which only study found a significant decrease in diastolic blood pressure [39], vascular and endothelial parameters

showed more positive results. It is more likely that such parameters will respond in a higher magnitude than blood pressure in acute studies, due to the excess postprandial production of pro-oxidant molecules following the HFMC. This may in turn inactivate endothelial dependent factors, in particular nitric oxide, leading to impaired vasodilation and the onset of an inflammatory response, which further leads to the generation of more free radicals [10,41]. In this matter, açai consumption was associated with improvements in endothelial vascular function, measured by FMD, in healthy overweight man, which was also followed by an increase in total oxidant capacity in plasma, assessed as a measure of total peroxide concentrations [29]. The significant improvement in FMD found in this study[29] was 1% higher than in controls, a magnitude of effect that has been shown in a meta-analysis to be associated with an overall 8 % reduction in CVD risk (RR= 0.92; 95%CI: 0.88; 0.95) for each percentage increase [42] . Flow-mediated dilatation is a non-invasive measurement of endothelium function that has been associated with CVD risk prediction[42,43]. Another study found a decrease in arterial stiffness, measured by AI, after consumption of blood orange juice anthocyanins in individual with at least one CVD risk factor (overweight, hypertension, smoking, high serum cholesterol or triacylglycerol levels) [39].

A recent systematic review evaluated the postprandial inflammatory response to HFM challenge, in which IL-6 was stated as the inflammatory marker with the stronger response to this stress [44]. IL-6 has a pleiotropic nature showing both anti and pro-inflammatory roles and regulating a plethora of immune and metabolic responses, however a high concentration of this cytokine has been associated with CVD and mortality [45,46]. Still, IL-6 has a high expression on vascular endothelium and the pharmacological inhibition of IL-6 improves endothelial function [47]. The inhibitory effect on postprandial IL-6 concentrations found within the studies added in this review demonstrates a potential therapeutic effect of anthocyanins for CVD [26,31,36]. One possible mechanism that anthocyanins may exert this effect is through

decreasing the activity of the NF-κB pathway, which is a transcription factor responsible for triggering and regulating inflammatory processes, leading to the expression of pro-inflammatory cytokines and enzymes [11,48]. Concerning the clinical significance of the magnitude of effects reported in the studies that observed benefits associated with anthocyanin intake, the significant changes of between 0.34 and 0.90 pg/mL represent changes from baseline of >2 SD[26,36] and >3 SD[31]. These results are clinically meaningful considering the predictive roles of IL-6 concentration in CVD risk. Hazard ratios of 1.80 are reported according to each 1-SD increase in IL-6 for risk of first-ever cerebrovascular events in individuals with vascular risk factors without any pre-existing cardiovascular disease[49]. Further, a positive predictive value of 100% is reported for coronary artery disease when IL-6 concentrations exceed 1.0 pg/mL in patients who have an intermediate cardiovascular risk profile and chest pain[50]. In a meta-analysis of 17 prospective studies investigating clinical coronary outcomes (i.e., myocardial infarction or coronary death), an odds ratio of 1.61 (95% CI 1.42–1.83) was found per 2 SD increase in baseline IL-6 [51]. Another meta-analysis of 17 studies comprising 288,738 healthy individuals reported a significantly higher IL-6 concentration in CVD cases compared to non-CVD controls (standardized mean difference [95% CI]) of 0.14 [0.09, 0.20]/mean difference of 0.36 [0.28, 0.44] pg/mL) [52]. These significant changes in IL-6 concentration were found only in studies which the mean BMI of participants were >25kg/m^2. Overweight and obesity are an independent risk factor for CVD, as well as are associated with a low-grade continuous inflammation with high implications in the atherosclerotic process. The possibility of regulating this persistent not resolved inflammatory state can be crucial in attenuating the progress of the atherosclerosis disease, especially in the early stages. This is the same scenario, in which the only study [26] that evaluated CRP found a significant reduction of 0.4 (SD 0.1) mg/L in a study population with a mean BMI >29kg/m^2. This effect reduced the hsCRP concentration in the intervention arm to

values <3.0 mg/L, which is considered a clinical threshold for many cardiovascular conditions, including a reduced hospitalisation rate for heart failure in subjects with stable coronary heart disease[53]. CRP is also associated with CVD and mortality [54,55], and has been implicated in endothelial dysfunction in *in vitro* and *in vivo* studies [56,57]. On the other hand, the cytokines IL-1β and TNF-α not appear to transiently and/or robustly change in the postprandial period after a HFMC, thus a decrease in concentration of these molecules is not likely to occur with acute diet interventions [44]. In the present review, the three studies that evaluate IL-1β were conducted in healthy normal weight [34], healthy overweight [26] and overweight/obese adults with atherosclerosis prone phenotype [33], however none of them found significant changes. TNF-α also plays a pleiotropic and major role in CVD, but high concentrations have been associated with deleterious effects mainly through vascular dysfunction and atherogenesis by many mechanisms such as regulation of the vascular permeability, disruption of the endothelial barrier, degradation of glycocalyx, increased production of ROS and decreasing NO bioavailability and increase its removal [58,59]. In line with the review by Emerson et al. (2017) [44], the studies included in our review found inconsistent changes of TNF-α concentrations after the HFMC, i.e. two studies found a decrease [33,34], one an increase [31] and other study reported no changes [26]. The study that had a postprandial increase in TNF-α concentration was the only one that found a significant lowering effect with the diet intervention with anthocyanins [31]. Another relevant finding in this same study was the inhibitory effect of on postprandial increase of IL-17, a cytokine with highly pro-inflammatory properties that are also associated with CVD, especially with cardiovascular events such as stroke and myocardial infarction [60]. There is accumulating evidence that IL-17 it is involved in the pathogenesis of cardiovascular diseases by amplifying the inflammation induced by other cytokines in synergistic interactions [61]. This cytokine is also positively correlated with

OxLDL-c, a molecule with a crucial role in the oxidative stress mediated atherosclerosis development.

OxLDL-c is a key factor in the initiation and progression of atherosclerosis and contributes to endothelial dysfunction and plaque destabilization through various mechanisms [62]. Among the four studies that measured postprandial concentration of Ox-LDL-c, the only study that found a significant reduction was conducted in participants with an obese and insulin resistant phenotype [35]. Several other oxidative stress and antioxidant status biomarkers were investigated within the added studies in this review, showing the most promising results in relation to the effects of anthocyanin intervention on parameters following the HFM challenge. MDA is an end product of lipid peroxidation, the radical-initiated oxidative decomposition of poly-unsaturated fatty acids [63]. Urquiaga et al. [40] found a reduction in postprandial concentration of MDA at multiple time points following two different anthocyanin interventions (i.e. added to food or beverage) using a berry concentrate. This same study also found a reduction in plasma protein carbonyls and an increase in the DPPH (2,2-diphenyl-1-picrylhydrazyl) plasma antioxidant capacity [40]. Protein carbonylation is one of the most harmful irreversible oxidative protein modifications, and is considered a major hallmark of oxidative stress-related disorders [64]. The DPPH assay is a method that is widely used to test the ability of compounds to act as free radical scavengers or hydrogen donors, and therefore can be used to evaluate antioxidant activity. Another anti-oxidant assay, the FRAP, (based on single electron transfer reaction to evaluate the antioxidant effect of nonenzymatic defense in biological fluids) was measured in three studies that reported no significant effect of the anthocyanin intervention in plasma [30,32,40]. However, one of these studies found a 35% increase in the urinary excretion of antioxidants ($P<0.01$), which was followed by an increase TRAP and an attenuation in the increase of endogenous antioxidants thiols and UA. TRAP differs from FRAP as an assay that measures the ability of antioxidants to buffer a reaction

probe against peroxidation, and it's determined by measuring the length of time that oxygen uptake is inhibited [65]. Results from both FRAP and TRAP methods have to be carefully interpreted considering that FRAP has low specificity in measuring the antioxidant activity of many important antioxidants such as ascorbic acid, glutathione and albumin, and that TRAP does not necessarily provide a reliable or sensitive measure of the ability of plasma to interfere with lipid peroxidation[66]. UA levels are related to oxidative status, especially antioxidant capacity and it is well known that high plasma UA levels are strongly associated CVD [67]. Taken together, the positive results of these three different oxidative stress biomarkers show a relevant anti-oxidant signalling effect of anthocyanins in these studies conducted in healthy adults [30,40]. Another relevant biomarker of antioxidant status is vitamin C, which is a readily water-soluble and not storable in tissues. Therefore, vitamin C is a good biomarker for short-term studies [68]. One study added in this review found an increase in plasma vitamin C [33]; however, even though the placebo was matched in macronutrients and energy, only the diet intervention had a relevant content of vitamin C (122.3 vs 0.3mg). Thus, it is unlikely that the plasma concentration of vitamin C was increased due to the anthocyanins. The ORAC of plasma/serum, which was evaluated in five studies in this review, appears to be a controversial method in regard to its application for *in vivo* studies, especially after the withdraw of the ORAC food database by the USDA in 2010. There is still debate regarding the absorbance and breakdown of polyphenols, such as flavonoids and subclasses, into smaller phenolics compounds with signalling, anti-inflammatory and anti-oxidant properties [41]. Nevertheless, two studies found an increase in plasma ORAC following 60 [33], 90 and 120 [37] minutes after the HFMC, and one study also found a significant increase in TAS [37], another non-specific assay that assess the overall antioxidant status of a sample.

The post-prandial response in the lipid profile, when compared to fasting lipids, can represent a different and even independent risk factor for CVD [4,23]. The transient lipid and

lipoprotein accumulation that occurs in the circulation after a high-fat meal represents the individual capacity to metabolize an acute fat input [69] and has been associated as an important risk factor in atherosclerosis development [5]. The most relevant postprandial lipid marker it is triacylglycerol. It is the lipid with the greatest post-prandial difference from fasting lipid markers [23], and has been associated as an independent risk factor for cardiovascular events [24]. The results found in our review support these statements, as significant changes were only found in triacylglycerol [33,39] concentrations and total cholesterol [31,39], which has a composition of 20% triacylglycerol in its formula.

The choice of placebo in this type of acute study design is important in order to identify whether it is indeed the anthocyanin effect that is observed in the results, or whether there are other nutrients or food constituents that may be affecting the study outcomes. All studies included in this review included a placebo that was matched in macronutrient and fibre content, however other nutrients such as vitamin C and other flavonoids that may also play a role in postprandial oxidative stress and inflammation are not commonly considered. It is complex, and often impossible, to provide a perfectly matched placebo in food studies of this type, therefore results from studies that use different placebos should be carefully scrutinized.

The most notable challenge and limitation of this study was to address a wide range of CVDs biomarkers assessed in this type of acute clinical trial. Overall, the comparison among studies had a relevant clinical importance of these metabolic, immune and physiological factors that has a synergistic impact on CVDs, however there was a variety of parameters addressed with different methods within each of such factors. This made the possibility of meta-analysis or other pooled analyses unfeasible, however it not impeded results to be compared narratively. Another source of heterogeneity in these studies may have resulted from variability in the HMF challenges regarding their macronutrient and energy content, particularly the types of fat, as well as the format in which the meals were delivered. Accumulating evidence suggests that the

health effects of dietary fats vary[6]. Substitution of saturated fatty acids from butterfat with omega-6 PUFA resulted in a decreased postprandial lipaemia, as well as reduced concentrations of IL-6, TNF-α, soluble TNF-α receptors, and soluble vascular cell adhesion molecule-1 in overweight men[8]. However, all studies included in this review used animal products as the main source of fat, and there were two main types of meals: 1) beverages that were enriched with cream and/or milk; or 2) mixed meals including animal products with a high content of saturated fat such as sausages, cheese, butter, eggs and bacon. A standardized meal for these type of studies would be preferred but may be difficult to implement because of cultural diversity in cuisine and dietary patterns. Despite that all included studies were conducted in older adults (mean age ranging from 20.2 to 46.9y), there were slightly differences in mean BMI with two studies having participants with BMI<25kg/m^2 [34,40] six with BMI from 25-30kg/m^2 [26,29–31,36,39] and three with BMI>30kg/m^2 [33,35,38] .Only three studies were not conducted in healthy adults, of which participants were not considered healthy due to lipidaemia [33], insulin-resistance phenotype [35] or with at least one CVD risk factor [39]. However, studies conducted in participants with major chronic diseases with implication on CVDs, such as diabetes and hypertension, were not included in this review. Another feature in the design of this type of study is that tests are conducted over multiple time following the HFM challenge, thereby raising a concern that the number of false positive findings may be inflated. For this reason, the interpretation of results found in only one or a few time points, and that are not sustained, has to be interpreted with caution. Still, parameters that have been used in the studies to investigate oxidative stress and antioxidant status represent a wide range of analytical methods, and there is no formal mechanism to establish consensus regarding the optimal biomarkers for such nutritional studies [68,70].

Conclusion

Despite some positive findings, there was heterogeneity for changes in some CVD risk factors between studies. The most promising results were for the attenuation of deleterious postprandial effects on oxidative stress and antioxidant status, triacylglycerol and total cholesterol concentrations, as well as for vascular endothelial function and inflammatory biomarkers. The post-prandial changes in blood pressure and lipoproteins were the parameters least affected by anthocyanin treatment. Further studies are required in order to advance in the knowledge of how post-prandial changes are associated with CVD incidence and progress, and to investigate how these imbalances can be attenuated by bioactive compounds such anthocyanins.

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