



## Interaction of plant phenols with food macronutrients: characterisation and nutritional–physiological consequences

Hao Zhang<sup>1</sup>, Dandan Yu<sup>1</sup>, Jing Sun<sup>1</sup>, Xianting Liu<sup>1</sup>, Lu Jiang<sup>1</sup>, Huiyuan Guo<sup>1,2</sup> and Fazheng Ren<sup>1\*</sup>

<sup>1</sup>Beijing Laboratory for Food Quality and Safety, and Key Laboratory of Functional Dairy, College of Food Science and Nutritional Engineering, China Agricultural University, Beijing 100083, People's Republic of China

<sup>2</sup>Beijing Higher Institution Engineering Research Center of Animal Product, Beijing 100083, People's Republic of China

### Abstract

Polyphenols are dietary constituents of plants associated with health-promoting effects. In the human diet, polyphenols are generally consumed in foods along with macronutrients. Because the health benefits of polyphenols are critically determined by their bioavailability, the effect of interactions between plant phenols and food macronutrients is a very important topic. In the present review, we summarise current knowledge, with a special focus on the *in vitro* and *in vivo* effects of food macronutrients on the bioavailability and bioactivity of polyphenols. The mechanisms of interactions between polyphenols and food macronutrients are also discussed. The evidence collected in the present review suggests that when plant phenols are consumed along with food macronutrients, the bioavailability and bioactivity of polyphenols can be significantly affected. The protein–polyphenol complexes can significantly change the plasma kinetics profile but do not affect the absorption of polyphenols. Carbohydrates can enhance the absorption and extend the time needed to reach a maximal plasma concentration of polyphenols, and fats can enhance the absorption and change the absorption kinetics of polyphenols. Moreover, as highlighted in the present review, not only a nutrient alone but also certain synergisms between food macronutrients have a significant effect on the bioavailability and biological activity of polyphenols. The review emphasises the need for formulations that optimise the bioavailability and *in vivo* activities of polyphenols.

**Key words:** Polyphenols: Macronutrients: Interactions: Bioavailability

### Introduction

Phenolic compounds are widely distributed throughout the plant kingdom, and several hundred are found in edible plants. Phenolic-rich foods have been consistently identified in epidemiological studies as the key components of dietary patterns that reduce the risk of developing chronic diseases, including type 2 diabetes and many cancers<sup>(1–3)</sup>. However, the adequate bioavailability of phenolic compounds is a prerequisite for the compounds' health benefits<sup>(4)</sup>. In the human diet, phenolic-rich foods, such as tea and coffee, are usually consumed along with food macronutrients, such as proteins, fats and carbohydrates. For example, the addition of milk to black tea has a long tradition in the Western world, especially in the UK. The co-administered dietary components may have an impact on the bioavailability of phenolic compounds. Most studies have concentrated on the *in vitro* interactions between polyphenols and proteins. After the pioneering work of Haslam and colleagues<sup>(5,6)</sup>, the interaction of polyphenols with proteins has become a well-studied topic. It has been reported that polyphenol binding to salivary proteins

leads to the precipitation of insoluble complexes, causing the perception of an astringent flavour<sup>(7)</sup>. Polyphenols are also thought to interact with dietary proteins, plasma proteins and digestive enzymes in the gut<sup>(8)</sup>. However, the biological fate of protein–polyphenol complexes *in vivo* is unclear. Recently, we showed that milk protein–polyphenol complexes lead to significant changes in the plasma kinetics profile but do not affect the absorption and bioactivity of polyphenols both in rats and in human subjects<sup>(9,10)</sup>. It was also found that milk fats can participate in the interactions between proteins and polyphenols during digestion, resulting in remarkable aggregation and thus significantly inhibiting the bioavailability of polyphenols<sup>(9,10)</sup>. The results suggested that not only a nutrient alone but also certain synergisms between food macronutrients can significantly affect the bioavailability and biological activity of polyphenols. In addition, other researchers have reported that co-consumed carbohydrates can affect the bioavailability of polyphenols<sup>(11)</sup>. These findings represent novel contributions to the literature and are important for a better understanding of the effects of the interactions of plant phenols with food macronutrients.

\* Corresponding author: Dr Fazheng Ren, fax +86 10 62736344, email renfazheng@263.net

Therefore, in the present review, we focused on both the *in vitro* and the *in vivo* effects of food macronutrients on the bioavailability and bioactivity of polyphenols. The mechanisms of interactions between polyphenols and food macronutrients are also discussed. A better understanding of these factors is essential to the development of formulation strategies specifically designed to optimise the health benefits of polyphenols.

## Nature, intake and health benefits of polyphenols

### Nature of dietary phenols

To understand the relationship between the intake of polyphenols and a reduced risk of developing diseases, it is essential to know the nature and distribution of phenolic compounds in our diet. Phenolic compounds can be classified into different groups according to the number of phenol rings in the molecule and the substitution groups of the phenol rings. Distinctions are thus made between phenolic acids, flavonoids, stilbenes and lignans<sup>(12)</sup>. Among these compounds, flavonoids and phenolic acids are the most abundant polyphenols in the human diet<sup>(13–17)</sup>. Attention should also be paid to proanthocyanidins which are believed to be ubiquitous in plant foods. Proanthocyanidins are polyhydroxyflavan oligomers or polymers. The most common monomers are the diastereomers (+)-catechin/(-)-epicatechin, (-)-gallocatechin/(-)-epigallocatechin and (+)-afzelechin/(-)-epiafzelechin, and the respective oligo- and polymers are called procyanidins, prodelphinidins and propelargonidins. It has been suggested that they account for a significant fraction of the polyphenols ingested in a Western diet<sup>(18)</sup>. Phenolic compounds are secondary metabolites of plants and afford protection against UV radiation, pathogens and herbivores<sup>(19)</sup>. The anthocyanin co-pigments in flowers attract pollinating insects<sup>(19)</sup> and are responsible for the characteristic red and blue colours of berries, wines and certain vegetables<sup>(20–26)</sup>. In addition, polyphenols contribute to the organoleptic properties of plant foods, especially by their astringency, bitter taste and participation in haze formation<sup>(27)</sup>. To play these roles, most polyphenols are concentrated in the peels of many fruits and vegetables. It has been shown that for the jujube (*Ziziphus jujuba* Mill.), a traditional Chinese fruit, the peel has the highest content of total polyphenols<sup>(28)</sup>. The results are consistent with the data reported by Tomás-Barberán *et al.*<sup>(29)</sup>, who found that the peel tissues of nectarines, peaches and plums contained two-fold more flavonoids than other tissues.

### Content of polyphenols in food and their absorption after intake

In the human diet, coffee, tea and red wine are major sources of polyphenols because of these liquids' high polyphenol content and relatively large serving sizes.

**Table 1.** Main sources of polyphenols in the human diet

Food	Polyphenol content
Tea	150–250 mg per 200 ml serving <sup>(30)</sup>
Coffee	150–180 mg per 200 ml serving <sup>(31)</sup>
Dark chocolate	340 mg per 40 g serving <sup>(31)</sup>
Red wine	200–500 mg per 200 ml serving <sup>(32,33)</sup>
Beer	50–100 mg per 200 ml serving <sup>(34)</sup>
White wine	40–60 mg per 200 ml serving <sup>(32)</sup>

The polyphenol content of main food sources is shown in Table 1<sup>(30–34)</sup>. Considering the amounts of total phenols in our diet, it has been reported that a well-balanced diet can provide well over 1000 mg of total phenols per d.

After the intake of polyphenols, aglycones can be absorbed from the small intestine, and the maximal plasma concentrations often reach 1–2 h after ingestion<sup>(35–37)</sup>. However, most polyphenols in food are in the form of esters, glycosides or polymers that cannot be absorbed in the native form. These substances must be hydrolysed by intestinal enzymes before the substances can be absorbed<sup>(12)</sup>. In the case of quercetin glucosides, it has been suggested that these compounds could be hydrolysed inside cells by a cytosolic  $\beta$ -glucosidase<sup>(38)</sup>. Another pathway involves lactase phloridzine hydrolase, a glucosidase of the brush-border membrane of the small intestine that catalyses the extracellular hydrolysis of certain glucosides, which is followed by the diffusion of aglycones across the brush border<sup>(39)</sup>. Certain polyphenols with special structures cannot be hydrolysed by intestinal enzymes and thus cannot be absorbed until reaching the colon. Unlike intestinal enzymes, colonic microflora catalyse the breakdown of polyphenols into more simple compounds, such as phenolic acids. For example, when quercetin-3-*O*-rhamnoside was incubated anaerobically with human intestinal bacteria, quercetin, 3,4-dihydroxyphenylacetic acid and 4-hydroxybenzoic acid were found to be metabolites<sup>(31)</sup>. Proanthocyanidins are a subclass of polyphenols. Since they are associated with the cell wall in plants by non-covalent or covalent bindings, it is believed that they undergo two main processes in the intestinal tract after intake: (1) partial depolymerisation into their constituent units<sup>(40)</sup>, mainly by the gastric milieu coupled with absorption of the free monomers and small oligomers (dimers, trimers) in the small intestine<sup>(41)</sup>; and (2) direct fermentation by the intestinal microbiota into smaller metabolites such as phenolic acids and their subsequent absorption<sup>(42,43)</sup>. It has been suggested that the chain length of proanthocyanidins has a more crucial role in their microbial metabolism than the dose. Short-chain proanthocyanidins exhibited a strong metabolite formation and a higher concentration of proanthocyanidins could be tolerated without inhibition of metabolite formation<sup>(44)</sup>. On the other hand, proanthocyanidins with high polymerisation were able to inhibit the conversions by the intestinal microbiota<sup>(45)</sup>. The total

yields of metabolites decrease significantly with increasing polymerisation<sup>(43,44,46)</sup>. It is possible for proanthocyanidins to pass through the entire gastrointestinal digestion largely intact, especially if their molecular weight is large<sup>(18)</sup>. Thus, there can be some intact parent compounds<sup>(47)</sup> and non-absorbable metabolites (probably mid-molecular-weight tannins)<sup>(18)</sup> after the metabolism of proanthocyanidins that remain in the colonic lumen where they may contribute to the health of the gastrointestinal tract.

After the hydrolysis of polyphenols into free aglycones and before passage into the bloodstream, polyphenols are conjugated by methylation, sulfation or glucuronidation, or a combination<sup>(48,49)</sup>. This conjugation is a metabolic detoxification process common to many xenobiotics. The conjugation is particularly important for increasing the molecular weight and solubility of phenolic aglycones, which reduces compounds' potential toxic effects and enhances their elimination ability<sup>(50)</sup>. The relative contribution of different types of conjugation (methylation, sulfation and glucuronidation) appears to vary according to the nature of the substrate and the dose ingested. Sulfation is generally a higher-affinity, lower-capacity pathway than glucuronidation, so that when the ingested dose increases, a shift from sulfation toward glucuronidation occurs<sup>(51,52)</sup>. The balance between the sulfation and the glucuronidation of polyphenols also seems to vary with species, sex and food deprivation<sup>(52)</sup>.

### Health benefits of polyphenols

**Antioxidant activity.** Polyphenols are strong antioxidants *in vitro*, mainly due to their low redox potential and capacity to donate electrons or hydrogen atoms<sup>(53,54)</sup>. There is ample evidence that the addition of polyphenols or polyphenol-rich food extracts to human plasma or lipoproteins effectively protects endogenous lipids and proteins from oxidation. For example, apple extracts effectively delay the oxidation of  $\alpha$ -tocopherol and the formation of lipid hydroperoxides in human plasma<sup>(55)</sup>. In addition, colonic metabolites of chlorogenic acids such as *m*-coumaric acid and dihydroferulic acid showed high antioxidant activity in a study carried out by Gómez-Ruiz *et al.*<sup>(56)</sup>. Another study showed that catechins, procyanidins and procyanidin-rich extracts protect plasma components from oxidation<sup>(57)</sup>.

*In vivo*, several studies have shown that phenolic compounds can increase the antioxidant capacity of the plasma acutely and after long-term consumption<sup>(58–60)</sup>. This phenomenon has been observed for a wide array of foodstuffs, such as tea<sup>(61,62)</sup>, red wine<sup>(63,64)</sup> and apple juice<sup>(65)</sup>. The maximal increase produced by juices is approximately 30% in the case of elderberry juice, which has a high phenolic content. An increase of 18% in plasma antioxidant activity was observed after an intake of 100 g dark chocolate<sup>(66)</sup>. Due to increased plasma antioxidant activity, the consumption of polyphenols with a

high-fat meal has been shown to decrease plasma lipid hydroperoxides. Natella *et al.*<sup>(67)</sup> showed that in eight healthy men who consumed a high-fat meal or meal of potatoes with (active) or without (placebo) 300 mg polyphenols, plasma lipid hydroperoxides were 1.5-fold higher in the placebo meal than in the polyphenol-active meal. Similarly, Nakagawa *et al.*<sup>(68)</sup> reported a reduction in plasma hydroperoxide levels in healthy subjects after acute ingestion of tea extract, equivalent to two cups of tea, and Miura *et al.*<sup>(69)</sup> observed a decreased oxidisability of LDL obtained from subjects who had ingested green tea extract daily for 1 week. In addition, plasma obtained from rats fed quercetin was more resistant to copper sulfate-induced lipid peroxidation than the control plasma on the basis of the accumulation of hydroperoxides and the degradation of  $\alpha$ -tocopherol. Based on the fact that quercetin is recovered in rat blood plasma principally as sulfate and glucuronide conjugates, these observations indicate that at least some metabolites of quercetin retain the ability to act as effective antioxidants<sup>(70)</sup>.

**Anticarcinogenic activity.** It has been shown that phenylacetic acids possess anticarcinogenic activities<sup>(71,72)</sup>. After the ingestion of polyphenols, the concentration in the gut should be much higher than in the plasma. For example, the dilution of 500 mg polyphenols with a digestive bolus in the colon would yield a local concentration of 3 mmol/l. Such a high local concentration in the colon may contribute to anticarcinogenic effects<sup>(31)</sup>. In addition, evidence exists for an inverse relationship between a moderate intake of red wine and the incidence of rectal cancer<sup>(73)</sup>, and this could be attributed to the colonic metabolites of malvidin-3-*O*-glucoside and other anthocyanins, which along with procyanidins are major components in many red wines. Protocatechuic acid is one of the catabolites derived from colonic microbial degradation of cyanidin-*O*-glucosides<sup>(74,75)</sup>, and it has apoptotic effects on human gastric adenocarcinoma cells in a time- and dose-dependent manner<sup>(76)</sup>. Forester & Waterhouse<sup>(77)</sup> found the anthocyanin microbial catabolites gallic acid, 3-*O*-methyl-gallic acid, vanillic acid, syringic acid and 2,4,6-trihydroxybenzaldehyde have the ability to induce apoptosis and inhibit cell proliferation in the human colon cancer cell. The effects of quercetin metabolites on lung cancer cells have also been investigated. Yang *et al.*<sup>(78)</sup> demonstrated that quercetin glucuronides were able to inhibit proliferation and induce apoptosis via the caspase-3 cascade in the human lung cancer cell.

**Other bioactivities.** In addition to their antioxidant and anticarcinogenic properties, polyphenols have several other biological actions. For instance, polyphenols modulate the activity of a wide range of enzymes and cell receptors<sup>(79,80)</sup> and also interfere with the activity and expression of several cell membrane transporters<sup>(81)</sup>. In addition, certain flavonoids could act as cytochrome-P450 inhibitors and enhance drug bioavailability. Increased plasma concentrations of many drugs have been shown

following co-administration with grapefruit juice<sup>(82)</sup>. Certain polyphenols, such as quercetin, are also efficient inhibitors of sulfotransferases<sup>(83–86)</sup> and thus may have an effect on the function of thyroid hormones, steroids and catecholamines<sup>(87)</sup>. Platelet activation and subsequent aggregation play a major role in the pathogenesis of thromboembolic diseases such as myocardial infarction and IHD. Hyperactive platelets with a high predisposition for activation are known to be apparent under conditions such as diabetes and heart disease<sup>(88)</sup>. Dihydroferulic and chlorogenic acids partly reversed hyper-reactivity of platelets induced by oxidative stress<sup>(89,90)</sup>, and could also counteract the negative effects of hormonal stress-induced platelet hyper-reactivity<sup>(91)</sup>. Moreover, certain microbial metabolites of polyphenols, such as 3,4-dihydroxyphenylacetic acid and 4-hydroxyphenylacetic acid, have been suggested to inhibit platelet aggregation<sup>(92)</sup>. From the inflammation perspective, protocatechuic acid has been reported to inhibit monocyte adhesion to TNF- $\alpha$ -activated mouse aortic endothelial cells, and also to reduce intercellular adhesion molecule 1 expression and the nuclear content of p65<sup>(93)</sup>. Modulation by quercetin metabolites of endothelial function, which has a strong connection with inflammation, has also been investigated. All quercetin metabolites partially prevented the impairment of the endothelial-derived NO response under conditions of high oxidative stress induced by diethyldithiocarbamic acid, a superoxide dismutase inhibitor, and protected the biological activity of exogenous NO<sup>(94)</sup>.

### Interaction of plant phenols with food macronutrients: *in vitro* evidence

#### Interaction of plant phenols with proteins

The interaction of polyphenols with proteins is an old but continuous research topic. Principally, two types of interactions can be classified between phenolic compounds and proteins: covalent and non-covalent binding<sup>(95,96)</sup>. The formation of covalent bonds between proteins and polyphenols is an irreversible reaction<sup>(97)</sup>, involving the oxidation of phenolic compounds and the formation of *o*-quinones or *o*-semi-quinones<sup>(98–100)</sup> or the cleavage of proanthocyanidin interflavanic bonds in an acid medium with the formation of carbocations<sup>(101)</sup>. Physiologically and technologically relevant data from the literature suggest that the majority of protein–polyphenol interactions may occur by non-covalent binding<sup>(102)</sup>, although both covalent and non-covalent binding are likely to occur simultaneously, as shown for the binding of chlorogenic acid to proteins<sup>(103)</sup>. Three types of non-covalent interactions have been suggested: hydrogen, hydrophobic and ionic bonding<sup>(104)</sup>.

Plasma proteins are the most studied binding targets, especially albumin. Albumin is the primary protein that interacts with polyphenols in the blood. The incubation

of quercetin with human plasma revealed that quercetin extensively binds to plasma proteins<sup>(105)</sup>. Smith *et al.*<sup>(106)</sup> found that the binding of polyphenols, such as quercetin, myricetin and morin, to albumin reduces polyphenols' antioxidant activity. Similarly, Rohn *et al.*<sup>(107)</sup> showed that the quercetin–albumin interaction decreases total antioxidant activity in comparison with an equivalent amount of free quercetin.

In addition to plasma proteins, interactions may occur between polyphenols and food proteins. In many countries, phenolic-rich foods, such as coffee and tea, are usually consumed with milk. It was observed that the radical-scavenging activity of black tea alone was significantly higher than with milk<sup>(108)</sup>. Lorenz *et al.*<sup>(109)</sup> showed that the addition of milk to black tea blunted the tea's beneficial vascular effects, and milk caseins were identified as interfering agents via interaction with tea catechins and the subsequent formation of complexes. Similarly, Hasni *et al.*<sup>(110)</sup> reported preferred binding sites in  $\alpha$ - and  $\beta$ -caseins for tea catechins and suggested that the binding involves hydrogen bonding and hydrophobic interactions. For coffee–milk beverages, an immediate decrease of *in vitro* bioaccessible polyphenols was found when milk was mixed with coffee, which was also due to the binding of polyphenols to milk proteins<sup>(111)</sup>. In addition, soya proteins behave in a similar manner to milk caseins, resulting in protein–polyphenol binding and a net loss of antioxidant activity<sup>(112)</sup>. This is reasonable considering the structural similarities of soya proteins and milk caseins. A cross-reactivity of milk caseins with soya-bean glycinin and  $\beta$ -conglycinin has been described<sup>(113)</sup>. Further support is that polyphenols bind to the proline-rich regions of proteins, with subsequent complexation<sup>(114)</sup>, and both soyabean glycinin and  $\beta$ -conglycinin contain proline-rich regions<sup>(115)</sup>.

In addition to food proteins, polyphenols have been reported to bind to enzymes. Phenolic extracts from a number of plants were found to be effective inhibitors of intestinal  $\alpha$ -glucosidase/maltase activity<sup>(116)</sup>. The inhibitory effect is generally attributed to the ability of polyphenols to bind to the enzymes<sup>(117–119)</sup>. Similarly,  $\alpha$ -glucosidase activity *in vitro* was significantly inhibited by anthocyanin-rich extracts of blueberry and blackcurrant<sup>(120)</sup>. Extracts of *Salacia reticulata* are used to prevent diabetes and obesity in Japan and exhibit pancreatic lipase inhibition, which has been partly attributed to (–)-epigallocatechin, (–)-epigallocatechin dimers, and a 'tannin' fraction<sup>(121)</sup>. A comprehensive study on the inhibition of pancreatic lipase by tea polyphenols suggested that epigallocatechin 3-*O*-gallate was an effective inhibitor<sup>(122)</sup>. Proteases have also been shown to be inhibited by polyphenols. Trypsin was inhibited by phenolic-rich extracts of cocoa, pears and lentils<sup>(123)</sup>.

Factors influencing the *in vitro* interactions of polyphenols with proteins are related to the physical and chemical properties of both proteins and polyphenols. It has been

suggested that high-molecular-weight polyphenols bind to proteins more effectively<sup>(124,125)</sup>. In contrast, when the conformation of a polyphenol is constrained, its capacity to interact with proteins is dramatically reduced regardless of the polyphenol's molecular weight<sup>(126–129)</sup>. In addition, hydrophobicity favours a strong association between proteins and polyphenols<sup>(130)</sup>. The ability of proteins to bind to polyphenols also depends on protein size, secondary/tertiary structure and amino acid composition. In general, proteins that interact strongly with polyphenols have a high basic-residue content and a high proline content, are relatively large and hydrophobic, and have a conformationally open and flexible structure<sup>(131–138)</sup>. More details on the structure–affinity relationship of the interactions between polyphenols and proteins can be found in the review by Xiao & Kai<sup>(139)</sup>.

### Interaction of plant phenols with carbohydrates

A study of a phenolic acid–starch model system indicated that the interactions of phenolic acid with starch significantly contributed to the inhibitory effect of starch hydrolysis<sup>(140)</sup>. The carboxyl and hydroxyl groups of phenolic acids are capable of binding to starch and other polysaccharides through hydrogen bonds, chelation or covalent bonds, forming bridges or cross-links<sup>(141)</sup>. The effect of tannic acid and catechin on legume starch hydrolysis<sup>(142)</sup> and the interference of gallic and chlorogenic acids with the starch–iodine reaction have been reported<sup>(143)</sup>. In addition to phenolic acids, various studies have shown that proanthocyanidins can interact with the different polysaccharides<sup>(144,145)</sup>. Oligomeric and polymeric procyanidins have the ability to bind non-covalently on apple cell walls by simple incubation in aqueous buffer<sup>(146–148)</sup>. Moreover, the amount of procyanidins bound to the cell wall increases with procyanidin concentrations, degree of polymerisation and percentage of galloylation<sup>(146–148)</sup>. In addition, the apparent affinity constants between procyanidins and polysaccharides were found to decrease as follows: pectins > xyloglucan > starch > cellulose<sup>(148)</sup>. Higher affinities are obtained with pectin, a polysaccharide having the ability to develop a gel-like network, forming hydrophobic pockets to encapsulate procyanidins. It has been reported that complex formation between soluble pectin and tannins reduces the astringency of both fresh juice and a solution of tannins purified from persimmon fruit<sup>(149)</sup>. Filamentous and globular polysaccharides, like cellulose and xyloglucan, bind procyanidins weakly. The results are consistent with the results of Renard *et al.*<sup>(150)</sup> which showed that xyloglucan has no marked effect for the procyanidins with a high degree of polymerisation. It was reported that nearly 35% of the polyphenols in red wine are bound to soluble dietary fibre<sup>(151)</sup>. It has also been reported that polyphenol–pectin complexes show no superoxide-scavenging capacity, have reduced hydroxyl

radical-scavenging activity, and have high 2,2-diphenyl-1-picrylhydrazyl radical-scavenging activity, indicating potential changes in functionality because of complex formation<sup>(152)</sup>. Another cellular study showed that when the extract was ingested along with carbohydrate-rich food, an enhanced uptake of polyphenols was observed<sup>(153)</sup>. This finding is in agreement with the results of Schramm *et al.*<sup>(154)</sup>, who reported an enhanced activity of carbohydrate-rich foods and suggested that this effect may be mediated by a yet-unidentified carbohydrate–flavanol transporter.

### Interaction of plant phenols with fats

Only a few studies have focused on the *in vitro* interactions between fats and polyphenols. A positive relationship has been observed between fat concentration and bioaccessibility of polyphenols after *in vitro* gastropancreatic digestion<sup>(111)</sup>. Results have indicated that a high fat content in food seems to have a protective effect, as hydrophobic interactions between fats and polyphenols increase the stability of polyphenols during digestion<sup>(155)</sup>. Similarly, the lipid fraction (rich in PUFA) showed a protective effect on the recovery of phenolic compounds during duodenal digestion. Disruption of the natural matrix under digestive conditions led to the release of PUFA, which could establish interactions with phenolic compounds, enhancing the compounds' recovery and stability during digestion<sup>(156)</sup>. Certain indirect evidence has been provided by Langley-Evans<sup>(157)</sup>, who found that the addition of soya milk or cows' milk appeared to diminish the antioxidant potential of black tea preparations. This effect was greatest when whole milk was used and appeared to be primarily related to the fat content of the added milk<sup>(158)</sup>.

### Interaction of plant phenols with food macronutrients: *in vivo* results

#### Interaction of plant phenols with proteins

Bioavailability refers to the extent to which and rate at which a substance becomes available to target tissue after administration. The clarification of polyphenol bioavailability is important because the polyphenol content and biological activity observed *in vitro* have little nutritional relevance unless the active metabolites of polyphenols can gain access to appropriate sites within the body<sup>(159)</sup>. So far, few studies have investigated the effect of proteins alone on the bioavailability of phenolic compounds. Most researchers used foodstuffs directly. Milk is the most often chosen food because phenolic-rich foods are usually consumed with milk. Serafini *et al.*<sup>(61)</sup> found that compared with tea consumed without milk, the antioxidant potential of tea with milk decreased. Mullen *et al.*<sup>(160)</sup> reported that milk significantly lowered the excretion of urinary flavan-3-ol metabolites. The overall 0–24 h excretion of metabolites corresponded to 18.3% of intake after ingestion of a

cocoa–water beverage compared with 10.5% after ingestion of a cocoa–milk beverage. Moreover, they emphasised that, with a lower flavan-3-ol content, which is typical of commercial cocoas that are available to the general public, milk does have the capacity to interfere with absorption. Lorenz *et al.*<sup>(109)</sup> showed that the addition of milk to black tea blunted the tea's beneficial vascular effects. Similarly, yoghurt was also reported to have a marked impact on the urinary excretion of phenolic acids. The overall 0–24 h excretion of phenolic acids was 62  $\mu\text{mol}$  after drinking orange juice alone and this fell markedly to 9.3  $\mu\text{mol}$  when the orange juice was ingested with yoghurt<sup>(161)</sup>. There were also several other studies that showed that the absorption of phenolic compounds or increased plasma antioxidant capacity is suppressed when the compounds are consumed with milk<sup>(162,163)</sup>. Most studies have attributed this inhibitory effect of milk to milk proteins because phenolic compounds can bind to milk proteins through hydrogen bonds and hydrophobic interactions<sup>(124,164)</sup>. However, this speculation is based on *in vitro* studies. In addition to proteins, there are other macronutrients, such as carbohydrates and fats, in whole milk. These nutrients' possible effects cannot be excluded. In our recent study, after excluding the effects of other macronutrients, it was found that milk proteins led to significant changes in the plasma kinetics profile of polyphenols but did not affect the overall absorption of polyphenols in rats<sup>(9)</sup>. Similarly, it was also found that milk proteins extended the time needed to reach a maximal plasma polyphenol concentration in human subjects<sup>(10)</sup>. Casein, which is a major component of milk

protein, can form curds in the stomach that delay casein's absorption compared with other proteins<sup>(165)</sup>. It has been suggested that polyphenols can bind to milk proteins and subsequently form complexes<sup>(166,167)</sup>. Therefore, the *in vivo* results may be explained by the formation of protein–polyphenol complexes that remain in the stomach for an extended period of time, thereby delaying the appearance of polyphenols in the blood. Additionally, the absence of an effect on overall polyphenol absorption indicated that polyphenols could be released from the complexes and be absorbed later. Certainly, more studies are needed to evaluate the effect of different types of proteins on the bioavailability and *in vivo* bioactivity of polyphenols.

### Interaction of plant phenols with carbohydrates

Consistent with the *in vitro* results, it has been shown that sugar and bread increase flavanol AUC values to 140% of controls. The ability of treated meals to affect AUC values has been found to be positively correlated with carbohydrate content<sup>(154)</sup> (Table 2). Moreover, Neilson *et al.*<sup>(168)</sup> reported that the presence of sucrose in chocolate may positively influence the bioavailability of flavan-3-ols compounds. Several studies have attempted to clarify the mechanism associated with this increase in polyphenol bioavailability. The positive effects observed for carbohydrate-rich foods (bread, sucrose and grapefruit juice) may have been mediated by a carbohydrate-specific effect on gastrointestinal motility and/or secretion<sup>(154)</sup>. Along with an increase in the absorption of cocoa flavanols, a

**Table 2.** *In vivo* studies assessing the effects of food macronutrients on the bioavailability and bioactivity of polyphenols

Food	Subjects	Experimental diet	Main results	Reference
Milk proteins	Rats ( <i>n</i> 8 per group)	0.9 mg polyphenols with 41.2 mg proteins	Biphasic profile of absorption	Zhang <i>et al.</i> (2012) <sup>(9)</sup>
Milk proteins	Human subjects ( <i>n</i> 20)	64.3 mg polyphenols with 6.6 g proteins	Delay the absorption	Zhang <i>et al.</i> (2013) <sup>(10)</sup>
Sugar	Human subjects ( <i>n</i> 6)	0.125 g flavanol-rich cocoa/kg body weight with 17.5 kJ sugar/kg body weight	↑ Absorption and antioxidant activity	Schramm <i>et al.</i> (2003) <sup>(154)</sup>
Difrutose anhydride III	Rats ( <i>n</i> 10 per group)	100 $\mu\text{mol}$ $\alpha\text{-G-rutin}$ with 100 $\mu\text{mol}$ difrutose anhydride III	↑ Absorption	Matsumoto <i>et al.</i> (2007) <sup>(169)</sup>
Oligosaccharides	Rats ( <i>n</i> 5 per group)	8.5 mg genistein and 33 mg daidzein/kg body weight with 5% (w/w) oligosaccharides in diet	Prolong the clearance of polyphenols	Uehara <i>et al.</i> (2001) <sup>(174)</sup>
Oatmeal	Rats ( <i>n</i> 5 per group)	250 mg polyphenols/kg body weight with 6.7% (w/w) oatmeal	Delay the absorption	Walton <i>et al.</i> (2009) <sup>(189)</sup>
Lard	Pigs ( <i>n</i> 7 per group)	30 $\mu\text{mol}$ quercetin/kg body weight with 17% (w/w) lard in diet	↑ Absorption	Lesser <i>et al.</i> (2004) <sup>(192)</sup>
Soyabean oil, fish oil and beef tallow	Rats ( <i>n</i> 5 per group)	3.94 mg quercetin aglycone equivalent with 9.5% (w/w) fat in diet	↑ Absorption	Azuma <i>et al.</i> (2003) <sup>(193)</sup>
Octanoic and decanoic acid	Pigs ( <i>n</i> 6 per group)	30 $\mu\text{mol}$ quercetin/kg body weight with 15% (w/w) fat in diet	Delay the absorption	Lesser <i>et al.</i> (2006) <sup>(194)</sup>
Olive oil	Human subjects ( <i>n</i> 5)	292 mg polyphenols with 5% (w/w) olive oil in diet	Biphasic profile of absorption	Tulipani <i>et al.</i> (2012) <sup>(195)</sup>
Cream	Human subjects ( <i>n</i> 8)	222 $\mu\text{mol}$ pelargonidin-3- <i>O</i> -glucoside with 100 ml cream	Delay the absorption	Mullen <i>et al.</i> (2008) <sup>(196)</sup>
Milk fats	Human subjects ( <i>n</i> 6)	180 mg anthocyanins with a high-fat meal	Delay the absorption	Murkovic <i>et al.</i> (2000) <sup>(197)</sup>
Milk fats	Rats ( <i>n</i> 8 per group)	0.9 mg polyphenols with 47.5 mg milk fats	No effects	Zhang <i>et al.</i> (2012) <sup>(9)</sup>
Milk fats	Human subjects ( <i>n</i> 20)	64.3 mg polyphenols with 7.6 g milk fats	No effects	Zhang <i>et al.</i> (2013) <sup>(10)</sup>

↑, Increase.

faster rate of flavanol elimination following sugar treatment has been observed. This observation is consistent with the concept of an increased tubular secretion of xenobiotics with increased solute filtration. Increased solute filtration can result from higher blood solute (xenobiotic) concentrations and an increased glomerular filtration rate<sup>(154)</sup>. In addition, an indigestible saccharide, difructose anhydride III, has been demonstrated to promote rutin absorption after a single bolus administration using portally and duodenally cannulated rats<sup>(169)</sup>. This disaccharide is an enhancer of paracellular transport in the small intestine<sup>(170)</sup>. Furthermore, difructose anhydride III is fermentable in the large intestine<sup>(171)</sup>, and it has been suggested that the bacterial fermentation of difructose anhydride III affects the bioavailability of flavonoid glycosides<sup>(172)</sup>. It has also been suggested that fructo-oligosaccharides, which are the most popular non-digestible oligosaccharides and are well established to be readily fermentable<sup>(173)</sup>, increase isoflavone glycoside absorption with the promotion of intestinal fermentation<sup>(174)</sup>. The results strongly suggest that increased fermentation by oligosaccharides in the large intestine enhances polyphenol bioavailability. Moreover, the fermentation of oligosaccharides enlarges the intestinal mucosa<sup>(175)</sup>, suppresses the bacterial degradation of polyphenols in the caecum<sup>(176)</sup> and stimulates mucosal blood flow<sup>(177)</sup>, which may also contribute to polyphenol absorption in the large intestine. In addition, the cell walls are major components in fruits and vegetables and their impact cannot be ignored. Proanthocyanidins are associated with cell walls through either weak (hydrophilic/hydrophobic)<sup>(147,148)</sup> or strong (covalent) interactions<sup>(178)</sup>, which may influence their absorption<sup>(179)</sup>. Early studies suggested that condensed tannins were not absorbed from the digestive tract of chicken and sheep<sup>(180,181)</sup>. Recent rat and human studies suggested that proanthocyanidins with more than three subunits could be more resistant to degradation due to their chemical structure and, therefore, higher levels are observed in the colon<sup>(47)</sup>. Similar results were observed for hydroxycinnamic acid derivatives. In wheat, ferulic acid is ester-linked to position O-5 of the arabinosyl side chains of cell wall arabinoxylans. In fact, the presence of ester-linked monomeric and dimeric phenolics leads to reduced biodegradability of the cell wall polysaccharide, and limits the release of ferulic acid. Diferulates have a dramatic effect on both the rate and extent of polysaccharide degradation. Cross-linking through diferulates may inhibit the binding of endoxylanases, thus limiting the extent of arabinoxylan degradation and consequently the release of esterified ferulic acid<sup>(182)</sup>. Furthermore, cross-linking may prevent localised areas from swelling, excluding key enzymes for dietary fibre degradation<sup>(183)</sup>. Likewise, Aprikian *et al.*<sup>(184)</sup> showed that procyanidins with high polymerisation inhibit enzymic degradation of cell walls in apples. Finally, covalently bound phenolics are released only after extensive microbial digestion in the colon<sup>(185)</sup>.

In addition to the effect on absorption, carbohydrates have been observed to change the plasma kinetics profile of polyphenols. Bub *et al.*<sup>(186)</sup> reported that the mean time required to achieve a maximal plasma concentration of malvidin 3-glucoside was extended after the ingestion of red grape juice compared with red wine in human subjects. The researchers concluded that the delaying effect of the sugar present in the red grape juice could result from the competition of glucose and malvidin 3-glucoside for the Na-dependent GLUT, as reported for quercetin 3-glucoside<sup>(187,188)</sup>. The viscosities of certain types of carbohydrates also cannot be ignored. Anthocyanins were absorbed and excreted more slowly when administered in an acidified oatmeal solution than in an acidified water solution<sup>(189)</sup>. The addition of sucrose resulted in a slight delay in reaching a maximal plasma concentration. This delay may be partly due to the increase in the viscosity of sucrose<sup>(11)</sup>. Sucrose formulations were observed to have viscosities approximately six times higher than non-sucrose-containing formulations. Increased viscosity is known to have an impact on gastric emptying and can influence the kinetics of absorption for phenolic compounds in the small intestine<sup>(190)</sup>. As non-extractable proanthocyanidins are associated with the food matrix, particularly with insoluble polymers such as dietary fibre, their absorption may be slower compared with that of extractable proanthocyanidins. This deferred release would make non-extractable proanthocyanidin metabolites bioavailable for a long time after intake and may result in long-term health effects<sup>(41)</sup>. There is supporting evidence that the presence of ferulic acid–arabinoxylans bonds in the food matrix increases the occurrence time of ferulic acid in the organism. The phenomenon may be explained by a slower hydrolysis rate of phenolics–cell wall bonds by intestinal enzymes<sup>(191)</sup>.

### Interaction of plant phenols with fats

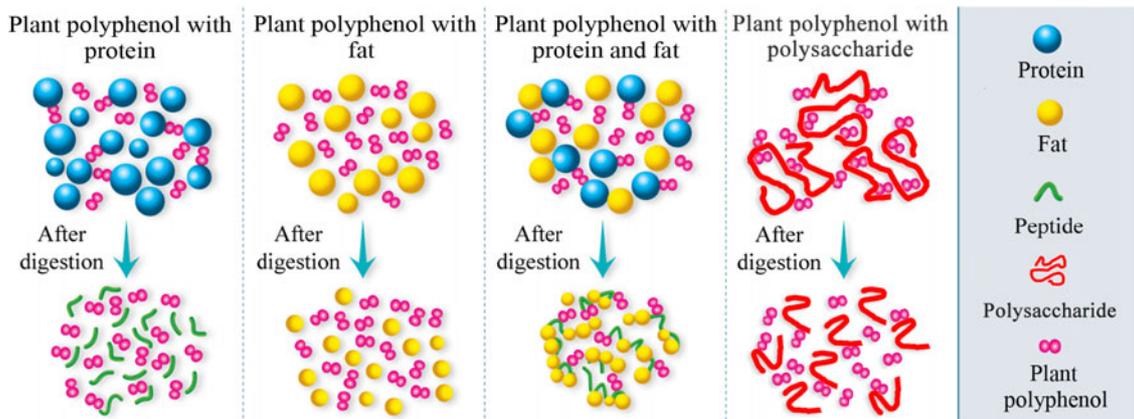
Many investigations have shown that the co-ingestion of lipids could affect the bioavailability of polyphenols (Table 2)<sup>(192–197)</sup>. In a pig study, the bioavailability of quercetin was significantly higher in a 17% fat diet compared with a 3% fat diet<sup>(192)</sup>. Azuma *et al.*<sup>(198)</sup> observed that the co-administration of lipids (soyabean oil or lecithin) and emulsifiers was able to enhance the intestinal absorption of quercetin in rats. In another rat study, the absorption of catechin was enhanced when green tea was administered as a phospholipid complex rather than as free catechins<sup>(199)</sup>. It has also been shown that more than 4.6% (w/w) of soyabean oil in diets significantly enhanced the accumulation of quercetin metabolites in the plasma. Fish oil and beef tallow increased this accumulation to an extent similar to that of soyabean oil<sup>(193)</sup>. In addition to fat concentration, the effects of different fat types on the bioavailability of polyphenols have also been assessed. For example, the chain length of fatty acids has been

reported to influence the micellarisation of phenolic compounds during digestion. Bioavailability was enhanced by 38% and 12% after intake along with medium-chain fatty acid and long-chain fatty acid diets, respectively, compared with the standard diet<sup>(194)</sup>. Moreover, the degree of saturation may affect the bioavailability of polyphenols. Goltz *et al.*<sup>(200)</sup> observed the increased absorption of carotenoids from a vegetable salad with higher levels of lipids and found that unsaturated fat promoted carotenoid absorption to a greater extent than saturated fat. For the mechanism associated with this increase in polyphenol bioavailability, it has been suggested that dietary fat can probably promote the solubility of polyphenols<sup>(192,201)</sup>.

In addition, fat has been reported to affect the absorption kinetics of polyphenols. After the ingestion of oil-enriched tomato sauces, naringenin metabolites showed a biphasic profile of absorption in the plasma, suggesting that the lipid matrix added to the sauce may stimulate reabsorption events via the enterohepatic circulation, thus potentially affecting the apparent plasma half-life of the flavanone before excretion<sup>(195)</sup>. Additionally, a delay in attaining a maximal plasma concentration was observed in subjects consuming strawberries with cream<sup>(196)</sup>. These observations are consistent with an earlier study showing that the time needed to reach a maximal serum level was significantly extended when anthocyanins were consumed together with a high-fat meal<sup>(197)</sup>. It was suggested that the fat present in the cream slowed the transit of anthocyanins due to duodenal and ileal brakes activated by fat<sup>(196,202)</sup>. It has also been shown that a maximal plasma concentration of quercetin was reached significantly later for a medium-chain fatty acid diet than for a long-chain fatty acid or a standard diet<sup>(194)</sup>.

Recently, a novel effect of fat on the bioavailability and antioxidant activity of polyphenols was found. At a relatively low content (3.8% (w/v) in milk), milk fat alone did not interact with polyphenols and did not have an effect on the bioavailability and antioxidant activity of polyphenols in rats and human subjects<sup>(9,10)</sup>. Similarly, milk proteins did not affect the absorption and antioxidant

activity of polyphenols. However, the combination of milk proteins and fats showed the highest degree of inhibition for both the bioavailability and the antioxidant capacity of polyphenols. To clarify the exact mechanism of this phenomenon, further *in vitro* and *in vivo* experiments were performed. The results showed that no significant difference was found in the median diameters of the emulsions between the consumption of polyphenols with milk fat and the consumption of milk fat alone, in accordance with the *in vivo* results, which did not show any interaction between milk fats and polyphenols. The median diameter of the mixture was significantly higher when polyphenols were consumed along with milk proteins than when milk proteins alone were consumed. The findings suggested the formation of milk protein–polyphenol complexes. However, during digestion, the decreasing trend of the median diameter indicated the breakdown of the milk protein–polyphenol complexes. Nevertheless, when polyphenols, milk proteins and fats were ingested together, a significant increase in the median diameter of the emulsion was found during digestion<sup>(9)</sup>. Considering that polyphenols can bind to milk proteins<sup>(114)</sup> and that proteins can be adsorbed to the surface of lipid droplets<sup>(203)</sup>, the data evidenced the participation of milk fat in the interactions between milk proteins and polyphenols during digestion, resulting in remarkable aggregation. Unlike polyphenol–protein complexes, the complexes formed with proteins and fats did not completely break during digestion and thus impaired the bioavailability and antioxidant activity of the polyphenols. One possible reason is that the aggregation of the fat globules affects the way that gastrointestinal enzymes access substrates<sup>(204)</sup>. Another explanation is that lipase activity is inhibited by phenolic compounds<sup>(205)</sup> and long-chain fatty acids generated during digestion<sup>(206–208)</sup>. The findings show that there are synergisms between food macronutrients in affecting the bioavailability and bioactivity of polyphenols. Based on these results, we propose a hypothesis (Fig. 1) that allows the prediction of the effects of different food macronutrients on the bioavailability and bioactivity of polyphenols.



**Fig. 1.** A simplified scheme of the physico-chemical processes occurring before and after digestion when different food macronutrients are added to polyphenols. (A colour version of this figure can be found online at <http://www.journals.cambridge.org/nrr>)

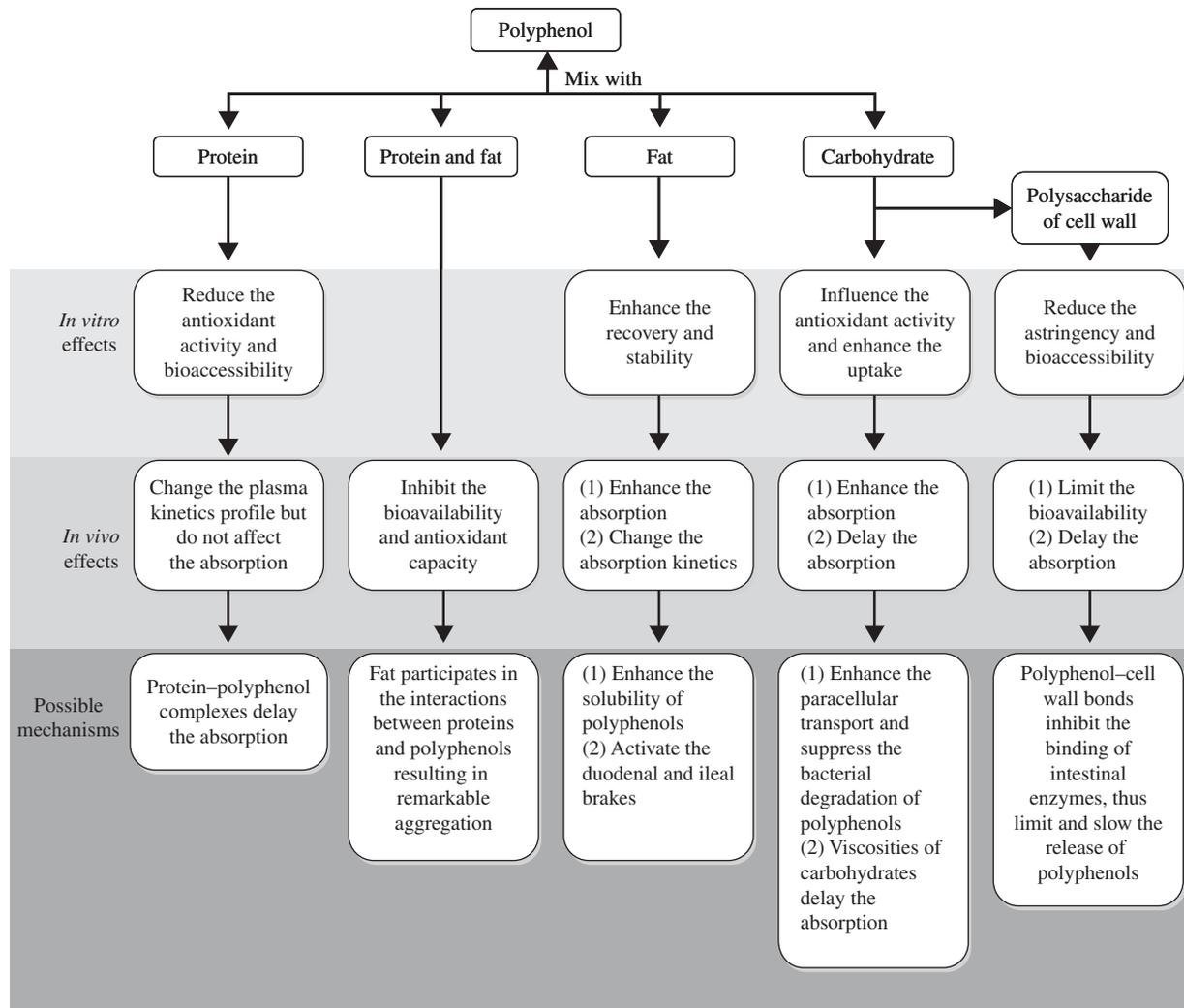


Fig. 2. Summary of the *in vitro* and *in vivo* effects of food macronutrients on the bioavailability and bioactivity of polyphenols.

### Conclusions and future directions

Epidemiological studies have demonstrated that polyphenols can reduce the risk of many diseases. Because the health benefits of polyphenols are critically based on the compounds' bioavailability, more direct attention should be paid to the factors affecting polyphenols' bioavailability. The evidence collected in the present review suggests that when plant phenols are consumed along with food macronutrients, the bioavailability and bioactivity of polyphenols can be significantly affected. As summarised in Fig. 2, proteins can reduce the *in vitro* antioxidant activity and significantly change the plasma kinetics profile of polyphenols without affecting the absorption. Carbohydrates can extend the time needed to reach a maximal plasma concentration. Fats can enhance the absorption and change the absorption kinetics of polyphenols. Moreover, as highlighted in the present review, not only a nutrient alone but also certain synergisms between food macronutrients have a significant effect on the bioavailability and biological activity of polyphenols.

In the future, it will be necessary to gain further insight into the interactive effects of food macronutrients on the bioavailability and bioactivity of polyphenols, including, but not limited to, the following. (1) More studies are needed to evaluate the *in vivo* fate of protein–polyphenol complexes for different types of proteins and the effect on the bioavailability and bioactivity of polyphenols. (2) More studies are necessary to further evaluate the interactions between different macronutrients and whether the nutrients' combination can have a collaborative or antagonistic effect on the healthy benefits of polyphenols. (3) Many studies have shown that many phenolic compounds are present in the plasma, largely in the form of metabolites. Therefore, future research efforts should better assess the effect of interactions with food macronutrients on the metabolism of polyphenols.

### Acknowledgements

The present review was a China Postdoctoral Science Foundation-funded project (no. 2012M520463) and

supported by the Beijing Higher Institution Engineering Research Center of Animal Product, National Science and Technology Support Program 'Twelfth Five-Year Plan' (no. 2012BAD12B08). The funders had no role in the design, analysis or writing of this article.

We acknowledge the contribution of all authors to the writing of the present review and H. Z. for conceiving the article. All authors approved the final manuscript.

The authors declare that they have no conflicts of interest.

## References

- Hu FB, Rimm EB, Stampfer MJ, *et al.* (2000) Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr* **72**, 912–921.
- Kart AK, Graubard BI & Schatzkin A (2004) Dietary patterns predict mortality in a national cohort: The National Health Interview Surveys, 1987 and 1992. *J Nutr* **134**, 1793–1799.
- McGinnis JM & Foege WH (1993) Actual causes of death in the United States. *JAMA* **270**, 2207–2212.
- Amarowicz R, Carle R, Dongowski G, *et al.* (2009) Influence of postharvest processing and storage on the content of phenolic acids and flavonoids in foods. *Mol Nutr Food Res* **53**, S151–S183.
- Haslam E (1974) Polyphenol–protein interactions. *Biochem J* **139**, 285–288.
- Halsam E & Lilley TH (1988) Natural astringency in foodstuffs – a molecular interpretation. *Crit Rev Food Sci Nutr* **27**, 1–40.
- Baxter NJ, Lilley TH, Haslam E, *et al.* (1997) Multiple interactions between polyphenols and a salivary proline-rich protein repeat result in complexation and precipitation. *Biochemistry* **36**, 5566–5577.
- Brunet MJ, Blade C, Salvado MJ, *et al.* (2002) Human apo A-I and rat transferrin are the principal plasma proteins that bind wine catechins. *J Agric Food Chem* **50**, 2708–2712.
- Zhang H, Zheng J, Liu X, *et al.* (2012) Milk protein and fat play different roles in affecting the bioavailability and the antioxidant activity of jujube juice phenolics in rats. *Mol Nutr Food Res* **56**, 1511–1519.
- Zhang H, Jiang L, Guo H, *et al.* (2013) The inhibitory effect of milk on the absorption of dietary phenolic acids and the change in human plasma antioxidant capacity through a mechanism involving both milk proteins and fats. *Mol Nutr Food Res* **57**, 1228–1236.
- Peters CM, Green RJ, Janle EM, *et al.* (2010) Formulation with ascorbic acid and sucrose modulates catechin bioavailability from green tea. *Food Res Int* **43**, 95–102.
- Manach C, Scalbert A, Morand C, *et al.* (2004) Polyphenols: food sources and bioavailability. *Am J Clin Nutr* **79**, 727–747.
- RiceEvans CA, Miller NJ & Paganga G (1996) Structure–antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic Biol Med* **20**, 933–956.
- Sampson L, Rimm E, Hollman PCH, *et al.* (2002) Flavonol and flavone intakes in US health professionals. *J Am Diet Assoc* **102**, 1414–1420.
- Hertog MGL, Kromhout D, Aravanis C, *et al.* (1995) Flavonoid intake and long-term risk of coronary-heart-disease and cancer in the 7 countries study. *Arch Intern Med* **155**, 381–386.
- Hertog MGL, Feskens EJM & Kromhout D (1997) Antioxidant flavonols and coronary heart disease risk. *Lancet* **349**, 699.
- Perez-Jimenez J, Neveu V, Vos F, *et al.* (2010) Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the phenol-explorer database. *J Agric Food Chem* **58**, 4959–4969.
- Serrano J, Puupponen-Pimiä R, Dauer A, *et al.* (2009) Tannins: current knowledge of food sources, intake, bioavailability and biological effects. *Mol Nutr Food Res* **53**, S310–S329.
- Harborne JB & Williams CA (2000) Advances in flavonoid research since 1992. *Phytochemistry* **55**, 481–504.
- Hammerstone JF, Lazarus SA & Schmitz HH (2000) Procyandin content and variation in some commonly consumed foods. *J Nutr* **130**, S2086–S2092.
- Carando S, Teissedre PL, Pascual-Martinez L, *et al.* (1999) Levels of flavan-3-ols in French wines. *J Agric Food Chem* **47**, 4161–4166.
- Lopez M, Martinez F, Del Valle C, *et al.* (2001) Analysis of phenolic constituents of biological interest in red wines by high-performance liquid chromatography. *J Chromatogr A* **922**, 359–363.
- Kreft S, Knapp M & Kreft I (1999) Extraction of rutin from buckwheat (*Fagopyrum esculentum* Moench) seeds and determination by capillary electrophoresis. *J Agric Food Chem* **47**, 4649–4652.
- Stewart AJ, Bozonnet S, Mullen W, *et al.* (2000) Occurrence of flavonols in tomatoes and tomato-based products. *J Agric Food Chem* **48**, 2663–2669.
- Rouseff RL, Martin SF & Youtsey CO (1987) Quantitative survey of narirutin, naringin, hesperidin, and neohesperidin in citrus. *J Agric Food Chem* **35**, 1027–1030.
- Reinli K & Block G (1996) Phytoestrogen content of foods – a compendium of literature values. *Nutr Cancer* **26**, 123–148.
- Le Bourvellec C & Renard CM (2012) Interactions between polyphenols and macromolecules: quantification methods and mechanisms. *Crit Rev Food Sci Nutr* **52**, 213–248.
- Zhang H, Jiang L, Ye S, *et al.* (2010) Systematic evaluation of antioxidant capacities of the ethanolic extract of different tissues of jujube (*Ziziphus jujuba* Mill.) from China. *Food Chem Toxicol* **48**, 1461–1465.
- Tomás-Barberán FA, Gil MI, Cremin P, *et al.* (2001) HPLC-DAD-ESIMS analysis of phenolic compounds in nectarines, peaches, and plums. *J Agric Food Chem* **49**, 4748–4760.
- Astill C, Birch MR, Dacombe C, *et al.* (2001) Factors affecting the caffeine and polyphenol contents of black and green tea infusions. *J Agric Food Chem* **49**, 5340–5347.
- Scalbert A & Williamson G (2000) Dietary intake and bioavailability of polyphenols. *J Nutr* **130**, S2073–S2085.
- Lotito SB, Renart ML & Fraga CG (2002) Assessing the antioxidant capacity in the hydrophilic and lipophilic domains: study of a sample of Argentine wines. *Ann N Y Acad Sci* **957**, 284–287.
- Actis-Goretta L, Mackenzie GG, Oteiza PI, *et al.* (2002) Comparative study on the antioxidant capacity of wines and other plant-derived beverages. *Ann N Y Acad Sci* **957**, 279–283.
- Rivero D, Perez-Magarino S, Gonzalez-Sanjose ML, *et al.* (2005) Inhibition of induced DNA oxidative damage by beers: correlation with the content of polyphenols and melanoidins. *J Agric Food Chem* **53**, 3637–3642.
- Aziz AA, Edwards CA, Lean Lean, *et al.* (1998) Absorption and excretion of conjugated flavonols, including quercetin-4'-O-β-glucoside and isorhamnetin-4'-O-β-glucoside by human volunteers after the consumption of onions. *Free Radic Res* **29**, 257–269.
- Hollman PC, Gaag MVD, Mengelers MJ, *et al.* (1996) Absorption and disposition kinetics of the dietary antioxidant quercetin in man. *Free Radic Biol Med* **21**, 703–707.

37. Kivits GAA, van der Sman FJP & Tijburg LBM (1997) Analysis of catechins from green and black tea in humans: a specific and sensitive colorimetric assay of total catechins in biological fluids. *Int J Food Sci Nutr* **48**, 387–392.
38. Day AJ, DuPont MS, Ridley S, *et al.* (1998) Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver  $\beta$ -glucosidase activity. *FEBS Lett* **436**, 71–75.
39. Day AJ, Cañada FJ, Díaz JC, *et al.* (2000) Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Lett* **468**, 166–170.
40. Spencer JPE, Chaudry F, Pannala AS, *et al.* (2000) Decomposition of cocoa procyanidins in the gastric milieu. *Biochem Biophys Res Commun* **272**, 236–241.
41. Mateos-Martín ML, Pérez-Jiménez J, Fuguet E, *et al.* (2012) Non-extractable proanthocyanidins from grapes are a source of bioavailable (epi)catechin and derived metabolites in rats. *Br J Nutr* **108**, 290–297.
42. Deprez S, Brezillon C, Rabot S, *et al.* (2000) Polymeric proanthocyanidins are catabolized by human colonic microflora into low-molecular-weight phenolic acids. *J Nutr* **130**, 2733–2738.
43. Rios LY, Gonthier MP, Rémésy C, *et al.* (2003) Chocolate intake increases urinary excretion of polyphenol-derived phenolic acids in healthy human subjects. *Am J Clin Nutr* **77**, 912–918.
44. Bazzocco S, Mattila I, Guyot S, *et al.* (2008) Factors affecting the conversion of apple polyphenols to phenolic acids and fruit matrix to short-chain fatty acids by human faecal microbiota *in vitro*. *Eur J Nutr* **47**, 442–452.
45. Aura AM, Mattila I, Hyötyläinen T, *et al.* (2013) Characterization of microbial metabolism of Syrah grape products in an *in vitro* colon model using targeted and non-targeted analytical approaches. *Eur J Nutr* **52**, 833–846.
46. Gonthier MP, Donovan JL, Texier O, *et al.* (2003) Metabolism of dietary procyanidins in rats. *Free Radic Biol Med* **35**, 837–844.
47. Choy YY, Jagers GK, Oteiza PI, *et al.* (2013) Bioavailability of intact proanthocyanidins in the rat colon after ingestion of grape seed extract. *J Agric Food Chem* **61**, 121–127.
48. Walle T (2004) Absorption and metabolism of flavonoids. *Free Radic Biol Med* **36**, 829–837.
49. Karakaya S (2004) Bioavailability of phenolic compounds. *Crit Rev Food Sci Nutr* **44**, 453–464.
50. Day AJ, Bao Y, Morgan MR, *et al.* (2000) Conjugation position of quercetin glucuronides and effect on biological activity. *Free Radic Biol Med* **29**, 1234–1243.
51. Koster H, Halsema I, Scholtens E, *et al.* (1981) Dose-dependent shifts in the sulfation and glucuronidation of phenolic compounds in the rat *in vivo* and in isolated hepatocytes: the role of saturation of phenolsulfo-transferase. *Biochem Pharmacol* **30**, 2569–2575.
52. Piskula MK (2000) Soy isoflavone conjugation differs in fed and food-deprived rats. *J Nutr* **130**, 1766–1771.
53. Bors W & Saran M (1987) Radical scavenging by flavonoid antioxidants. *Free Radic Res Commun* **2**, 289–294.
54. Bors W, Michel C & Stettmaier K (2001) Structure–activity relationships governing antioxidant capacities of plant polyphenols. *Methods Enzymol* **335**, 166–180.
55. Lotito SB & Frei B (2004) Relevance of apple polyphenols as antioxidants in human plasma: contrasting *in vitro* and *in vivo* effects. *Free Radic Biol Med* **36**, 201–211.
56. Gómez-Ruiz JÁ, Leake DS & Ames JM (2007) *In vitro* antioxidant activity of coffee compounds and their metabolites. *J Agric Food Chem* **55**, 6962–6969.
57. Shafiee M, Carbonneau MA, Urban N, *et al.* (2003) Grape and grape seed extract capacities at protecting LDL against oxidation generated by Cu<sup>2+</sup>, AAPH or SIN-1 and at decreasing superoxide THP-1 cell production. A comparison to other extracts or compounds. *Free Radic Res* **37**, 573–584.
58. Crozier A, Jaganath IB & Clifford MN (2009) Dietary phenolics: chemistry, bioavailability and effects on health. *Nat Prod Rep* **26**, 1001–1043.
59. Fernandez-Panchon MS, Villano D, Troncoso AM, *et al.* (2008) Antioxidant activity of phenolic compounds: from *in vitro* results to *in vivo* evidence. *Crit Rev Food Sci Nutr* **48**, 649–671.
60. Prior RL, Go L, Wu X, *et al.* (2007) Plasma antioxidant capacity changes following a meal as a measure of the ability of a food to alter *in vivo* antioxidant status. *J Am Coll Nutr* **26**, 170–181.
61. Serafini M, Ghiselli A & Ferro-Luzzi A (1996) *In vivo* antioxidant effect of green and black tea in man. *Eur J Clin Nutr* **50**, 28–32.
62. van het Hof KH, de Boer HS, Wiseman SA, *et al.* (1997) Consumption of green or black tea does not increase resistance of low-density lipoprotein to oxidation in humans. *Am J Clin Nutr* **66**, 1125–1132.
63. Duthie GG, Pedersen MW, Gardner PT, *et al.* (1998) The effect of whisky and wine consumption on total phenol content and antioxidant capacity of plasma from healthy volunteers. *Eur J Clin Nutr* **52**, 733–736.
64. Serafini M, Maiani G & Ferro-Luzzi A (1998) Alcohol-free red wine enhances plasma antioxidant capacity in humans. *J Nutr* **128**, 1003–1007.
65. Young JF, Nielsen SE, Haraldsdottir J, *et al.* (1999) Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. *Am J Clin Nutr* **69**, 87–94.
66. Serafini M, Bugianesi R, Maiani G, *et al.* (2003) Plasma antioxidants from chocolate: dark chocolate may offer its consumers health benefits the milk variety cannot match. *Nature* **424**, 1013.
67. Natella F, Belevi F, Gentili V, *et al.* (2002) Grape seed proanthocyanidins prevent plasma postprandial oxidative stress in humans. *J Agric Food Chem* **50**, 7720–7725.
68. Nakagawa K, Ninomiya M, Okubo T, *et al.* (1999) Tea catechin supplementation increases antioxidant capacity and prevents phospholipid hydroperoxidation in plasma of humans. *J Agric Food Chem* **47**, 3967–3973.
69. Miura Y, Chiba T, Miura S, *et al.* (2000) Green tea polyphenols (flavan 3-ols) prevent oxidative modification of low density lipoproteins: an *ex vivo* study in humans. *J Nutr Biochem* **11**, 216–222.
70. da Silva EL, Piskula MK, Yamamoto N, *et al.* (1998) Quercetin metabolites inhibit copper ion-induced lipid peroxidation in rat plasma. *FEBS Lett* **430**, 405–408.
71. Samid D, Hudgins WR, Shack S, *et al.* (1997) Phenylacetate and phenylbutyrate as novel, nontoxic differentiation inducers. In *Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury 2*, vol. 400, pp. 501–505 [K Honn, S Nigam and L Marnett, editors]. New York: Springer.
72. Thibout D, Kraemer M, di Benedetto M, *et al.* (1999) Sodium phenylacetate (NaPa) induces modifications of the proliferation, the adhesion and the cell cycle of tumoral epithelial breast cells. *Anticancer Res* **19**, 2121–2126.
73. Pedersen A, Johansen C & Gronbaek M (2003) Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. *Gut* **52**, 861–867.
74. González-Barrio R, Edwards CA & Crozier A (2011) Colonic catabolism of ellagitannins, ellagic acid, and raspberry anthocyanins: *in vivo* and *in vitro* studies. *Drug Metab Dispos* **39**, 1680–1688.
75. Vitaglione P, Donnarumma G, Napolitano A, *et al.* (2007) Protocatechuic acid is the major human metabolite of cyanidin-glucosides. *J Nutr* **137**, 2043–2048.

76. Lin HH, Chen JH, Huang CC, *et al.* (2007) Apoptotic effect of 3,4-dihydroxybenzoic acid on human gastric carcinoma cells involving JNK/p38 MAPK signaling activation. *Int J Cancer* **120**, 2306–2316.
77. Forester SC, Waterhouse AL, *et al.* (2010) Gut metabolites of anthocyanins, gallic acid, 3-O-methylgallic acid, and 2,4,6-trihydroxybenzaldehyde, inhibit cell proliferation of Caco-2 cells. *J Agric Food Chem* **58**, 5320–5327.
78. Yang JH, Hsia TC, Kuo HM, *et al.* (2006) Inhibition of lung cancer cell growth by quercetin glucuronides via G(2)/M arrest and induction of apoptosis. *Drug Metab Dispos* **34**, 296–304.
79. Middleton E Jr, Kandaswami C & Theoharides TC (2000) The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev* **52**, 673–751.
80. Stoclet JC, Chataigneau T, Ndiaye M, *et al.* (2004) Vascular protection by dietary polyphenols. *Eur J Pharmacol* **500**, 299–313.
81. Martel F, Monteiro R & Calhau C (2010) Effect of polyphenols on the intestinal and placental transport of some bioactive compounds. *Nutr Res Rev* **23**, 47–64.
82. Fuhr U (1998) Drug interactions with grapefruit juice. Extent, probable mechanism and clinical relevance. *Drug Saf* **18**, 251–272.
83. Eaton EA, Walle UK, Lewis AJ, *et al.* (1996) Flavonoids, potent inhibitors of the human P-form phenolsulfotransferase. Potential role in drug metabolism and chemoprevention. *Drug Metab Dispos* **24**, 232–237.
84. Wong CK & Keung WM (1997) Daidzein sulfoconjugates are potent inhibitors of sterol sulfatase (*EC* 3.1.6.2). *Biochem Biophys Res Commun* **233**, 579–583.
85. Otake Y, Nolan AL, Walle UK, *et al.* (2000) Quercetin and resveratrol potentially reduce estrogen sulfotransferase activity in normal human mammary epithelial cells. *J Steroid Biochem Mol Biol* **73**, 265–270.
86. Marchetti F, De Santi C, Vietri M, *et al.* (2001) Differential inhibition of human liver and duodenum sulphotransferase activities by quercetin, a flavonoid present in vegetables, fruit and wine. *Xenobiotica* **31**, 841–847.
87. Coughtrie MW, Sharp S, Maxwell K, *et al.* (1998) Biology and function of the reversible sulfation pathway catalysed by human sulfotransferases and sulfatases. *Chem Biol Interact* **109**, 3–27.
88. Hirsh J (1987) Hyperactive platelets and complications of coronary artery disease. *N Engl J Med* **316**, 1543–1544.
89. Rechner AR, Smith MA, Kuhnle G, *et al.* (2004) Colonic metabolism of dietary polyphenols: influence of structure on microbial fermentation products. *Free Radic Biol Med* **36**, 212–225.
90. Stalmach A, Mullen W, Barron D, *et al.* (2009) Metabolite profiling of hydroxycinnamate derivatives in plasma and urine after the ingestion of coffee by humans: identification of biomarkers of coffee consumption. *Drug Metab Dispos* **37**, 1749–1758.
91. Rechner AR & Kroner C (2005) Anthocyanins and colonic metabolites of dietary polyphenols inhibit platelet function. *Thromb Res* **116**, 327–334.
92. Kim DH, Jung EA, Sohng IS, *et al.* (1998) Intestinal bacterial metabolism of flavonoids and its relation to some biological activities. *Arch Pharm Res* **21**, 17–23.
93. Wang DL, Wei XY, Yan XA, *et al.* (2010) Protocatechuic acid, a metabolite of anthocyanins, inhibits monocyte adhesion and reduces atherosclerosis in apolipoprotein E-deficient mice. *J Agric Food Chem* **58**, 12722–12728.
94. Del Rio D, Rodriguez-Mateos A, Spencer JPE, *et al.* (2013) Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid Redox Signal* **18**, 1818–1892.
95. Kroll NG, Rawel HM & Rohn S (2003) Reactions of plant phenolics with food proteins and enzymes under special consideration of covalent bonds. *Food Sci Technol Res* **9**, 205–218.
96. Harbourne N, Jacquier JC & O'Riordan D (2011) Effects of addition of phenolic compounds on the acid gelation of milk. *Int Dairy J* **21**, 185–191.
97. Sastry MCS & Rao MSN (1991) Effect of chemical modification of sunflower 11 S protein on the binding of chlorogenic acid. *J Agric Food Chem* **39**, 63–66.
98. Kalyanaraman B, Felix CC & Sealy RC (1985) Semiquinone anion radicals of catechol(amine)s, catechol estrogens, and their metal ion complexes. *Environ Health Perspect* **64**, 185–198.
99. Kalyanaraman B, Premovic PI & Sealy RC (1987) Semiquinone anion radicals from addition of amino acids, peptides, and proteins to quinones derived from oxidation of catechols and catecholamines. An ESR spin stabilization study. *J Biol Chem* **262**, 11080–11087.
100. Nicolas JJ, Richard-Forget FC, Goupy PM, *et al.* (1994) Enzymatic browning reactions in apple and apple products. *Crit Rev Food Sci Nutr* **34**, 109–157.
101. Beart JE, Lilley TH & Haslam E (1985) Polyphenol interactions. Part 2. Covalent binding of procyanidins to proteins during acid-catalysed decomposition; observations on some polymeric proanthocyanidins. *J Chem Soc Perkin* **1985**, 1439–1443.
102. Rawel HM, Meidtnr K & Kroll J (2005) Binding of selected phenolic compounds to proteins. *J Agric Food Chem* **53**, 4228–4235.
103. Prigent SV, Gruppen H, Visser AJ, *et al.* (2003) Effects of non-covalent interactions with 5-O-caffeoylquinic acid (chlorogenic acid) on the heat denaturation and solubility of globular proteins. *J Agric Food Chem* **51**, 5088–5095.
104. Rawel H & Rohn S (2010) Nature of hydroxycinnamate–protein interactions. *Phytochem Rev* **9**, 93–109.
105. Boulton DW, Walle UK & Walle T (1998) Extensive binding of the bioflavonoid quercetin to human plasma proteins. *J Pharm Pharmacol* **50**, 243–249.
106. Smith C, Halliwell B & Aruoma OI (1992) Protection by albumin against the pro-oxidant actions of phenolic dietary components. *Food Chem Toxicol* **30**, 483–489.
107. Rohn S, Rawel HM & Kroll J (2004) Antioxidant activity of protein-bound quercetin. *J Agric Food Chem* **52**, 4725–4729.
108. Sharma V, Kumar HV & Rao LJM (2008) Influence of milk and sugar on antioxidant potential of black tea. *Food Res Int* **41**, 124–129.
109. Lorenz M, Jochmann N, vonKrosigk A, *et al.* (2007) Addition of milk prevents vascular protective effects of tea. *Eur Heart J* **28**, 219–223.
110. Hasni I, Bourassa P, Hamdani S, *et al.* (2011) Interaction of milk  $\alpha$ - and  $\beta$ -caseins with tea polyphenols. *Food Chem* **126**, 630–639.
111. Tagliazucchi D, Helal A, Verzelloni E, *et al.* (2012) The type and concentration of milk increase the *in vitro* bioaccessibility of coffee chlorogenic acids. *J Agric Food Chem* **60**, 11056–11064.
112. Rawel HM, Czajka D, Rohn S, *et al.* (2002) Interactions of different phenolic acids and flavonoids with soy proteins. *Int J Biol Macromol* **30**, 137–150.
113. Rozenfeld P, Docena GH, Anón MC, *et al.* (2002) Detection and identification of a soy protein component that cross-reacts with caseins from cow's milk. *Clin Exp Immunol* **130**, 49–58.

114. Luck G, Liao H, Murray NJ, *et al.* (1994) Polyphenols, astringency and proline-rich proteins. *Phytochemistry* **37**, 357–371.
115. Maruyama Y, Maruyama N, Mikami B, *et al.* (2004) Structure of the core region of the soybean  $\beta$ -conglycinin  $\alpha'$  subunit. *Acta Crystallogr D Biol Crystallogr* **60**, 289–297.
116. Matsui T, Ueda T, Oki T, *et al.* (2001)  $\alpha$ -Glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of natural pigments with potent inhibitory activity. *J Agric Food Chem* **49**, 1948–1951.
117. Funke I & Melzig MF (2005) Effect of different phenolic compounds on  $\alpha$ -amylase activity: screening by microplate-reader based kinetic assay. *Pharmazie* **60**, 796–797.
118. Rohn S, Rawel HM & Kroll J (2002) Inhibitory effects of plant phenols on the activity of selected enzymes. *J Agric Food Chem* **50**, 3566–3571.
119. Shobana S, Sreerama YN & Malleshi NG (2009) Composition and enzyme inhibitory properties of finger millet (*Eleusine coracana* L.) seed coat phenolics: mode of inhibition of  $\alpha$ -glucosidase and pancreatic amylase. *Food Chem* **115**, 1268–1273.
120. McDougall GJ, Shpiro F, Dobson P, *et al.* (2005) Different polyphenolic components of soft fruits inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase. *J Agric Food Chem* **53**, 2760–2766.
121. Yoshikawa M, Shimoda H, Nishida N, *et al.* (2002) *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *J Nutr* **132**, 1819–1824.
122. Nakai M, Fukui Y, Asami S, *et al.* (2005) Inhibitory effects of oolong tea polyphenols on pancreatic lipase *in vitro*. *J Agric Food Chem* **53**, 4593–4598.
123. Quesada C, Bartolomé B, Nieto O, *et al.* (1996) Phenolic inhibitors of  $\alpha$ -amylase and trypsin enzymes by extracts from pears, lentils, and cocoa. *J Food Prot* **59**, 185–192.
124. Charlton AJ, Baxter NJ, Khan ML, *et al.* (2002) Polyphenol/peptide binding and precipitation. *J Agric Food Chem* **50**, 1593–1601.
125. Siebert KJ (2006) Haze formation in beverages. *LWT-Food Sci Technol* **39**, 987–994.
126. Frazier RA, Papadopoulou A & Green RJ (2006) Isothermal titration calorimetry study of epicatechin binding to serum albumin. *J Pharm Biomed Anal* **41**, 1602–1605.
127. Frazier RA, Papadopoulou A, Mueller-Harvey I, *et al.* (2003) Probing protein–tannin interactions by isothermal titration microcalorimetry. *J Agric Food Chem* **51**, 5189–5195.
128. Richard T, Lefeuvre D, Descendit A, *et al.* (2006) Recognition characters in peptide–polyphenol complex formation. *Biochim Biophys Acta* **6**, 951–958.
129. Deaville ER, Green RJ, Mueller-Harvey I, *et al.* (2007) Hydrolyzable tannin structures influence relative globular and random coil protein binding strengths. *J Agric Food Chem* **55**, 4554–4561.
130. Poncet-Legrand C, Edelmann A, Putaux JL, *et al.* (2006) Poly(L-proline) interactions with flavan-3-ols units: influence of the molecular structure and the polyphenol/protein ratio. *Food Hydrocoll* **20**, 687–697.
131. Lu Y & Bennick A (1998) Interaction of tannin with human salivary proline-rich proteins. *Arch Oral Biol* **43**, 717–728.
132. Naurato N, Wong P, Lu Y, *et al.* (1999) Interaction of tannin with human salivary histatins. *J Agric Food Chem* **47**, 2229–2234.
133. Sarni-Manchado P, Deleris A, Avallone S, *et al.* (1999) Analysis and characterization of wine condensed tannins precipitated by proteins used as fining agent in enology. *Am J Enol Vitic* **50**, 81–86.
134. de Freitas V & Mateus N (2001) Structural features of procyanidin interactions with salivary proteins. *J Agric Food Chem* **49**, 940–945.
135. Freitas VD & Mateus N (2002) Nephelometric study of salivary protein–tannin aggregates. *J Sci Food Agric* **82**, 113–119.
136. Verge S, Richard T, Moreau S, *et al.* (2002) First observation of solution structures of bradykinin-penta-O-galloyl-D-glucopyranose complexes as determined by NMR and simulated annealing. *Biochim Biophys Acta* **6**, 89–101.
137. Simon C, Barathieu K, Laguerre M, *et al.* (2003) Three-dimensional structure and dynamics of wine tannin–saliva protein complexes. A multitechnique approach. *Biochemistry* **42**, 10385–10395.
138. Richard T, Vitrac X, Merillon JM, *et al.* (2005) Role of peptide primary sequence in polyphenol–protein recognition: an example with neurotensin. *Biochim Biophys Acta* **30**, 238–243.
139. Xiao J & Kai G (2012) A review of dietary polyphenol–plasma protein interactions: characterization, influence on the bioactivity, and structure–affinity relationship. *Crit Rev Food Sci Nutr* **52**, 85–101.
140. Kandil A, Li J, Vasanthan T, *et al.* (2012) Phenolic acids in some cereal grains and their inhibitory effect on starch liquefaction and saccharification. *J Agric Food Chem* **60**, 8444–8449.
141. Chi TH, Chang YL & Mou TH (1992) Phenolic compounds in food and their effects on health I. In *Phenolic Compounds in Food and Their Effects on Health I: Analysis, Occurrence, and Chemistry*, vol. 506, pp. i–iv [C-T Ho, CY Lee and M-U Huang, editors]. Columbus: American Chemical Society.
142. Deshpande SS & Salunkhe DK (1982) Interactions of tannic acid and catechin with legume starches. *J Food Sci* **47**, 2080–2081.
143. Sharma SS, Sharma S, Kakkar RK, *et al.* (1992) Interference of gallic and chlorogenic acid with starch–iodine reaction. *Biochem Physiol Pflanzen* **188**, 267–271.
144. Nitta Y, Fang Y, Takemasa M, *et al.* (2004) Gelation of xyloglucan by addition of epigallocatechin gallate as studied by rheology and differential scanning calorimetry. *Biomacromolecules* **5**, 1206–1213.
145. Nishinari K, Kim B, Fang YP, *et al.* (2006) Rheological and related study of gelation of xyloglucan in the presence of small molecules and other polysaccharides. *Cellulose* **13**, 365–374.
146. LeBourvellec C, Guyot S & Renard C (2004) Non-covalent interaction between procyanidins and apple cell wall material: Part I. Effect of some environmental parameters. *Biochim Biophys Acta* **1672**, 192–202.
147. Le Bourvellec C & Renard C (2005) Non-covalent interaction between procyanidins and apple cell wall material. Part II: Quantification and impact of cell wall drying. *Biochim Biophys Acta* **1725**, 1–9.
148. Le Bourvellec C, Bouchet B & Renard C (2005) Non-covalent interaction between procyanidins and apple cell wall material. Part III: Study on model polysaccharides. *Biochim Biophys Acta* **1725**, 10–18.
149. Taira S, Ono M & Matsumoto N (1997) Reduction of persimmon astringency by complex formation between pectin and tannins. *Postharvest Biol Technol* **12**, 265–271.
150. Renard C, Baron A, Guyot S, *et al.* (2001) Interactions between apple cell walls and native apple polyphenols: quantification and some consequences. *Int J Biol Macromol* **29**, 115–125.
151. Saura-Calixto F & Díaz-Rubio ME (2007) Polyphenols associated with dietary fibre in wine: a wine polyphenols gap? *Food Res Int* **40**, 613–619.
152. Jacob JK & Paliyath G (2008) Physico-chemical characteristics of nanovesicle–carbohydrate complexes in grape juice concentrate. *J Agric Food Chem* **56**, 1305–1315.

153. Serra A, Macià A, Romero MP, *et al.* (2010) Bioavailability of procyanidin dimers and trimers and matrix food effects in *in vitro* and *in vivo* models. *Br J Nutr* **103**, 944–952.
154. Schramm DD, Karim M, Schrader HR, *et al.* (2003) Food effects on the absorption and pharmacokinetics of cocoa flavanols. *Life Sci* **73**, 857–869.
155. Ortega N, Reguant J, Romero MP, *et al.* (2009) Effect of fat content on the digestibility and bioaccessibility of cocoa polyphenol by an *in vitro* digestion model. *J Agric Food Chem* **57**, 5743–5749.
156. Ortega N, Macià A, Romero M-P, *et al.* (2011) Matrix composition effect on the digestibility of carob flour phenols by an *in-vitro* digestion model. *Food Chem* **124**, 65–71.
157. Langley-Evans SC (2000) Consumption of black tea elicits an increase in plasma antioxidant potential in humans. *Int J Food Sci Nutr* **51**, 309–315.
158. Langley-Evans SC (2000) Antioxidant potential of green and black tea determined using the ferric reducing power (FRAP) assay. *Int J Food Sci Nutr* **51**, 181–188.
159. Canon F, Pate F, Meudec E, *et al.* (2009) Characterization, stoichiometry, and stability of salivary protein–tannin complexes by ESI-MS and ESI-MS/MS. *Anal Bioanal Chem* **395**, 2535–2545.
160. Mullen W, Borges G, Donovan JL, *et al.* (2009) Milk decreases urinary excretion but not plasma pharmacokinetics of cocoa flavan-3-ol metabolites in humans. *Am J Clin Nutr* **89**, 1784–1791.
161. Roowi S, Mullen W, Edwards CA, *et al.* (2009) Yoghurt impacts on the excretion of phenolic acids derived from colonic breakdown of orange juice flavanones in humans. *Mol Nutr Food Res* **53**, S68–S75.
162. Serafini M, Testa MF, Villano D, *et al.* (2009) Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med* **46**, 769–774.
163. Duarte GS & Farah A (2011) Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem* **59**, 7925–7931.
164. Spencer CM, Cai Y, Martin R, *et al.* (1988) Polyphenol complexation – some thoughts and observations. *Phytochemistry* **27**, 2397–2409.
165. Barth CA, Pfeuffer M & Scholtissek J (1990) Animal models for the study of lipid metabolism, with particular reference to the Gottingen minipig. *Adv Anim Physiol Anim Nutr* **S20**, 39–49.
166. Rawel HM, Kroll J & Hohl UC (2001) Model studies on reactions of plant phenols with whey proteins. *Nahrung* **45**, 72–81.
167. Dupas CJ, Marsset-Baglieri AC, Ordonaud CS, *et al.* (2006) Coffee antioxidant properties: effects of milk addition and processing conditions. *J Food Sci* **71**, S253–S258.
168. Neilson AP, George JC, Janle EM, *et al.* (2009) Influence of chocolate matrix composition on cocoa flavan-3-ol bioaccessibility *in vitro* and bioavailability in humans. *J Agric Food Chem* **57**, 9418–9426.
169. Matsumoto M, Matsukawa N, Chiji H, *et al.* (2007) Diffructose anhydride III promotes absorption of the soluble flavonoid  $\alpha$ G-rutin in rats. *J Agric Food Chem* **55**, 4202–4208.
170. Mineo H, Hara H, Shigematsu N, *et al.* (2002) Melibiose, diffructose anhydride III and diffructose anhydride IV enhance net calcium absorption in rat small and large intestinal epithelium by increasing the passage of tight junctions *in vitro*. *J Nutr* **132**, 3394–3399.
171. Afsana K, Shiga K, Ishizuka S, *et al.* (2003) Ingestion of an indigestible saccharide, diffructose anhydride III, partially prevents the tannic acid-induced suppression of iron absorption in rats. *J Nutr* **133**, 3553–3560.
172. Tamura A, Nishimukai M, Shigematsu N, *et al.* (2006) Supplementation of diffructose anhydride III enhanced elevation of plasma equol concentrations and lowered plasma total cholesterol in isoflavone-fed rats. *Br J Nutr* **96**, 442–449.
173. Bomba A, Nemcova R, Gancarcikova S, *et al.* (2002) Improvement of the probiotic effect of micro-organisms by their combination with maltodextrins, fructo-oligosaccharides and polyunsaturated fatty acids. *Br J Nutr* **88**, S95–S99.
174. Uehara M, Ohta A, Sakai K, *et al.* (2001) Dietary fructooligosaccharides modify intestinal bioavailability of a single dose of genistein and daidzein and affect their urinary excretion and kinetics in blood of rats. *J Nutr* **131**, 787–795.
175. Shiga K, Nishimukai M, Tomita F, *et al.* (2006) Ingestion of diffructose anhydride III, a non-digestible disaccharide, improves postgastroectomy osteopenia in rats. *Scand J Gastroenterol* **41**, 1165–1173.
176. Matsukawa N, Matsumoto M, Shinoki A, *et al.* (2009) Non-digestible saccharides suppress the bacterial degradation of quercetin aglycone in the large intestine and enhance the bioavailability of quercetin glucoside in rats. *J Agric Food Chem* **57**, 9462–9468.
177. Younes H, Alphonse JC, Hadj-Abdelkader M, *et al.* (2001) Fermentable carbohydrate and digestive nitrogen excretion. *J Ren Nutr* **11**, 139–148.
178. Pérez-Jiménez J, Arranz S & Saura-Calixto F (2009) Proanthocyanidin content in foods is largely underestimated in the literature data: an approach to quantification of the missing proanthocyanidins. *Food Res Int* **42**, 1381–1388.
179. Touriño S, Pérez-Jiménez J, Mateos-Martín ML, *et al.* (2011) Metabolites in contact with the rat digestive tract after ingestion of a phenolic-rich dietary fiber matrix. *J Agric Food Chem* **59**, 5955–5963.
180. Jimenez-Ramsey LM, Rogler JC, Housley TL, *et al.* (1994) Absorption and distribution of  $^{14}$ C-labeled condensed tannins and related sorghum phenolics in chickens. *J Agric Food Chem* **42**, 963–967.
181. Terrill T, Waghorn GC, Woolley D, *et al.* (1994) Assay and digestion of  $^{14}$ C-labelled condensed tannins in the gastrointestinal tract of sheep. *Br J Nutr* **72**, 467–477.
182. Grabber JH, Hatfield RD & Ralph J (1998) Diferulate cross-links impede the enzymatic degradation of non-lignified maize walls. *J Sci Food Agric* **77**, 193–200.
183. Bunzel M, Ralph J, Marita JM, *et al.* (2001) Diferulates as structural components in soluble and insoluble cereal dietary fibre. *J Sci Food Agric* **81**, 653–660.
184. Aprikian O, Duclos V, Guyot S, *et al.* (2003) Apple pectin and a polyphenol-rich apple concentrate are more effective together than separately on cecal fermentations and plasma lipids in rats. *J Nutr* **133**, 1860–1865.
185. Chesson A, Provan GJ, Russell WR, *et al.* (1999) Hydroxycinnamic acids in the digestive tract of livestock and humans. *J Sci Food Agric* **79**, 373–378.
186. Bub A, Watzl B, Heeb D, *et al.* (2001) Malvidin-3-glucoside bioavailability in humans after ingestion of red wine, dealcoholized red wine and red grape juice. *Eur J Nutr* **40**, 113–120.
187. Walgren RA, Lin JT, Kinne RK, *et al.* (2000) Cellular uptake of dietary flavonoid quercetin 4'- $\beta$ -glucoside by sodium-dependent glucose transporter SGLT1. *J Pharmacol Exp Ther* **294**, 837–843.
188. Arts IC, Sesink AL & Hollman PC (2002) Quercetin-3-glucoside is transported by the glucose carrier SGLT1 across the brush border membrane of rat small intestine. *J Nutr* **132**, 2823–2824.



189. Walton MC, Hendriks WH, Broomfield AM, *et al.* (2009) Viscous food matrix influences absorption and excretion but not metabolism of blackcurrant anthocyanins in rats. *J Food Sci* **74**, H22–H29.
190. Marciani L, Gowland PA, Spiller RC, *et al.* (2000) Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans. *J Nutr* **130**, 122–127.
191. Andreasen MF, Kroon PA, Williamson G, *et al.* (2001) Esterase activity able to hydrolyze dietary antioxidant hydroxycinnamates is distributed along the intestine of mammals. *J Agric Food Chem* **49**, 5679–5684.
192. Lesser S, Cermak R & Wolfram S (2004) Bioavailability of quercetin in pigs is influenced by the dietary fat content. *J Nutr* **134**, 1508–1511.
193. Azuma K, Ippoushi K, Ito H, *et al.* (2003) Enhancing effect of lipids and emulsifiers on the accumulation of quercetin metabolites in blood plasma after the short-term ingestion of onion by rats. *Biosci Biotechnol Biochem* **67**, 2548–2555.
194. Lesser S, Cermak R & Wolfram S (2006) The fatty acid pattern of dietary fat influences the oral bioavailability of the flavonol quercetin in pigs. *Br J Nutr* **96**, 1047–1052.
195. Tulipani S, Martinez Huelamo M, Rotches Ribalta M, *et al.* (2012) Oil matrix effects on plasma exposure and urinary excretion of phenolic compounds from tomato sauces: evidence from a human pilot study. *Food Chem* **130**, 581–590.
196. Mullen W, Edwards CA, Serafini M, *et al.* (2008) Bioavailability of pelargonidin-3-O-glucoside and its metabolites in humans following the ingestion of strawberries with and without cream. *J Agric Food Chem* **56**, 713–719.
197. Murkovic M, Toplak H, Adam U, *et al.* (2000) Analysis of anthocyanins in plasma for determination of their bioavailability. *J Food Compos Anal* **13**, 291–296.
198. Azuma K, Ippoushi K, Ito H, *et al.* (2002) Combination of lipids and emulsifiers enhances the absorption of orally administered quercetin in rats. *J Agric Food Chem* **50**, 1706–1712.
199. Pietta P, Simonetti P, Gardana C, *et al.* (1998) Relationship between rate and extent of catechin absorption and plasma antioxidant status. *Biochem Mol Biol Int* **46**, 895–903.
200. Goltz SR, Campbell WW, Chitchumroonchokchai C, *et al.* (2012) Meal triacylglycerol profile modulates postprandial absorption of carotenoids in humans. *Mol Nutr Food Res* **56**, 866–877.
201. Mateo Anson N, van den Berg R, Havenaar R, *et al.* (2009) Bioavailability of ferulic acid is determined by its bioaccessibility. *J Cereal Sci* **49**, 296–300.
202. Welch IM, Bruce C, Hill SE, *et al.* (1987) Duodenal and ileal lipid suppresses postprandial blood glucose and insulin responses in man: possible implications for the dietary management of diabetes mellitus. *Clin Sci* **72**, 209–216.
203. Ye A, Cui J & Singh H (2011) Proteolysis of milk fat globule membrane proteins during *in vitro* gastric digestion of milk. *J Dairy Sci* **94**, 2762–2770.
204. Michalski MC, Briard V, Desage M, *et al.* (2005) The dispersion state of milk fat influences triglyceride metabolism in the rat. *Eur J Nutr* **44**, 436–444.
205. Ikeda I, Tsuda K, Suzuki Y, *et al.* (2005) Tea catechins with a galloyl moiety suppress postprandial hypertriacylglycerolemia by delaying lymphatic transport of dietary fat in rats. *J Nutr* **135**, 155–159.
206. Borel P, Armand M, Ythier P, *et al.* (1994) Hydrolysis of emulsions with different triglycerides and droplet sizes by gastric lipase *in vitro*. Effect on pancreatic lipase activity. *J Nutr Biochem* **5**, 124–133.
207. Armand M, Borel P, Pasquier B, *et al.* (1996) Physicochemical characteristics of emulsions during fat digestion in human stomach and duodenum. *Am J Physiol* **271**, G172–G183.
208. Gargouri Y, Pieroni G, Riviere C, *et al.* (1986) Kinetic assay of human gastric lipase on short- and long-chain triacylglycerol emulsions. *Gastroenterology* **91**, 919–925.