The role of polyphenols in modern nutrition

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Abstract
Polyphenols are found in plant-based foods and beverages, notably apples, berries, citrus fruit, plums, broccoli, cocoa, tea and coffee and many others. There is substantial epidemiological evidence that a diet high in polyphenol-rich fruit, vegetables, cocoa and beverages protects against developing cardiovascular disease and type 2 diabetes. The absorption and metabolism of these compounds have been well described and, for many, the gut microbiota play a critical role in absorption; taking into consideration the parent compound and the metabolites from colon bacteria catabolism, more than 80% of a dose can be absorbed and ultimately excreted in the urine. Common polyphenols in the diet are flavanols (cocoa, tea, apples, broad beans), flavanones (hesperidin in citrus fruit), hydroxycinnamates (coffee, many fruits), flavonols (quercetin in onions, apples and tea) and anthocyanins (berries). Many intervention studies, mechanistic in vitro data and epidemiological studies support a role for polyphenols against the development of chronic diseases. For example, flavanols decrease endothelial dysfunction, lower blood pressure and cholesterol, and modulate energy metabolism. Coffee and tea both reduce the risk of developing type 2 diabetes, through action of their constituent polyphenols. Despite extensive research, the exact mechanisms of action of polyphenols in the human body have not been decisively proven, but there is strong evidence that some targets such as nitric oxide metabolism, carbohydrate digestion and oxidative enzymes are important for health benefits. Consumption of polyphenols as healthy dietary components is consistent with the advice to eat five or more portions of fruit and vegetables per day, but it is currently difficult to recommend what ‘doses’ of specific polyphenols should be consumed to derive maximum benefit.

Keywords: cardiovascular disease, coffee, flavonoids, fruit, tea, type 2 diabetes

Introduction
Modern nutrition is a multidisciplinary subject and draws from epidemiology, biochemistry, chemistry, behavioural science, biology, food science and medicine. It is necessary for human beings to consume food throughout their life, and so any biological effects will occur every day and have the potential to accumulate over a lifetime. Food choice, food availability, genetics, calories consumed and energy expenditure are additional factors which combine to make the subject of nutrition treacherous for the scientist hoping to develop hypotheses and prove theories. Biochemistry underlies all nutritional interactions, and understanding the pathways of metabolism, enzyme action and cellular regulation are essential for understanding how diet interacts with the body to affect health. Without this understanding, nutrition is a black box where scientific progress would be impossible. Nutrients comprise macronutrients (carbohydrate, fat and protein),
which are digested and stored or used in the body, the micronutrients (vitamins and minerals), which are stored or temporarily retained in the body and are essential for facilitating basic biochemical processes, and the numerous other compounds that are not stored in the body and do not contribute directly to basic biochemical processes but which fine-tune cells and protect against stress, helping to improve long-term health in many different ways. Polyphenols belong to the latter and are a diverse group of molecules that are consumed in all diets ( Scalbert & Williamson 2000). They originate only from plant-based foods and have been termed non-nutrients, plant secondary metabolites, phytonutrients, ‘antioxidants’, dietary bioactives and protective factors. Although there are a large number of chemical types, fortunately the number of polyphenols which are important in the diet is much smaller (Hertog et al. 1995).

**What are polyphenols? Nomenclature, classifications and occurrence in foods**

‘Polyphenol’ is not a strict chemical term. Today, it is used to refer to flavonoids, tannins and phenolic acids and their various chemically modified or polymerised derivatives. The main classes of polyphenols in the UK diet are flavanols (including the catechins and tannins from tea), flavanones (mostly hesperidin from citrus fruit), flavonols (including quercetin from tea, apples and onions), hydroxycinnamic acids (phenolic acids, often called ‘chlorogenic acids’ and abundant in coffee and many fruit and vegetables) and anthocyanins (coloured polyphenols in fruit and vegetables). For more detailed information on the classes and distribution, the reader is referred to compositional databases such as Phenol-Explorer (www.phenol-explorer.eu; Neveu et al. 2010) and to various reviews on intake amongst different populations (Perez-Jimenez et al. 2011; Vogiatzoglou et al. 2014, 2015; Nishimuro et al. 2015; Pinto & Santos 2017). Most of the examples here will cover catechins and their oligomeric ‘tannins’, quercetin, hesperidin, anthocyanins and phenolic acids, which comprise the majority of the dietary polyphenols in Europe and the US (Table 1).

**Absorption, metabolism and bioavailability**

Absorption and metabolism of polyphenols have been extensively studied and the biochemical pathways related to bioavailability are well understood for the most common classes (Fig. 1). The subject is, however, complicated by the extensive metabolism and the complex reactions catalysed by the gut microbiota in the colon. Classical bioavailability studies using radiolabelled compounds indicate that most tested polyphenols are well absorbed. For example, after consumption of either $^{14}$C-labelled epicatechin by volunteers or $^{14}$C-procyanidin B2 by rats, the proportion absorbed and subsequently appearing in the urine was over 80% (Stoupi et al. 2010; Ottaviani et al. 2016). This value includes absorption both of the parent molecule and of the lower molecular weight compounds produced by the gut microbiota. In addition, studies on ileostomist volunteers show that several polyphenols, such as quercetin, are well absorbed in the small intestine (Hollman et al. 1995) and studies using direct intestinal perfusion of volunteers show

| Table 1 | Content of polyphenols in foods and beverages |
| --- | --- |
| Chemical class | Most common examples | Rich sources | Mean UK intake (mg/day)* | Comments on possible variations from the mean in individual diets |
| Flavanols | Catechins, gallocatechins (monomeric and oligomeric) | Tea (epicatechins, gallocatechins, theaflavins), cocoa (epicatechin, procyanidins), apples, broad beans (epicatechin) | 590 (600) | Much higher in heavy tea drinkers |
| Flavanones | Hesperidin | Citrus fruit | 25 (32) | Orange juice up to 500 mg/l |
| Flavonols | Quercetin, rutin | Tea, apples, onions | 61 (40) | Up to 2000 mg/day in heavy coffee drinkers |
| Hydroxycinnamic acids | Chlorogenic acids (caffeoylquinic acids) | Coffee, chicory, artichoke, plum, pears | 478 (517) | |
| Anthocyanins | Cyanidin | Berry fruits | 20 (24) | A 100 g portion of blackberries contains ~170 mg anthocyanins |

*Data from Yahya et al. (2016) (Leeds Wellbeing study) but intakes are dependent on individual diets and highly variable. Value in parentheses shows standard deviation.

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that enterocytes absorb and extensively metabolise several polyphenols (Petri et al. 2003; Actis-Goretta et al. 2015). Nevertheless, the concentration reaching the blood is highly dependent on the parent polyphenol administered and it is likely that the concentrations of gut microbiota metabolites in the plasma generally exceed that of the parent compound (and its conjugates; Pimpao et al. 2015). The complex pathways of metabolism and conjugation have been well described in the literature, and most of the general principles are well understood (Del Rio et al. 2013; Fig. 1), but only limited information is available on the complex pathways of catabolism by gut microbiota (Woodward et al. 2011; Romo-Vaquero et al. 2015; Williamson & Clifford 2017). In general, the peak concentrations of polyphenols in the blood post-prandially are usually less than 1 μM, whereas, for gut catabolites, concentrations can well exceed this figure and are typically >10–100-fold higher than the parent compound (Kay et al. 2009). Most of the circulating metabolites, both parent compound and gut microbiota metabolites, with some exceptions, are in the form of glucuronides and/or sulphates and may also be methylated (Fumeaux et al. 2010; Del Rio et al. 2013; Borges et al. 2016; Fig. 1). For example, several studies on bioavailability have clarified the pathways of absorption of epicatechin in detail. The predominant species in the plasma are 3′-methyl-epicatechin-5-O-sulphate, epicatechin-3′-O-sulphate and epicatechin-3′-O-β-D-glucuronide, with epicatechin-7-O-β-D-glucuronide additionally present in urine, and these have been quantified based on synthesised authentic standards (Actis-Goretta et al. 2012; Ottaviani et al. 2012). Other detailed structures in vivo have also been reported for quercetin (Mullen et al. 2006), hesperidin (Leveques et al. 2012) and phenolic acids (Fumeaux et al. 2010). The extent of absorption is also influenced by numerous factors, such as chemical attachments on the polyphenol (Jaganath et al. 2006; Guo & Bruno 2015), solubility, processing (Neilson & Ferruzzi 2011; Cifuentes-Gomez et al. 2015) and fat content (Cermak et al. 2003).

**Biological effects**

Historically, polyphenols were mostly of interest to plant scientists as they play many roles in plants and form part of the class of secondary metabolites or phytochemicals. In planta, they protect against stresses such as UV light, deter attacks from pests and provide colour to attract certain insects. In the 1930s, one of the flavonoids, hesperidin, was proposed to be classified as a vitamin, vitamin P, and although this did not lead to an accepted classification, it was followed by numerous papers in the 1950s showing protective effects on the vascular system (e.g. Drezner et al. 1955). In the 1990s, polyphenols were classified as general antioxidants (Serafini et al. 1994) and this was...
originally thought to be a panacea to explain their global mechanism of action. However, the reality is much more complex and biological effects involve detailed biochemical interactions with pathways at the molecular level and, in this direction, much progress has been made in the last two decades. Although chemically polyphenols are antioxidants, this does not necessarily transfer to biological activity because any actions on the body depend both on bioavailability and cellular molecular targets. The overall effect on reducing the risk of disease is underpinned by epidemiology, where polyphenol-rich foods and beverages are protective against development of some chronic diseases, especially type 2 diabetes and cardiovascular diseases (Yang et al. 2014a; Jumar & Schmieder 2016; Lee et al. 2016; Martin et al. 2016; Pang et al. 2016; Santos & Lima 2016). These studies are further supported by animal studies, in vitro cell mechanistic studies and a growing number of human intervention studies on both healthy and at risk volunteers, which are outlined below for selected classes of polyphenols.

Human intervention studies on flavanols and flavanol-rich foods such as cocoa

Many human intervention studies have been reported on cocoa, with a focus on its constituent flavanols (−)-epicatechin and its oligomers (procyanidins). In a review of 28 human intervention studies conducted between 2000 and 2007 on the effect of cocoa consumption (Cooper et al. 2008), the main outcomes were improved endothelial function, decreased susceptibility of low-density lipoprotein (LDL) to oxidation, inhibition of platelet aggregation and activation, and decreased levels of F2-isoprostanes. Further intervention studies have been reported and reviewed (Ding et al. 2006; Hooper et al. 2008; Buitrago-Lopez et al. 2011; Jimenez et al. 2012; Ellam & Williamson 2013; Kerimi & Williamson 2015; Peluso et al. 2015; Martin et al. 2016; Vlachojannis et al. 2016). In many studies, regular consumption of cocoa, or a flavanol extract of cocoa, reduced blood pressure, blood cholesterol, F2-isoprostanes and susceptibility of LDL to oxidation. These data indicate that the most significant changes remain as endothelial function, blood pressure and cholesterol levels, and, together with additional unpublished intervention studies, have enabled a claim on cocoa flavanols to be accepted by the European Food Safety Authority (EFSA NDA Panel 2014) on endothelium-dependent vasodilation. Human intervention studies supporting the claim continue to be published (Heiss et al. 2015; Mastroiacovo et al. 2015). At the molecular level, many of the effects are mediated through interactions with nitric oxide metabolism in the blood vessel endothelium (Kerimi & Williamson 2015), improving endothelial dysfunction, increasing vasodilation and lowering blood pressure. All of these biomarkers indicate cardiovascular disease risk, hence providing evidence for the protective effect of flavanols against developing chronic cardiovascular conditions.

Human intervention studies on flavanols and flavanol-rich foods such as tea

Tea is a rich source of catechins and gallicatechins. Green tea contains the ‘monomeric’ compounds as found in the plant but black tea contains mostly oxidised catechins, a chemically diverse group of polymerised molecules called theaflavins and thearubigins. Cocoa, green tea and black tea all contain various amounts of epicatechin, which is one of the most active polyphenols in these foods. It is not surprising, therefore, to find that some of the benefits associated with cocoa have also been found for tea, such as reduced risk of cardiovascular diseases (Pang et al. 2016). A Cochrane review summarises the effects of tea, after 3- to 6-month intervention, as lowering blood pressure, lowering LDL-cholesterol, not affecting high-density lipoprotein (HDL)-cholesterol and with no side effects, with a grading of the evidence as low/moderate quality (Santesso & Manheimer 2014). Regular consumption of tea is also associated with reduced risk of developing type 2 diabetes in meta-analyses (Yang et al. 2014a, 2014b; Fig. 2). Despite numerous studies, the mechanisms of action in humans in vitro are still controversial and the associated anti-diabetic activities have been ascribed to decreased rates of digestion and nutrient absorption (Hara & Honda 1990), such as attenuation of post-prandial glucose spikes (Williamson 2013), activation of AMP-activated protein kinase leading to changes in energy metabolism (Yang et al. 2016) and effects on gut microbiota (Yang et al. 2016).

Human intervention studies on the flavonol, quercetin

Quercetin is mainly found in tea, apples and onions. All of these foods contain other biologically active components in addition to quercetin, and so some of the effects observed for tea described above could be partly ascribed to quercetin, and similarly for onions and apples. Regular consumption of the latter, for
example, reduces the risk of type 2 diabetes according to a recent meta-analysis (Guo et al. 2017). As quercetin is one of the most biologically active polyphenols in vitro, there have been several human intervention studies on the effects of pure quercetin. When given in the 4′-O-glucoside form, which is highly bioavailable, platelet aggregation and thrombus formation were reduced and coincided with the appearance of quercetin (metabolites) in plasma (Hubbard et al. 2004). When given chronically over 4 weeks, quercetin (as 3-O-glucoside, also bioavailable) improved endothelial function and reduced inflammation (Dower et al. 2015a), but did not affect flow-mediated dilation or insulin resistance (Dower et al. 2015b). When given as aglycone (no sugars attached), which is much less bioavailable than the forms present in food (Shi & Williamson 2015), quercetin as a supplement decreased plasma uric acid in mildly hyperuricaemic males over a period of 4 weeks (Shi & Williamson 2016), but did not affect blood pressure in normal weight volunteers (Conquer et al. 1998; Egert et al. 2010b), platelet aggregation or serum cholesterol and triglyceride (Conquer et al. 1998), nor protect against oxidative stress after exercise (Nieman et al. 2007; McAnulty et al. 2008). When given acutely, quercetin reduced plasma endothelin-1 (Loke et al. 2008), reduced blood pressure in overweight volunteers but only of a certain genotype (Egert et al. 2010a), but did not reduce urinary F2-isoprostanes (Loke et al. 2008), nor blood pressure in normal weight volunteers (Egert et al. 2010b). When given in the form of onion skin extract, quercetin did not affect systemic inflammation in overweight women (Kim & Yim 2016), post-prandial blood pressure, endothelial function, serum leptin nor adiponectin in overweight adults (Brull et al. 2016, 2017). These various studies suggest that quercetin exerts some effects in humans but the exact effect is highly dependent on the individual’s metabolic and genetic status, and on the form given. As many of the studies gave relatively high doses, at this stage, more research is required to define the effect of quercetin from dietary sources.

### Human intervention studies on hydroxycinnamic acids and coffee

Many reviews and intervention studies have been reported on coffee and its constituent hydroxycinnamic acids (chlorogenic acids). The epidemiological evidence for a protective effect of coffee consumption against the risk of developing type 2 diabetes is very strong and shows a convincing dose-dependent effect (Fig. 2). Data from systematic reviews and meta-analyses show that the reduction in risk is ~8% for each cup of coffee consumed per day and that this is independent of whether the coffee is decaffeinated or not (Bhupathiraju et al. 2013; Ding et al. 2014). Some well-publicised studies indicated that when coffee was boiled in the ‘Scandinavian’ way, there was an increase in plasma cholesterol (Zock et al. 1990), but these effects were due to cafestol and kahweol (Urgert et al. 1996). These components are not polyphenols and are present only in certain types of coffee (Urgert & Katan 1997). Intervention studies on coffee are more mixed and study designs are complicated by the fact that it is difficult to examine the effect of coffee consumption in regular coffee drinkers. The amount can either be increased to try to measure an additional effect of higher consumption, or coffee can be withdrawn for a period before reintroduction. In studies of the latter design, coffee over 4 weeks, after a 4-week washout, attenuated DNA damage, reduced bodyweight and body fat (Bakuradze et al. 2011), and exerted beneficial effects on subclinical inflammation and HDL-cholesterol (Kempf et al. 2010). Coffee consumption over 1 week has been reported to increase (Olthof et al. 2001) or not affect (Esposito et al. 2003) plasma homocysteine. Unfavourable effects of coffee on endothelial function (Buscemi et al. 2010) were in contrast to favourable effects of decaffeinated coffee (Buscemi et al. 2009). A more recent intervention where healthy volunteers received coffee for 2 months had no effect on markers of oxidation of...
DNA and lipids, plasma glucose and insulin, cholesterol, triglycerides, inflammatory markers, nor on blood pressure (Shaposhnikov et al. 2016). Nevertheless, a recent review on the effects of coffee from 26 intervention studies suggests that coffee consumption increases glutathione levels and protects against DNA damage, but with inconclusive effects on protein and lipid damage (Martini et al. 2016). Studies showing convincing mechanisms of action of coffee hydroxycinnamic acids are also lacking, but include effects on fat metabolism and the gut microbiota (Pan et al. 2016). The metabolism of chlorogenic acids from coffee is now well understood, involving critical action of gut microbiota, and knowledge on the plasma metabolites of chlorogenic acids should facilitate more mechanistic studies in the future. While the epidemiological data for coffee reducing the risk of type 2 diabetes are very convincing, the data are not yet backed up by well-designed larger-scale intervention studies and convincing mechanisms. Coffee consumption may also reduce the risk of colon cancer (Schmit et al. 2016), does not increase hypertension (Rhee et al. 2016) nor cancer risk (Arab 2010) and may be protective against cardiovascular disease (Crippa et al. 2014). Although many of the protective effects of coffee have been assigned to the constituent chlorogenic acids, there are very few intervention studies on pure chlorogenic acids in humans. A chlorogenic acid-rich green coffee extract given for 12 weeks decreased both systolic and diastolic blood pressure, but did not affect body mass index nor pulse rate in patients with mild hypertension (Watanabe et al. 2006), and after consumption of an acute high dose of chlorogenic acid, there was no change in glucose tolerance via effects on incretin hormone secretion (Olthof et al. 2011). Clearly, one of the difficulties in making conclusions on the polyphenol component of coffee is separating out the effects of caffeine, which has substantial biological activity both positive and negative, and in addition, the presence of hydroxycinnamic acids may protect against some of the effects of caffeine.

Supplements or not?

Supplements have the advantage of delivering a suitably active dose but also have several drawbacks. Often polyphenols act with other nutrients and a key example is where polyphenols already present in food slow down the rate of carbohydrate digestion to blunt post-prandial glucose spikes (Williamson 2013). If taken without food, a supplement would be unable to have any effect on this parameter and so the ideal situation would be to consume the polyphenol with food (i.e. in its natural state). In addition, supplements may have modified bioavailability and can also discourage the consumption of a ‘healthy’ diet in favour of supplementing a poor diet. The use of plant food supplements (botanical supplements) in Europe has been reviewed (Vargas-Murga et al. 2011), and in a survey of people from six countries (Finland, Germany, Italy, Romania, Spain and the UK), almost 20% of those asked consumed plant food supplements, containing a total of more than 490 different ingredients, with the most common ones being Ginkgo biloba, Oenothera biennis (Evening primrose) and Cynara scolymus (Artichoke) (Garcia-Alvarez et al. 2014).

Future perspectives

Most micronutrients such as vitamins and minerals have an officially approved daily intake recommended value, with these varying between countries and regions. Although initially proposed for polyphenols (Williamson & Holst 2008), differences between polyphenols and vitamins suggest that a somewhat different approach is needed. This is based on the assumption that a sufficient dose for an effect is needed every time of consumption and that, unlike minerals and vitamins, the active component is not stored or temporarily retained in the body. For example, a food containing 10 mg of a certain mineral will contribute 10% to a daily intake recommended value of 100 mg, and 10 doses will therefore constitute sufficient daily intake. On the other hand, for components with a proposed beneficial effect, such as cocoa flavanols, but not stored in the body, the magnitude of the effect is dependent on dose. The critical question is how much is needed for the smallest biologically significant effect, which would then be effective and observable over a suitable period of time. This is a truly important question in this area if we consider a situation where the daily effect of an acute dose is not measurable by current biomarker technology, but the effect (not the actual compound) builds up and becomes apparent over a period of weeks, months or even years. Let us consider that the amount necessary for a given effect by a hypothetical flavonoid is 10 mg per day and that the effect is apparent after 2 months. If we give a food containing a ‘dose’ of 5 mg, this may not elicit this threshold effect and so the dose could be considered as ‘wasted’, at least in terms of affecting the desired biomarker. Therefore, one proposition is that the recommended daily intake for these
compounds cannot be achieved by administering 2 × 5 mg doses separately, only by a single 10 mg bolus. This needs to be considered and scientifically evaluated before any compound-specific recommendations on intake can be made.

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**References**

Actis-Goreta L, Leveques A, Giuffrida F et al. (2012) Elucidation of (-)-epicatechin metabolites after ingestion of chocolate by healthy humans. Free Radical Biology and Medicine 53: 787–95.

Actis-Goreta L, Dew TP, Leveques A et al. (2015) Gastrointestinal absorption and metabolism of hesperetin-7-O-rutinoside and hesperetin-7-O-glucose in healthy humans. Molecular Nutrition and Food Research 59: 1651–62.

Arab L (2010) Epidemiologic evidence on coffee and cancer. Nutrition and Cancer 62: 271–83.

Bakuradze T, Boehm N, Janzowski C et al. (2011) Antioxidant-rich coffee reduces DNA damage, elevates glutathione status and contributes to weight control: results from an intervention study. Molecular Nutrition and Food Research 55: 793–7.

Bhupathiraju SN, Pan A, Malik VS et al. (2013) Caffeinated and caffeine-free beverages and risk of type 2 diabetes. American Journal of Clinical Nutrition 97: 155–66.

Borges G, van der Hooft JJ & Crozier A (2016) A comprehensive evaluation of the [2-14C](-)-epicatechin metabolome in rats. Free Radical Biology and Medicine 99: 128–38.

Brull V, Burak C, Stoffel-Wagner B et al. (2016) No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-)hypertension: a randomised double-blind, placebo-controlled crossover trial. European Journal of Nutrition. https://doi.org/10.1007/s00394-016-1267-0 [Epub ahead of print].

Brull V, Burak C, Stoffel-Wagner B et al. (2017) Acute intake of quercetin from onion skin extract does not influence postprandial blood pressure and endothelial function in overweight-to-obese adults with hypertension: a randomized, double-blind, placebo-controlled, crossover trial. European Journal of Nutrition 56: 1347–57.

Buitrago-Lopez A, Sanderson J, Johnson L et al. (2011) Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. British Medical Journal 343: d4488.

Buscemi S, Verga S, Batsis JA et al. (2009) Dose-dependent effects of decaffeinated coffee on endothelial function in healthy subjects. European Journal of Clinical Nutrition 63: 1200–5.

Buscemi S, Verga S, Batsis JA et al. (2010) Acute effects of coffee on endothelial function in healthy subjects. European Journal of Clinical Nutrition 64: 483–9.

Cermak R, Landgraf S & Wolflfram S (2003) The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. Journal of Nutrition 133: 2802–7.

Cifuentes-Gomez T, Rodriguez-Mateos A, Gonzalez-Salvador I et al. (2015) Factors affecting the absorption, metabolism, and excretion of cocoa flavanols in humans. Journal of Agricultural and Food Chemistry 63: 7615–23.

Conquer JA, Mainai G, Azzini E et al. (1998) Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. American Society for Nutritional Sciences 128: 593–7.

Cooper KA, Donovan JL, Waterhouse AL et al. (2008) Cocoa and health: a decade of research. British Journal of Nutrition 99: 1–11.

Crippa A, Discacciati A, Larsson SC et al. (2014) Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. American Journal of Epidemiology 180: 763–75.

Del Rio D, Rodriguez-Mateos A, Spencer JP et al. (2013) Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxidants and Redox Signaling 18: 1818–92.

Ding EL, Huttlless SM, Ding X et al. (2006) Chocolate and prevention of cardiovascular disease: a systematic review. Nutrition and Metabolism (London) 3: 2.

Ding M, Bhupathiraju SN, Chen M et al. (2014) Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care 37: 569–86.

Dower JI, Geleijnse JM, Gijsbers L et al. (2015a) Supplementation of the pure flavonoids epicatechin and quercetin affects some biomarkers of endothelial dysfunction and inflammation in (pre) hypertensive adults: a randomized double-blind, placebo-controlled, crossover trial. Journal of Nutrition 145: 1459–63.

Dower JI, Geleijnse JM, Gijsbers L et al. (2015b) Effects of the pure flavonoids epicatechin and quercetin on vascular function and cardiometabolic health: a randomized, double-blind, placebo-controlled, crossover trial. American Journal of Clinical Nutrition 101: 914–21.

Drezner HL, Edwards WR, Warter PJ et al. (1955) Capillary integrity: a review and interim report after five year study of use of hesperidin-C. American Practitioner and Digest of Treatment 6: 912–9.

EFSA NDA Panel (European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies) (2014) Scientific Opinion on the modification of the authorisation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006 following a request in accordance with Article 19 of Regulation (EC) No 1924/2006. EFSA Journal 12: 3654.
Egert S, Boesch-Saadatmandi C, Wolfram S et al. (2010a) Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. *Journal of Nutrition* 140: 278–84.

Egert S, Rimbach G & Muller MJ (2010b) No evidence for a thermic effect of the dietary flavonol quercetin: a pilot study in healthy normal-weight women. *European Journal of Applied Physiology* 111: 869–73.

Ellam S & Williamson G (2013) Cocoa and human health. *Annual Review of Nutrition* 33: 105–28.

Esposito F, Morisco F, Verde V et al. (2003) Moderate coffee consumption increases plasma glutathione but not homocysteine in healthy subjects. *Alimentary Pharmacology and Therapeutics* 17: 595–601.

Fumeaux R, Menozzi-Smarrito C, Stalmach A et al. (2010) First synthesis, characterization, and evidence for the presence of hydroxycinnamic acid sulfate and glucuronide conjugates in human biological fluids as a result of coffee consumption. *Organic and Biomolecular Chemistry* 8: 5199–211.

Garcia-Alvarez A, Egan B, de Klein S et al. (2014) Use of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. *PLoS ONE* 9: e92265.

Guo Y & Bruno RS (2015) Endogenous and exogenous mediators of quercetin bioavailability. *Journal of Nutritional Biochemistry* 26: 201–10.

Guo XF, Yang B, Tang J et al. (2017) Apple and pear consumption and type 2 diabetes mellitus risk: a meta-analysis of prospective cohort studies. *Food and Function* 8: 927–34.

Hara Y & Honda M (1990) The Inhibition of alpha-amylase by quercetin. *American Journal of Clinical Nutrition* 52: 1002–07.

Hara Y & Honda M (1990) The inhibition of thrombin and trypsin by quercetin. *Bioscience, Biotechnology, and Biochemistry* 54: 136–37.

Heiss C, Sansone R, Karimi H et al. (2015) Impact of cocoa flavanol intake on age-dependent vascular stiffness in healthy men: a randomized, controlled, double-masked trial. *Age* 37: 9794.

Hertog MGL, Kromhout D, Aravanis C et al. (1995) Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. *Archives of Internal Medicine* 155: 381–6.

Hollman PC, de Vries JH, van Leeuwen SD et al. (1995) Absorption of dietary quercetin glycosides and quercitin in healthy ileostomy volunteers. *American Journal of Clinical Nutrition* 62: 1276–82.

Hooper L, Koon PA, Rimm EB et al. (2008) Flavonoids, flavonoid-rich foods and cardiovascular risk: a meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition* 88: 38–50.

Hubbard GP, Wolfram S, Lovegrove JA et al. (2004) Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. *Journal of Thrombosis and Haemostasis* 2: 2138–45.

Jaganath IB, Mullen W, Edwards CA et al. (2006) The relative contribution of the small and large intestine to the absorption and metabolism of rutin in man. *Free Radical Research* 40: 1035–46.

Jimenez R, Duarte J & Perez-Vizcaíno F (2012) Epicatechin: endothelial function and blood pressure. *Journal of Agricultural and Food Chemistry* 60: 8823–30.

Jumar A & Schmieder RE (2016) Cocoa flavanol cardiovascular effects beyond blood pressure reduction. *Journal of Clinical Hypertension (Greenwich)* 18: 352–8.

Kay CD, Kroon PA & Cassidy A (2009) The bioactivity of dietary anthocyanins is likely to be mediated by their degradation products. *Molecular Nutrition and Food Research* 53(Suppl. 1): S92–101.

Kempf K, Herder C, Eurlund I et al. (2010) Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial. *American Journal of Clinical Nutrition* 91: 950–7.

Kerimi A & Williamson G (2015) The cardiovascular benefits of dark chocolate. *Vascular Pharmacology* 71: 11–5.

Kim KA & Yim JE (2016) The effect of onion peel extract on inflammatory mediators in Korean overweight and obese women. *Clinical Nutrition Research* 5: 261–9.

Lee AH, Tan L, Hiramatsu N et al. (2016) Plasma concentrations of coffee polyphenols and plasma biomarkers of diabetes risk in healthy Japanese women. *Nutrition and Diabetes* 6: e212.

Leveques A, Actis-Goreta L, Rein MJ et al. (2012) UPLC-MS/MS quantification of total hesperetin and hesperetin enantiomers in biological matrices. *Journal of Pharmaceutical and Biomedical Analysis* 57: 1–6.

Loko WM, Hodgson JM, Proudfoot JM et al. (2008) Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. *American Journal of Clinical Nutrition* 88: 1018–25.

Martin MA, Goya L & Ramos S (2016) Antidiabetic actions of cocoa flavanols. *Molecular Nutrition and Food Research* 60: 1756–69.

Martini D, Del Bo C, Tassotti M et al. (2016) Coffee consumption and oxidative stress: a review of human intervention studies. *Molecules* 21: pii: E9799.

Mastroiacovo D, Kwik-Uribe C, Grassi D et al. (2015) Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) study-a randomized controlled trial. *American Journal of Clinical Nutrition* 101: 538–48.

McAnulty SR, McAnulty LS, Nieman DC et al. (2008) Chronic quercetin ingestion and exercise-induced oxidative damage and inflammation. *Applied Physiology, Nutrition, and Metabolism* 33: 254–62.

Mullen W, Edwards CA & Crozier A (2006) Absorption, excretion and metabolite profiling of methyl-, glucuronyl-, glucosyl- and sulpho-conjugates of quercetin in human plasma and urine after ingestion of onions. *British Journal of Nutrition* 96: 107–16.

Neilson AP & Ferruzzi MG (2011) Influence of formulation and processing on absorption and metabolism of flavan-3-ols from tea and cocoa. *Annual Review of Food Science and Technology* 2: 125–51.

Neveu V, Perez-Jimenez J, Vos F et al. (2010) Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database (Oxford)* 2010: bap024.

Nieman DC, Henson DA, Davis JM et al. (2007) Quercetin ingestion does not alter cytokine changes in athletes competing in the Western States Endurance Run. *Journal of Interferon and Cytokine Research* 27: 1003–11.

Nishimuro H, Ohnishi H, Sato M et al. (2015) Estimated daily intake and seasonal food sources of quercetin in Japan. *Nutrients* 7: 2345–58.

Othlof MR, Hollman PC, Zock PL et al. (2001) Consumption of high doses of chlorogenic acid, present in coffee, or of black tea...
increases plasma total homocysteine concentrations in humans. *American Journal of Clinical Nutrition* 73: 532–8.

Olthof MR, van Dijk AE, Deacon CF et al. (2011) Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on incretin hormones. *Nutrition and Metabolism* 8: 10.

Ottaviani JJ, Momma TY, Kuhnle GK et al. (2012) Structurally related (+)-epicatechin metabolites in humans: assessment using *de novo* chemically synthesized authentic standards. *Free Radical Biology and Medicine* 52: 1403–12.

Ottaviani JJ, Borges G, Momma TY et al. (2016) The metabolome of [2-(14)C](-)-epicatechin in humans: implications for the assessment of efficacy, safety, and mechanisms of action of polyphenolic bioactives. *Scientific Reports* 6: 29034.

Pan MH, Tung YC, Yang G et al. (2016) Molecular mechanisms of the anti-obesity effect of bioactive compounds in tea and coffee. *Food and Function* 7: 4481–91.

Pang J, Zhang Z, Zheng TZ et al. (2016) Green tea consumption and risk of cardiovascular and ischemic related diseases: a meta-analysis. *International Journal of Cardiology* 202: 967–74.

Peluso I, Palmery M & Serafini M (2015) Effect of cocoa products and flavanols on plateaulet aggregation in humans: a systematic review. *Food and Function* 6: 2128–34.

Perez-Jimenez J, Fezeu L, Touvier M et al. (2011) Dietary intake of 337 polyphenols in French adults. *American Journal of Clinical Nutrition* 93: 1220–8.

Petri N, Tannergren C, Holst B et al. (2015) Absorption/metabolism of sulforaphane and quercetin, and regulation of phase ii enzymes, in human jejunum *in vivo*. *Drug Metabolism and Disposition* 31: 805–13.

Pimpao RC, Ventura MR, Ferreira RB et al. (2015) Phenolic sulfates as new and highly abundant metabolites in human plasma after ingestion of a mixed berry fruit puree. *British Journal of Nutrition* 113: 454–63.

Pinto P & Santos CN (2017) Worldwide (poly)phenol intake: assessment methods and identified gaps. *European Journal of Nutrition* 56: 1393–408.

Rhee JJ, Qin F, Hedlin HK et al. (2016) Coffee and caffeine consumption and the risk of hypertension in postmenopausal women. *American Journal of Clinical Nutrition* 103: 210–7.

Romo-Vaquero M, Garcia-Villalba R, Gonzalez-Sarrias A et al. (2015) Interindividual variability in the human metabolism of ellagic acid: contribution of *Gordondhacter* to urolithin production. *Journal of Functional Foods* 17: 785–91.

Santesso N & Manheimer E (2014) A summary of a cochrane review: green and black tea for the primary prevention of cardiovascular disease. *Global Advances in Health and Medicine* 3: 66–7.

Santos RM & Lima DR (2016) Coffee consumption, obesity and type 2 diabetes: a mini-review. *European Journal of Nutrition* 55: 1345–58.

Scalbert A & Williamson G (2000) Dietary intake and bioavailability of polyphenols. *Journal of Nutrition* 130: 2073S–85S.

Schmit SL, Rennert HS, Rennert G et al. (2016) Coffee consumption and the risk of colorectal cancer. *Cancer Epidemiology, Biomarkers and Prevention* 25: 634–9.

Serafini M, Ghiselli A & Ferroluzzi A (1994) Red wine, tea, and antioxidants. *Lancet* 344: 626.

Shaposhnikov S, Hatzold T, Yamani NE et al. (2016) Coffee and oxidative stress: a human intervention study. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-016-1336-4.

Shi Y & Williamson G (2015) Comparison of the urinary excretion of quercetin glycosides from red onion and aglycone from dietary supplements in healthy subjects: a randomized, single-blinded, cross-over study. *Food and Function* 6: 1443–8.

Shi Y & Williamson G (2016) Quercetin lowers plasma uric acid in pre-hyperuricaemic males: a randomised, double-blinded, placebo-controlled, cross-over trial. *British Journal of Nutrition* 115: 800–6.

Stoupi S, Williamson G, Viton F et al. (2010) *In vivo* bioavailability, absorption, excretion, and pharmacokinetics of [14C]procyanidin B2 in male rats. *Drug Metabolism and Disposition* 38: 287–91.

Urgert R & Katan MB (1997) The cholesterol-raising factor from coffee beans. *Annual Review of Nutrition* 17: 303–24.

Urgert R, Kosmeijer-Schuij TG & Katan MB (1996) Intake levels, sites of action and excretion routes of the cholesterol-elevating diterpines from coffee beans in humans. *Biochemical Society Transactions* 24: 800–6.

Vargas-Murga L, Garcia-Alvarez A, Roman-Vinas B et al. (2011) Plant food supplement (PFS) market structure in EC Member States, methods and techniques for the assessment of individual PFS intake. *Food and Function* 2: 731–9.

Vlachojannis J, Erne P, Zimmermann B et al. (2016) The impact of cocoa flavanols on cardiovascular health. *Phytotherapy Research* 30: 1641–57.

Vogiatzoglou A, Mulligan AA, Luben RN et al. (2014) Assessment of the dietary intake of total flavan-3-ols, monomeric flavan-3-ols, proanthocyanidins and theaflavins in the European Union. *British Journal of Nutrition* 111: 1463–73.

Vogiatzoglou A, Mulligan AA, Lentjes MA et al. (2015) Flavonoid intake in European adults (18 to 64 years). *PLoS ONE* 10: e0128132.

Watanabe T, Arai Y, Mitsui Y et al. (2006) The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. *Climical and Experimental Hypertension* 28: 439–49.

Williamson G (2013) Possible effects of dietary polyphenols on sugar absorption and digestion. *Molecular Nutrition and Food Research* 57: 48–57.

Williamson G & Clifford MN (2017) Role of the small intestine, colon and microbiota in determining the metabolic fate of polyphenols. *Biochemical Pharmacology*. https://doi.org/10.1016/j.bcp.2017.03.012.

Williamson G & Holst B (2008) Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? *British Journal of Nutrition* 99(Suppl. 3): S55–8.

Woodward GM, Needs PW & Kay CD (2011) Anthocyanin-derived phenolic acids form glucuronides following simulated gastrointestinal digestion and microsomal glucuronidation. *Molecular Nutrition and Food Research* 55: 378–86.

Yahya HM, Day A, Lawton C et al. (2016) Dietary intake of 20 polyphenol subclasses in a cohort of UK women. *European Journal of Nutrition* 55: 1839–47.
Yang J, Mao QX, Xu HX et al. (2014a) Tea consumption and risk of type 2 diabetes mellitus: a systematic review and meta-analysis update. *British Medical Journal Open* 4: e005632.

Yang WS, Wang WY, Fan WY et al. (2014b) Tea consumption and risk of type 2 diabetes: a dose-response meta-analysis of cohort studies. *British Journal of Nutrition* 111: 1329–39.

Yang CS, Zhang J, Zhang L et al. (2016) Mechanisms of body weight reduction and metabolic syndrome alleviation by tea. *Molecular Nutrition and Food Research* 60: 160–74.

Zock PL, Katan MB, Merkus MP et al. (1990) Effect of a lipid-rich fraction from boiled coffee on serum cholesterol. *Lancet* 335: 1235–7.