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Berry anthocyanin intake and cardiovascular health

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ABSTRACT

Over half of all cardiovascular (CV) events could be prevented by improved diet. This is reflected in government targets for fruit/vegetable intake, yet these are variable across the world (UK: 5-a-day; USA: 9-a-day), do not identify specific fruits/vegetables, and prove hard to achieve. Mounting evidence from prospective studies, supported by recent randomised controlled trials suggest that the benefits of fruits/vegetables may be due to bioactive substances called flavonoids. Specifically one sub-class of flavonoids, the anthocyanins, responsible for the red/blue hue, are receiving growing attention. Although promising data is emerging from cohort studies, and cell/animal studies, proof of efficacy from longer-term randomised controlled trials, and an understanding of the importance of differential metabolism in relation to clinical efficacy are distinctly lacking. Diet related ill-health are among the leading priorities of our time and simple dietary change, including incorporating a few portions of anthocyanin-rich fruit into our diet could have a significant impact at a public health level.

Background

In an era where preventive medicine is becoming increasingly important, due to an expanding ageing population and increasing prevalence of obesity, an optimised diet is central for improving CV health. A sub-optimal diet is currently the leading risk factor for both disability and death worldwide (Lim et al., 2012). Worldwide, chronic diseases have been projected to costs $17 trillion of cumulative economic loss from 2011 to 2030 including healthcare costs and reduced productivity (Bloom et al., 2011). In the UK, the largest economic burden to the National Health Service (NHS) relates to a poor diet, with food-related ill-health costing the NHS £5.8 million per year (Scarborough et al., 2011). Although improved treatments have resulted in significant declines in incidence and mortality rates, cardiovascular disease (CVD) remains a considerable burden, in terms of ill-health, mortality and associated costs. In 2012–13 alone the NHS in England spent £6.8 billion on CVD, predominantly in secondary care and costs are set to rise further (Bhatnagar et al., 2015). Unless there are continued improvements in prevention past gains will not be sustained. Although >50% of contemporary public health problems could be prevented through dietary change (Ezzati and Riboli, 2013) it is still unclear what constitutes a healthy diet for different individuals: what are the key constituents in fruits/vegetables for optimal health, what are their physiological and molecular mechanisms of action, what is their metabolic fate, how extensive is inter-individual variability in metabolism and does this variability impact on CV health?

Fruit and CV health

Data suggest that diets rich in fruits are the third most important modifiable factor for reducing global rates of non-communicable diseases (Ezzati and Riboli, 2013). In a recent prospective study of over half a million Chinese adults, daily fruit intake was associated with 4 mmHg lower systolic blood pressure (BP), 0.5 mmol/L lower blood glucose levels and a 34% and 40% lower risk of incident major coronary events and CV mortality respectively (Du et al., 2016). If we assume that there is a causal association, the authors calculate that 16% of deaths from CV could be attributed to low fruit intake and >560,000 deaths from CV each year (including 200,000 before age 70), could be prevented if fruit was consumed daily (Du et al., 2016). There was evidence of a dose-response relationship (Du et al., 2016) and the inverse associations could be causal given that fruit is a rich source of a number of bioactive constituents including flavonoids (Hartley et al., 2013; Hooper et al., 2008; Liu, 2003). Growing evidence highlights the beneficial effect of flavonoids such as anthocyanins as likely key constituents in lowering CVD risk and the focus of this review relates only to the anthocyanin sub-class.

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Dietary flavonoids and the anthocyanin sub-class

Dietary flavonoids represent a diverse range of polyphenolic compounds that occur naturally in plant foods. Their structural complexity has led to their sub-classification as flavonols, flavones, flavanones, flavan-3-ols (and their oligomers, proanthocyanidins), isoflavones, and anthocyanins (Hooper et al., 2008). They are present in significant amounts in many commonly consumed fruits, vegetables, and beverages.

Anthocyanins are water-soluble plant pigments that are responsible for the red/blue colouration in plants, flowers, seeds and fruits (Smeriglio et al., 2016) and are predominantly found in the skin of fruit, except for berries where they are present in both the skin and flesh (Manach et al., 2004). They are present in a number of foods commonly consumed in the habitual diet with red, blue or purple fruits and vegetables containing concentrations ranging from 0.1% to up to 1.0% of dry weight (Pojer et al., 2013). Fruits such as berries, blackcurrants, red grapes, plums and cherries are rich dietary sources, as are fruit-derived products like red wine and juices; they are also present to a more limited extent in some vegetables such as radishes (Table 1, USDA, 2014; Perez-Jimenez et al., 2010). Although there is wide variability in levels depending on growing and storage conditions, two servings of fresh blueberries contain, on average, 240 mg, and two glasses of red wine 56 mg (Table 1).

Anthocyanins are glycosides of anthocyanidins and it is currently thought that only the following six are of relevance to the human diet (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin). In plants they play a key role in pollination and by absorbing light, protect plants from ultra-violet (UV)-induced damage (Castañeda-Ovando et al., 2009). Habitual dietary intake of anthocyanins is variable and in the US estimated daily intake was on average 12.5 mg/day (Wu et al., 2006), while in Europe mean intakes for men ranged from 19.8 (the Netherlands) to 64.9 mg/day (Italy), and for women, from 18.4 (Spain) to 44.1 mg/day (Italy) (Zamora-Ros et al., 2011). Fruits are the most common dietary source, and in the EU were responsible for up 61% of habitual intake, predominantly from apples, pears, berries, stone fruit and grapes. Wine contributed 14.4–24.5% of intake across Europe (contributing 24.5% in both Southern and Northern regions) (Zamora-Ros et al., 2011). In the US the main dietary sources are strawberries and blueberries (Cassidy et al., 2011). Although intakes are variable, given their presence in commonly consumed fruits the potential to increase intake is readily achievable. Just consuming 1–2 portions of either strawberries, raspberries or blueberries would significantly increase intakes of anthocyanins to levels that have been reported to be associated with a reduction in risk of CVD (Bhagwat et al., 2013; Cassidy et al., 2011, 2013; Jennings et al., 2012; McCullough et al., 2012).

Table 1
Common dietary Sources of Anthocyanins.

	mg/100 g[a]	Serving size	mg/serving
Blueberries	163.3	1/2 cup	120.8
Blackberries	100.6	1/2 cup	70.4
Plums	56.0	1 medium	37.0
Red grapes	48.0	1/2 cup	36.5
Raspberries	48.6	1/2 cup	30.2
Red wine	19.3	5 oz	28.3
Cherries	32.0	1/2 cup	22.4
Strawberries	27.0	1/2 cup	20.5
Radishes	63.1	2 medium	5.7

[a] mg/100 g based on USDA Database for the Flavonoid Content of Selected Foods, Release 3.1 (2014).

Population-based studies

A number of prospective cohort studies and cross-sectional studies have examined the associations between habitual anthocyanin intakes and cardiovascular disease (CVD) outcomes or biomarkers of CVD risk, predominantly based in US populations (Table 2). Coronary heart disease (CHD) and non-fatal myocardial infarction (MI) were examined in five studies, with evidence in four to suggest that increased habitual anthocyanin intake is significantly associated with a reduction in risk of CHD by 12–32% in multivariate analyses (Cassidy et al. 2013, 2016; McCullough et al., 2012; Mink et al., 2007) (Table 2). The magnitude of the protective effect of increased anthocyanin intake was smaller in the older women and men (12–21%) compared to a study which focused on younger and middle-aged women where a 32% reduction in risk was observed comparing extremes of anthocyanin intake. Median intakes were 12 mg per day in these women, and when extreme deciles of intake were compared those in the top decile had a 47% reduction in risk of MI, suggesting a continual dose-response at higher levels of intake (Cassidy et al., 2013); for every 15 mg increase in anthocyanin intake, the relative risk of MI decreased by 17% in the multivariate model (Cassidy et al., 2013). The relationship between anthocyanin intake and CVD mortality was also examined in several studies, with one study showing no association (Mursu et al., 2008), while two others observed 9–14% reductions in risk comparing higher with lower intake (McCullough et al., 2012; Mink et al., 2007). The impact of increased anthocyanin intake on stroke has to date been examined in five studies, and although there was long-term follow-up, there is currently no evidence for a protective effect (Cassidy et al., 2012, 2016; McCullough et al., 2012; Mink et al., 2007; Mursu et al., 2008) (Table 2).

In relation to CV risk biomarkers, prospective studies and cross-sectional data provide mechanistic support for the observed decrease in CHD risk with increased anthocyanin intakes, with evidence that higher intakes improve arterial stiffness (assessed by pulse wave velocity) and blood pressure (Cassidy et al., 2011; Jennings et al., 2012). The magnitude of the associations observed for systolic blood pressure (−4 mmHg decrease with higher intake) were similar to those previously reported for stopping smoking and 2 fold higher than that observed following a small (1.4 portion) increase in fruit/vegetable intake (Jennings et al., 2012). The available data on the effects on inflammatory biomarkers are equivocal (Table 2, Chun et al., 2008; Jennings et al., 2014; Landberg et al., 2011) although more recent work, using a combined inflammatory score suggests that reduced inflammation may be a key pathway (Cassidy et al., 2015); recent prospective data also support the importance of weight maintenance (Bertoia et al., 2016). Interestingly the greatest reduction in hypertension was observed in the younger/middle-aged women, supportive evidence for the observed reduction in risk of MI in this age group (Cassidy et al., 2011, 2013). Higher habitual anthocyanin intakes (35 mg, half a portion of berries), resulted in a 0.7 mIU/L reduction in insulin levels (Jennings et al., 2014) similar to the effects of a low-fat diet (Shikany et al., 2011) or 1hr/day walking (Fung et al., 2000). The magnitude of associations are clinically relevant and of significant public health importance. However, future research should focus on identifying and validating panels of anthocyanin metabolites that reflect intake and subsequent metabolism so that associations of bioavailable anthocyanins (and inter-individual variability) can be assessed in future prospective cohort studies.

Randomised controlled trials (RCTs)

To date, very few RCTs have examined the impact of