NUTRITION REVIEWS

Special Article

Dietary factors affecting polyphenol bioavailability

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While many epidemiological studies have associated the consumption of polyphenols within fruits and vegetables with a decreased risk of developing several chronic diseases, intervention studies have generally not confirmed these beneficial effects. The reasons for this discrepancy are not fully understood but include potential differences in dosing, interaction with the food matrix, and differences in polyphenol bioavailability. In addition to endogenous factors such as microbiota and digestive enzymes, the food matrix can also considerably affect bioaccessibility, uptake, and further metabolism of polyphenols. While dietary fiber (such as hemicellulose), divalent minerals, and viscous and protein-rich meals are likely to cause detrimental effects on polyphenol bioaccessibility, digestible carbohydrates, dietary lipids (especially for hydrophobic polyphenols, e.g., curcumin), and additional antioxidants may enhance polyphenol availability. Following epithelial uptake, polyphenols such as flavonoids may reduce phase II metabolism and excretion, enhancing polyphenol bioavailability. Furthermore, polyphenols may act synergistically due to their influence on efflux transporters such as p-glycoprotein. In order to understand polyphenol bioactivity, increased knowledge of the factors affecting polyphenol bioavailability, including dietary factors, is paramount.

INTRODUCTION

Polyphenols constitute a diverse class of secondary plant compounds, or phytochemicals, which are not essential for humans. The term polyphenols is increasingly being used in a broader sense and now includes a large variety of compounds produced in plants, via either the shikimate or the acetate pathway, and comprising several thousand molecules.[1] A number of these compounds are outlined in Table 1.[2–18]

Polyphenols can be categorized primarily into flavonoids and nonflavonoids. Flavonoids can be further subdivided into flavonols, flavones, isoflavones, etc., while nonflavonoids include diverse classes of polyphenols such as stilbenes and phenolic acids.[19] All classes listed as polyphenols in the Phenol-Explorer database[20] will be considered polyphenols in this article.

Epidemiological studies and meta-analyses have shown that a diet rich in fruit and vegetables can reduce the incidence of several chronic diseases, including cardiovascular disease,[21,22] stroke,[23] type 2 diabetes (T2D),[24] and several cancers.[25,26] Some studies have attempted to link the observed health effects of a diet rich in fruits and vegetables with the consumption of dietary polyphenols. In a meta-analysis of prospective cohort studies, Liu et al.[27] found that consuming flavonoids was associated with a reduced risk of developing T2D. In another meta-analysis of prospective cohort studies, the consumption of isoflavones was significantly related to a reduced incidence of breast[28] and prostate cancers.[29] In contrast, a meta-analysis by Hamer and Chida[30] did not indicate any positive effects of dietary flavonoids on T2D, and a meta-analysis of cohort studies did not suggest a relation between flavonoid consumption and cardiovascular disease.[31]

Since epidemiological studies are prone to many confounding factors, intervention trials have been undertaken to demonstrate the health effects of polyphenols. For example, one study showed that 250 mg of resveratrol

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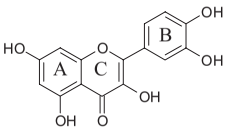
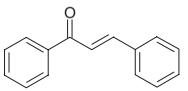
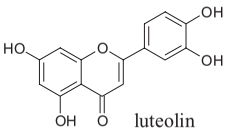
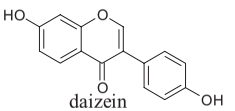
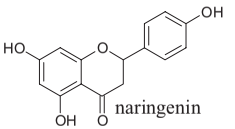
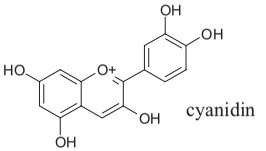
Table 1 **Major classes of dietary-derived polyphenols, along with selected characteristics that may affect bioavailability.**

Class	Subclass	Common representatives	Structure	Molecular mass range (Da)	Polarity (Approx. logP[a])
Flavonoids	Flavonols, dihydroflavonols	Kaempferol, quercetin, dihydroquercetin	 quercetin	>238	−1.1–3.1 (kaempferol)[2]
	Chalcones, dihydrochalcones	Chalcone		>208	3.8 (hydroxychalcone)[3]
	Flavones	Luteolin, apingenin,	 luteolin	>222	−1.1–3.2 (luteolin)[2]
	Isoflavones	Genistein, daidzein, glycitein, equol	 daizein	>238	0–3.2 (equol)[2]
	Flavanones	Naringenin, hesperetin,	 naringenin	>224	0.5 (naringenin)[4]
	Anthocyanidins	Cyanidin, malvidin, delphidin,	 cyanidin	>207	1.0 (cyanidin)[5]

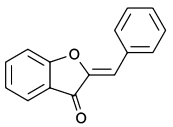
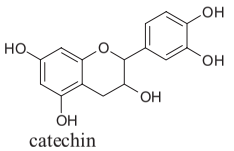
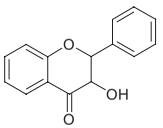
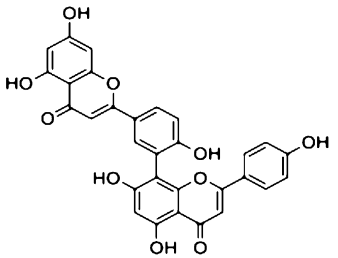
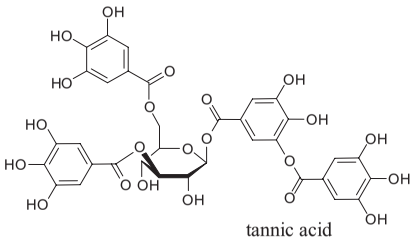
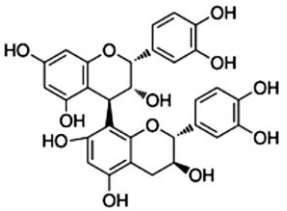
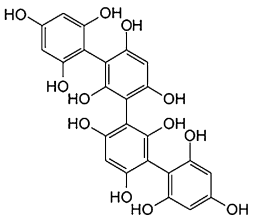
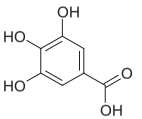
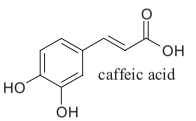
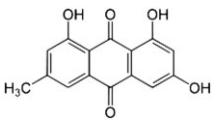
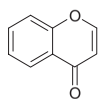
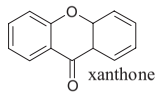
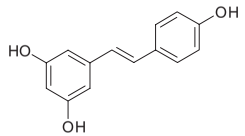
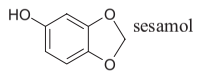
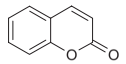
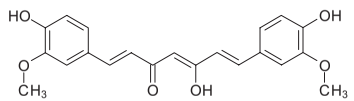
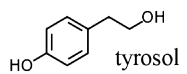
	Aurones	Aurone		>222	ca. 2.5–4.5[6]
	Flavanols	Catechin, gallocatechin, epicatechin,	 catechin	>226	–2.5–1.7 (EGCG)[7]
	Flavanonols	Flavanonol		>240	2.6 (flavanonol)[8]
	Biflavonoids	Amentoflavone		>360	4.9 (amentoflavone)[9]
Tannins	Hydrolyzable	Tannic acid, ellagitannins	 tannic acid	500–20,000	2.2 (tannic acid)[7]

Table 1 **Continued**

Class	Subclass	Common representatives	Structure	Molecular mass range (Da)	Polarity (Approx. logP[a])
	Condensed/ proanthocyanidins	Procyanidin B2		500–20,000	See tannic acid
	Phlorotannins	Tetrafucol A		500–20,000	See tannic acid
Phenolic acids	Hydroxybenzoic acids	Gallic acid		>138	1.5 (hydroxyl-benzoic acid)[10]
	Hydroxycinnamic acids	Chlorogenic acid, caffeic acid		>164	1.2 (caffeic acid)[11]
Anthraquinones	NA	Emodin		>208	0.9 (emodin)[12]

Chromones	NA	Chromone		>146	1.4 (chromone)[13]
Xanthones	NA	Xanthone, α-mangostin		>196	3.2 (xanthone)[14]
Stilbenes	NA	Resveratrol		>192	1.9 (resveratrol)[15]
Lignans	NA	Secoisolariciresinol, sesamol, enterodiol		>138	1.3 (sesamol)[16]
Lignins	NA	Not specified	Various	>10,000	
Coumarins, isocoumarins	NA	Coumarin		>146	1.4 (coumarin)[17]
Other	NA	Curcumin		>368	3.3 (curcumin)[18]
	NA	Tyrosols		>138	1.19 (tyrosol)[10]

Abbreviations: ca., circa; EGCG, epigallocatechin gallate; NA, not applicable.

[a] Log octanol-water partition coefficient, estimate for individual compound or range (aglycons, glycosides). 1.5–4 = moderately polar; >4 = apolar, <1.5 = polar.

per day has positive effects on the glycemic control of T2D,[32] and a meta-analysis of green tea catechin consumption showed a reduction in fasting blood glucose, though no effect on other T2D markers.[33] Interventions with food items rich in polyphenols suggested that consuming apples or dried plum for 12 months had positive effects on markers of cardiovascular disease in postmenopausal women.[34] Further, in a meta-analysis by Tokede et al.,[35] the consumption of flavonoid-rich dark chocolate improved low-density lipoprotein (LDL) cholesterol (but not triglycerides or high-density lipoprotein [HDL] cholesterol) in serum.

The majority of studies investigating polyphenol bioactivity include mechanistic in vitro studies, studies on cell lines, or animal trials. A plethora of studies exist, with many having shown advantageous effects such as decreased markers of inflammation,[36] reduced oxidative stress,[37] and improved anticancer markers.[38] Polyphenols can act as antioxidants by quenching reactive oxygen species[39] or, indirectly, by altering gene expression via intracellular signaling cascades by, for example, reducing NF-κB or enhancing nuclear factor-like 2 (Nrf2),[40] thus stimulating the body's own antioxidant and detoxification mechanisms. Furthermore, polyphenols can inhibit enzymes required for starch digestion, thereby reducing the glycemic load.[41,42]

Several factors were proposed in an attempt to explain the differences observed between the positive effects of polyphenol consumption reported in epidemiological studies and the often negative findings reported in intervention trials with supplements. These factors included the following: 1) differing doses of administered compounds; 2) additive/synergistic effects – such as those between polyphenols and other antioxidants – present in whole foods but not in supplements; 3) differences in bioavailability due to varying matrix release kinetics; and 4) compounds present in the matrix, enhancing or reducing polyphenol bioavailability.

In this review, dietary factors that may impact polyphenol bioavailability, i.e., during matrix release (bioaccessibility), uptake, transport in the body, and excretion, will be reviewed, including certain food preparation techniques that may alter dietary composition and structure and, therefore, polyphenol bioavailability, which is a prerequisite for bioactivity.

OVERVIEW OF POLYPHENOL BIOAVAILABILITY

Intake and general aspects of bioavailability

Since polyphenols have, at least in part, developed as a protection against herbivores, high concentrations can be found in the outer parts of fruits and vegetables, such as apple or potato peel, in leafy vegetables, in cereals, and in cacao and coffee beans, as indicated in Table 2.[20,43–46]

In some plant foods, concentrations can be as high as 500 mg per 100 g of food. The richest dietary polyphenol sources appear to be colored fruits (especially small berries), whole-grain cereals, cacao, coffee, and red wine, with red wine, coffee, apples, oranges, and green beans appearing to contribute most to total dietary polyphenol intake.[47] Dietary intake of around 1–1.1 g/day per capita has been reported for the United States,[19] around 1.2 ± 0.4 g/day for Poland,[48] and around 0.8 ± 0.4 g/day for Finland.[49] Manach et al.[1] who relied on somewhat vague data suggested that the major polyphenol classes consumed are biflavones (45%), anthocyanins (17%), and flavonols, flavones, and flavanones (16%), although differences between countries and seasons surely exist.[50]

Bioavailability can be defined as the fraction of a nutrient or non-nutrient that is available for the human body for physiological functions and/or storage. For polyphenols, this principally involves the following digestive processes (Figure 1): 1) release of polyphenols from the food matrix; 2) changes in polyphenols during gastric/small-intestinal digestion; 3) cellular uptake of aglycons and some conjugated polyphenols by enterocytes; 4) microbiological fermentation of nonabsorbed polyphenols or those re-excreted via bile or the pancreas to yield additional metabolites, 5) phase I/II enzyme modifications that occur upon uptake (in the small intestine/colon); 6) transport in the bloodstream and subsequent tissue redistribution; and 7) excretion via the kidney or re-excretion into the gut via bile and pancreatic juices. In the following section, these steps will be described briefly, as it is important to understand polyphenol absorption and metabolism prior to discussing the impact of dietary factors on these aspects.

Release of polyphenols from the food matrix during oral and gastrointestinal digestion

Within the food matrix, polyphenols are mostly linked to carbohydrates, organic acids, or to one another. Simple phenolics such as benzoic acid or benzaldehyde or their derivatives are usually covalently linked to polysaccharides in the plant cell wall, forming ester bonds with arabinose in the hemicellulose or with core lignin.[19] Other polyphenols, such as anthocyanins and proanthocyanidins, tend to accumulate in the vacuoles, whereas flavonoids may stay in the cytosol with the endoplasmatic reticulum, where they are synthesized,[51] present mostly in free form. Thus, for later bioavailability, disruption of the cell walls and cellular compartments and cleavage from carbohydrates would be required.

Digestion starts in the oral cavity, with amylase being the predominant enzyme. Due to the short interaction

Table 2 **Plant foods rich in polyphenols.**

Plant food	Latin name	Edible part	Concentration (mg/100 g)	Major polyphenols present	Reference
Apple	*Malus domestica*	Peel	50–120[b]	Phlorizin, phenolic acids (chlorogenic acid), quercetin	Volz & McGhie (2011)[43]
		Flesh	0.2–0.9		Volz & McGhie (2011)[43]
		Total	ca. 5–50		Bouayed et al. (2012)[44]
Potato	*Solanum tuberosum*	Peel	180–5,000	Phenolic acids (cholorgenic acid)	Deusser et al. (2012)[45c]
		Flesh	1–1,000		
		Total	10–50		Rothwell et al. (2013)[20]
Plum, dark	*Prunus domestica*	Total	130–240	Phenolic acids (chlorogenic acid), procyanidins, anthocyanins	Rothwell et al. (2013)[20]
Spinach	*Spinacia oleracea*	Leaf	30–290	Flavonols	Rothwell et al. (2013)[20]
Wheat	*Triticum aestivum*	Whole grain	85–220	Phenolic acids (hydroxybenzoic acids, hydroxycinnamic acids)	Rothwell et al. (2013)[20]
Red wine	*Vitis vinifera*	Final product	25–300[a]	Phenolic acids, anthocyanins, tannins, stilbenes (resveratrol)	Rothwell et al. (2013)[20]
Coffee	*Coffea arabica*	Beverage, filtered	90	Phenolic acids (chlorogenic acid)	Rothwell et al. (2013)[20]
Cacao	*Theabroma cacao*	Bean, powder	300–1,100[a]	Flavanols (EC)	Rothwell et al. (2013)[20]
Green tea	*Camellia sinensis*	Drinkable extract	29–103[a]	Flavanols (EC, EGCG)	Rothwell et al. (2013)[20]
Pomegranate	*Punica granatum*	Juice	240[a]	Punicalagin (and ellagitannin)	Rojanathammanee et al. (2013)[46]
Grapefruit	*Citrus x paradisi*	Flesh	15–115	Flavonoids, phenolic acids	Rothwell et al. (2013)[20]
Blueberry, highbush	*Vaccinium corymbosum*	Whole	160–480	Anthocyanins, flavonols (quercetin), phenolic acids (chlorogenic acid)	Rothwell et al. (2013)[20]
Blackberry	*Rubus fruticosus*	Whole	130–405	Anthocyanins, flavanols (EC), phenolic acid (ellagic acid)	Rothwell et al. (2013)[20]
Olive oil, extra virgin	*Olea europaea*	Whole oil	4–200	Tyrosols, lignans (pinoresinol), phenolic acids, hydrolyzable tannins	Rothwell et al. (2013)[20]
Chestnut, raw	*Castanea sativa*	Whole nut	547–1,960	Hydroxybenzoic acids (gallic acid, ellagic acid), tannins	Rothwell et al. (2013)[20]

Abbreviations: ca., circa; EC, epicatechin; EGCG, epigallocatechin gallate.
[a] In juices, wine, and other beverages: mg/100 mL.
[b] Concentration in mg/cm^2.
[c] Calculated from dry weight assuming 80% water content. Note that polyphenol content in purple potatoes is approximately five times higher than that in other varieties.

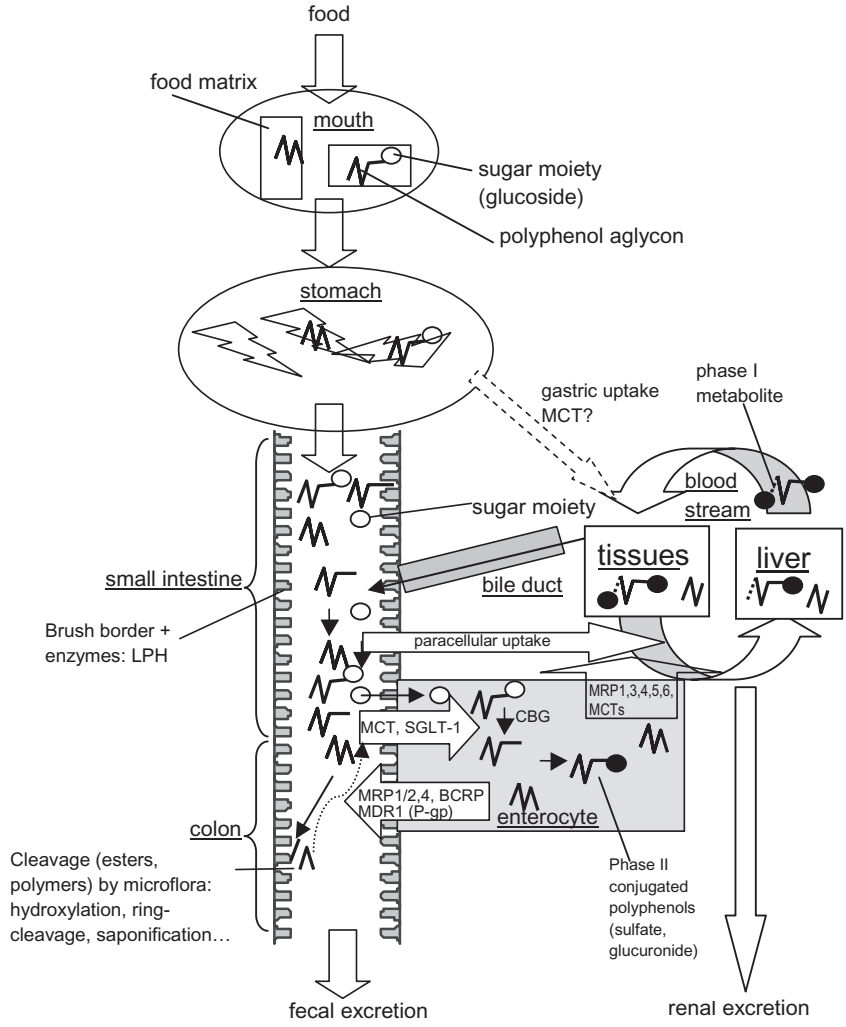


Figure 1 **Overview of polyphenol bioavailability, showing critical steps that occur during release, digestion, uptake, transport, and excretion.**

Abbreviations: BRCP, breast cancer resistance protein; CBG, cytosolic β-glucosidase; LPH, lactase-phlorizin hydrolase; MCT, monocarboxylic acid transporter; MRP, multidrug resistance proteins; Pgp, P-glycoprotein; SGLT1, sodium-glucose linked transporter 1, MDR1, multidrug resistance protein.

time, the impact of enzymatic digestion on polyphenol release is assumed to be low.[52] On the other hand, particle size reduction also takes place, resulting in particles of several 100 µm to 1,000 µm in diameter,[53] allowing enhanced enzyme access during the following stages of digestion through enlargement of the surface area of the digesta.

The majority of polyphenols appear to be released during the gastric phase. For example, in a study with apple polyphenols, around 65% of the total amount of phenolics and flavonoids were released in the stomach, and an additional 10% in the small intestine,[54] similar to other matrices such as pistachios.[55] In the gastric phase, pepsin digestion, in conjunction with peristaltic movements and low pH, results in a finely ground digesta, with further decreased particle size, usually below 500 µm in diameter.[56] In addition, the low pH may favor the presence of polyphenols in undissociated form, which may foster the transition/diffusion from the matrix into the aqueous phase due to reduced ionic interactions.

As digesta passes from the stomach to the small intestine, the pH usually increases from around 2–4 to approximately 7. This allows the activation of enzymes secreted by the pancreas and bile, including phospholipase, sterol esterase, amylase, carboxypeptidase, trypsinogen, chymotrypsinogen, lipase, and bile salts, with the last two especially aiding in the digestion of the more apolar food compounds such as lipids, apolar micronutrients, and phytochemicals such as carotenoids,[57] which results in the formation of water-soluble mixed micelles. Apolar polyphenols such as curcumin and xanthones, as well as flavonoid and

isoflavonoid aglycones, may also be micellarized via this pathway,[58,59] which often results in rather low bioaccessibility. For example, only approximately 15% of xanthones from mangosteen juice were bioaccessible during in vitro digestion.[59] However, a large proportion of polyphenols and their degradation products and metabolites with remaining phenolic structure are potentially available for absorption. In a study with hot pepper polyphenols, around 75% (expressed as their antioxidant capacity) were available after in vitro digestion,[60] similar to the proportion of bioaccessible apple polyphenols.[44,54]

The pH increase in the small intestine was shown to especially influence anthocyanins, which form colorless chalcone pseudobases that may be further degraded upon opening at the C ring. Several studies have shown that anthocyanins were mostly degraded in the small intestine, contributing to a low overall uptake into serum, typically below 1%.[61] Interestingly, a recent study employing isotopically labeled cyanidin-3-glucoside suggested a comparably high combined recovery from urine and breath (approx. 12%), implying higher anthocyanin bioavailability than previously assumed, at least when metabolites such as hippuric acid are also considered.[62] Stable isotope studies have the advantage of investigating truly newly absorbed polyphenols and allow for improved sensitivity in detecting polyphenol metabolites. Disadvantages include the limited availability of labeled polyphenol standards and difficulties in producing intrinsically labeled food items.[63]

It is assumed that the majority of polyphenols, unlike aglycons, need to be cleaved from their sugar moiety by brush border enzymes, i.e., lactase-phlorizin hydrolase (LPH), prior to cellular uptake.[64] It has been estimated that approximately 80% of all flavonoids are ingested in the form of glycosides.[65] Only when pharmacological polyphenol doses are administered can glycosides be detected in the bloodstream, due to the saturation of LPH.[66] Esterases, such as carboxylesterases, may also be present on the brush border but are certainly present within human enterocytes,[67] shown to be active against, e.g., hydroxcinnamates and diferulates. Kahle et al.[68] showed that a long incubation period with simulated duodenal juice resulted in the isomerization and hydrolysis of chlorogenic acid into quinic acid, suggesting, in line with earlier studies,[69] esterase activity, though only a small fraction was cleaved. In some studies, cleaved polyphenol esters such as caffeic acid (some minutes postprandial) appeared rapidly in plasma, supporting this view.[70] The uptake of intact esters, i.e., chlorogenic acid, has also been demonstrated in humans.[71,72] However, in general, the bioavailability of phenolic acid esters appears to be low compared with that of their free form, by a factor of 3–10 or even 100, depending on polyphenol type/dose,[69] suggesting not only that cleavage capacity would be limited but also that the majority of esters would be cleaved by the microflora of the colon.[73,74]

Uptake of polyphenols by enterocytes

For some polyphenols, such as anthocyanins and their glycosides,[75] isoflavonoid aglycons (daidzein, genistein),[76] flavonols (quercetin[77]), and phenolic acids (caffeic acid, chlorogenic acid, gallic acid),[78] gastric absorption has been strongly suggested due to the rapid postprandial appearance of these polyphenols in plasma. However, as indicated by studies with ileostomists,[79,80] the majority of polyphenols are thought to be absorbed in the small intestine.

Following cleavage into the respective aglycons, polyphenols may be taken up into the enterocytes of the small (or large) intestine via passive diffusion or facilitated or active transport. Passive diffusion is likely to constitute the major absorptive pathway for low-weight polyphenols such as phenolic acids, several flavonoid aglycons,[19] green tea,[81,82] and cocoa polyphenols (epicatechin, catechin, procyanidin B2),[83] based on Caco-2 cell trials.

It has been suggested that some glycoside polyphenols are taken up actively via sodium-glucose transport proteins, especially sodium-glucose-linked transporter 1 (SGLT1).[84,85] The role for polyphenol uptake is still controversial, as not all studies with flavonoid glycosides could confirm its participation. In a study with several flavonoids and their glycosides, SGLT1 did not appear to be involved in cellular uptake,[86] and human intervention trials have failed to detect significant amounts of such compounds in the blood plasma,[87] although low amounts of genistin and daidzin (10-fold less, compared with their respective aglycons) were taken up by Caco-2 cells.[88] These results suggest that glycosides may either be taken up to a low extent by SGLT1 and are then resecreted back into the gut, or be further cleaved by cytosolic β-glucosidase.[89]

Lower lipophilicity also appears to dampen epithelial uptake. Based on Caco-2 cell trials, Murota et al.[90] reported a correlation between lipophilicity and enterocyte uptake/permeability, which was higher for the more lipophilic isoflavonoids, following the sequence genistin= daidzin<daidzein<genistein<flavonoid aglycones. Similarly, in a study by Wen and Walle,[91] methylated flavones were taken up in amounts 5–8 times larger through Caco-2 cells than nonmethylated ones and were more slowly glucuronated and sulfated in human liver cells, which may indicate good bioavailability. On the other hand, when considering the total digestion process, glucosides are more water soluble, perhaps explaining the higher C_{max} but similar plasma half-life following ingestion of isoflavonoid glucosides versus their aglycons.[92]

The degree of polymerization also appears to have a substantial impact on cellular uptake. While absorption of monomers such as epicatechin is usually high, around 45% as determined in human studies,[93] it is already much lower for dimers of procyanidins,[94] with some studies reporting less than 1% compared with absorption of monomeric flavonoids.[95] Polymeric procyanidins and tannins are assumed to be unavailable.[96,97] It is also noteworthy that dimers, in contrast to monomers of procyanidins were not conjugated, at least in rats.[94]

Other polyphenol uptake mechanisms include facilitated transport by monocarboxylic acid transporters (MCTs). To be recognized as a substrate, a monoanionic carboxylic acid group and a nonpolar side chain or aromatic hydrophobic moiety may be required.[98] For a number of polyphenols, uptake via MCTs has been demonstrated (usually based on Caco-2 cell models), e.g., for caffeic and ferulic acid.[99] It is still being investigated which of the MCTs are involved in polyphenol uptake, but MCTs 3, 4, 5, and 6 have been suggested.[100]

Effect of microbial fermentation in the colon

Bacteria may participate in the metabolism of polyphenols or of phase I and II conjugates re-excreted via enterohepatic recirculation. Common reactions include deglycosylation, dehydroxylation, demethylation, or deconjugation,[101] as well as epimerization, ring cleavage (typical of C-ring), hydrolysis, and chain-shortening reactions.[102] It has been noted that the extent of metabolism may vary considerably, due to differences in microflora and food matrices.[103] While microbiological fermentation decreases the bioavailability of the native polyphenols, it also gives rise to metabolites, which may be more bioactive than the native polyphenols,[104] as is the case for, e.g., equol, which originates from the soy isoflavone daidzein,[105] and dihydroresveratrol, from resveratrol,[106] both of which act as stronger phytoestrogens than their parental compounds. Some polyphenols, especially those of more complex and larger structure, such as condensed tannins (interconnected via carbon-carbon bonds), have been shown to be comparatively resistant to degradation by the microflora.[107,108]

Metabolism and reconjugation in the enterocytes

The intestine constitutes the first place for phase II metabolism.[109] The presence of uridine-5′-diphosphate, glucuronosyltransferase (UGT), and sulfotransferases (SULTs) in human enterocytes has been confirmed.[110,111] Studies with apigenin (a flavone), resveratrol (a stilbene), and chrysophanol (a quinone) showed that a large proportion was reconjugated until reaching the apical side: 8.7%, 16.0%, and 13.8% in the form of glucuronides and 3.8%, 24.0%, and 2.5% as sulfates, compared with 16.4%, 12.8%, and 32.2% as aglycones, respectively.[109] In humans, glucuronidation takes place faster (0–6 hours postprandial), and glucuronides appear sooner in urine than sulfates.[112] In addition to glucuronidation/sulfation, methylation has also been observed, e.g., of green tea polyphenols[81] and quercetin (up to 20–30% of the consumed dose),[113] possibly via catechol-*O*-methyltransferase.[95]

As phase II reactions occur at quite a limited speed, high doses of polyphenols may especially favor the uptake of less metabolized forms. When 2 g of catechin was administered to humans, the free form was detected in plasma after 30 minutes,[114] contrary to what was observed with smaller doses (35 mg).[115] Moreover, compounds offering no target for conjugation (no hydroxyl groups), such as dimethoxycinnamic acid, were shown to be absorbed without further metabolism.[116]

Once in the enterocyte, active excretion back into the gut lumen may occur via ATP-binding cassette transporters (Figure 1).[117,118] Other transporters, including MCTs 1, 4, and 5 and multidrug resistance proteins (MRPs) 1, 3, and 5, may play a role in transport to the vascular side (i.e., bloodstream).[82,119] Results from Teng et al.[109] suggested that MRP2 and P-glycoprotein also play a role in the efflux uptake of the anthraquinones emodin and chrysophanol and, to a lesser extent, apigenin and resveratrol in a Caco-2 cell model, possibly depending on polarity and the number of hydroxyl groups.

Compared with phase II metabolites, phase I products appear to be less abundant. Enzymes include primarily cytochrome-P450 (CYP)-dependent mixed-function oxidases, which may result in hydroxylated or hydrogenated products. However, no such reactions have been clearly demonstrated for polyphenols, although demethylation reactions have been demonstrated, for example, from biochanin to genistein, at least in vitro.[113]

Bloodstream transport, tissue distribution, and excretion

Polyphenols may be transported in the blood in free form, bound to proteins, or bound to lipoproteins. The majority of polyphenols appear to be bound to proteins. Based on in vitro and rat studies, quercetin was shown to be bound to albumin at over 99%.[120,121] A similar distribution was found for kaempferol and isorhamnetin in humans.[122] In contrast, lipoprotein (mostly LDL and HDL) incorporation of water-soluble polyphenols appears low.[1] Rather, it has been reported that apolar polyphenols such as isoflavonoids have been incorporated into LDL, albeit to a much lower extent than, for example, carotenoids.[123] The same may be hypothesized for other lipophilic polyphenols such as curcumin,

although this has never been proven; instead, transport with albumin has been suggested.[124]

Upon reaching the liver, further phase I/II metabolism of polyphenols may take place. Following transport in the bloodstream, polyphenols can be distributed in most tissues and can cross the blood-brain barrier[125,126] that, normally, only lipid compounds are able to cross.[127,128] Further cellular uptake mechanisms remain to be elucidated but may be similar to those at the enterocyte level. Tissue concentrations may be quite variable compared with plasma concentrations, indicating that plasma polyphenols may not necessarily be the best biomarker of exposure. Some isoflavonoid metabolites, e.g., equol, tend to accumulate in breast tissue[129] and others, e.g., enterodiol and enterolactone, in the prostate.[129]

Excretion of polyphenols is thought to occur mostly via the kidney, at least for the more polar ones. The amount of polyphenols recovered in urine (including conjugates) varies widely and was found to be highest (over 60%) for gallic acid and isoflavones,[1,130,131] 0.5–10% for tea and wine catechins, 0.3–1.4% for flavonols, and 5–27% for caffeic acid and ferulic acid, but was much lower for anthocyanins (0.005–0.1%). Caution is warranted, however, as often only a limited number of metabolites are determined, which may lead to underestimates of bioavailability. For the isoflavone genistein[132] and the more apolar polyphenols such as curcumin,[133] biliary excretion may constitute the major pathway of excretion. Due to varying structure and lipophilicity (higher lipophilicity may result in decreased metabolism and longer t1/2 due to stronger protein binding and lower renal clearance[134]), plasma half-lives also vary greatly, from 2 hours for anthocyanins to up to 8 hours for isoflavones.[1]

EFFECT OF ORIGIN AND FOOD PROCESSING ON BIOAVAILABILITY

Origin of polyphenols

Since most food items consumed on a daily basis are processed foods, and the majority of foods are not consumed raw, an understanding of how food processing changes the food matrix and composition is important, as such changes often alter the concentration and bioavailability of polyphenols.

Polyphenol content and profile patterns depend, in addition to the types of fruits and vegetables, on aspects such as growth conditions (climate, soil, etc.). As stress is usually a signal for the plant to increase polyphenol production, higher concentrations are often found after plant infection[1] as well as in organically grown crops,[135] although findings are not always consistent. Furthermore, storage and ripening have been shown to impact polyphenol content. It has been reported that ripeness decreases the content of phenolic acids while increasing that of anthocyanins,[136] and storage is claimed to reduce phenolic acids in wheat products, for example, by up to 70% over 6 months in flour.[137] Possible reasons for this include the enzymatic oxidation of polyphenols, resulting in polymerization/browning products. Two comprehensive reviews provide further information on the impact of environmental conditions on polyphenol formation.[138,139]

Drying

Methods to enhance shelf-life and prevent microbiological contamination, such as freeze-drying, have also been shown to cause polyphenol losses, possibly via the disruption of cell compartments and the enzymatic degradation of polyphenols via, e.g., polyphenol oxidase. In a study by Shofian et al.,[140] freeze-drying fruits (watermelon, papaya, starfruit, muskmelon, and mango) resulted in losses of up to approximately 30–50% of the phenolic content, while vitamin C and β-carotene levels were largely unaffected. Various dehydration methods for raspberries were compared in another study, which concluded that polyphenol losses were lowest with microwave vacuum drying but were as high as 80% with freeze-drying and hot-air drying.[141] In cacao beans, freeze-drying resulted in lower losses than hot-air or sun drying,[142] underlining that methods applying vacuum or microwaves, which avoid prolonged heating, can increase polyphenol retention in plant foods.

Grinding

Grinding may result in polyphenol losses by facilitating contact between compartments rich in polyphenol oxidase, such as the cytosol, and those rich in polyphenols, such as the vacuoles, resulting in the formation of polymeric browning products.[143] If such reactions can be avoided, for example, by low temperature or initial temperature inactivation of such enzymes (blanching), then grinding, which results in smaller particles and increased surface area, is expected to enhance polyphenol bioaccessibility due to the enhanced access of the digestion enzymes. Very few studies, however, have investigated these effects. In a study with green tea polyphenols, the plasma areas under the curve (AUCs) of epigallocatechin gallate (EGCG) and epicatechin-3-*O*-gallate (ECG) in rats were about two times higher when 3-μm tea powder particles were administered instead of 19–76-μm particles.[144] In a study on various cell lines, green tea particle-size reduction from 3,500 to 220 nm significantly enhanced antioxidant and antitumor activities up to a factor of 2, also suggesting higher bioavailability.[145]

Heating

Heat treatment of a plant matrix containing polyphenols may be a two-edged sword with respect to influencing bioavailability. On one hand, heating increases the risk of degradation and oxidation of polyphenols, but may, on the other hand, soften or disrupt cell walls, facilitating polyphenol release during digestion. Thus, if losses can be avoided, heating applied during food production (e.g., in the production of vegetable juices) or kitchen preparation may result in increased polyphenol bioavailability. Following consumption of cooked tomatoes,[146] human plasma levels of naringenin and chlorogenic acid, measured as AUC, increased several times compared with levels observed after consumption of fresh tomatoes, with effects being stronger than those for lycopene and β-carotene enhancements following heating. In tomatoes, naringenin is especially associated with the cutin of the outer waxy surface and binds to insoluble polyesters,[147] and thus even mild heating affecting the outer layers could have pronounced effects.

In contrast to the observations described above, heat treatment, such as that used during juice production, has often been shown to decrease concentrations of total polyphenols.[148] For example, degradation of chlorogenic acids from apple and peach juices was found after treatment at 120°C (20 minutes), and even following short treatments of 45 seconds at 105°C.[149] The addition of pectinase, added during the production of clear juices, resulted in further degradation of phloretin and chlorogenic acid, possibly due to cleavage into caffeic acid and quinic acid. In a study employing accelerated storage conditions (40°C, 75% humidity), polyphenol losses of up to 33% were found in powder made from spray-dried mate leaves,[150] presumably via polyphenol oxidase/peroxidase.

Different heat treatments have also been compared. Losses of quercetin in onions and tomatoes were 75–80% after boiling for 15 minutes, 65% after microwaving, and only 30% after frying.[151] Methods that do not result in the leakage of plant juice material, such as steaming, are assumed to result in lower losses, as shown for other water-soluble micronutrients and phytochemicals.[152] Xu and Chang[153] compared the effects of various heat treatments, including boiling, steaming, pressure boiling, and pressure steaming, on the polyphenolic constituents of several legumes. While all heat treatments caused loss of polyphenolic constituents, steaming, as well as pressure cooking for shorter times, tended to cause lower losses of polyphenols.

Encapsulation

A novel and interesting way to enhance the bioavailability of polyphenols and alter their interaction with the food matrix may by via encapsulation, though this is rather a technological approach. Encapsulation may be used for product stabilization, to enhance bioavailability, or to achieve controlled polyphenol release during digestion.[154,155] For enhanced bioavailability, encapsulation strategies that aim to improve polyphenol solubility, thereby minimizing interactions with other dietary ingredients, and to achieve targeted gut release have been sought. In particular, enhancing the solubility of poorly soluble polyphenols such as resveratrol or curcumin may be an interesting strategy. For example, curcumin was incorporated into bread (1 g/portion) in the form of a double-coated cellulose derivative (using hydrogenated vegetable oil as an external layer of microcapsules) and tested in humans.[156] The AUC was approximately seven times higher for encapsulated curcumin than for free curcumin in bread, possibly due to protection from degradation in the gut into phenolic acids. In another study, curcumin dispersed in colloidal nanoparticles of approximately 400 nm in diameter with gum (ghati) polysaccharides improved bioavailability in humans by up to 27-fold.[157] Other strategies for encapsulation included, for example, molecular inclusion by β-cyclodextrins, suitable for small hydrophobic molecules such as genistein,[158] or encapsulation into liposomes.[159] A more complete overview of processes employed in encapsulation can be found in the literature.[154,158]

POLYPHENOL BIOACCESSIBILITY: EFFECTS OF MATRIX AND DOSE

Liquid versus solid foods

A first distinction that can be made between foods is liquid versus solid form. Most liquid foods possess a lower viscosity, pass through the stomach more rapidly than solid food,[160] and are, due to a higher water content, typically lower in proteins or complex carbohydrates that may bind to polyphenols. While several studies have reported rapid absorption of polyphenols from liquid foods such as coffee, i.e., peaking after 30–60 minutes postprandial,[72] there is no general evidence that this increases their overall bioavailability compared with solid foods. However, Chow et al.[161] found negative effects of the food bolus on polyphenol bioavailability, reporting higher concentrations of the green tea polyphenols epigallocatechin (EGC) and EGCG in blood plasma (>65% increase) when tea extract was consumed during fasting than during the fed state, at least within the 24-hour observation period. The absence of absorption inhibitors may not be the only effect of an "empty stomach." It has also been suggested that fasting may reduce the glucuronidation rate.[162] Thus, it could be speculated that the intake of polyphenols after fasting

may result in increased amounts of unconjugated forms in the body. It is also possible that the lower gastric pH seen in fasting conditions (pH 1.5–3), as opposed to that observed during meal intake (pH >5), has a stabilizing effect on some polyphenol fractions, such as anthocyanins, which are more stable at a lower pH.[163]

Even between various liquid matrices, differences in polyphenol bioavailability appear to exist. For example, a matrix effect was observed for the availability of caffeolyquinic acids (expressed as AUC), their bioavailability being higher from cloudy (nonclarified) apple juice than from apple juice or coffee.[164] The reason for this is unknown. Hagl et al.[165] found "apple smoothie" to have a higher colonic availability of polyphenols than cloudy apple juice, as determined by examination of ileostomist effluents. This was attributed to the protective effect of the smoothie, which contained larger amounts of cell wall and matrix components. In a human study by Goldberg et al.,[166] 25 mg of catechin, quercetin, and resveratrol were consumed with white wine, grape juice, or a vegetable juice, and plasma concentrations (over a rather short 4-hour period) and 24-hour urine samples were investigated. When expressed as AUC of total plasma (sum of free and conjugated) polyphenols, quercetin uptake was highest from wine (approx. 50% higher), and catechin uptake was highest from juice (over 2-fold higher), while no difference was found for uptake of resveratrol. Urinary patterns were similar but were not significant, possibly due to a large standard deviation and a low number of subjects ($n = 4$). The reason for these differences was not discussed further, but results may suggest that, even for comparably simple, liquid food items, differences between matrices, such as the presence of alcohol, fiber, or other nutrients, could impact polyphenol bioavailability.

In a recent study,[167] the impact of consuming red wine versus dealcoholized red wine on microbial polyphenol metabolites in feces was investigated. Although it could be speculated that alcohol may slightly increase the solubility of rather apolar polyphenols, no considerable differences between the two treatments were observed with respect to the total polyphenol concentration or the polyphenol profile in feces, indicating that the presence of alcohol had a negligible effect on the microbiota and its ability to metabolize red wine polyphenols. An earlier human trial likewise indicated that catechin concentrations in blood plasma were not different following intake of either red wine or dealcoholized red wine.[115] However, the red wine appeared to result in a more rapid urinary excretion of catechin, suggesting diuretic effects, in line with later findings that showed catechin excretion and urine volume were also higher (by approx. 20%) after consumption of red wine versus dealcoholized red wine.[168] Wine per se may be good matrix for polyphenol uptake, as an earlier study in rats showed that tartaric acid (1% in water), as present in wine, enhanced catechin absorption by over 50% as determined by AUC in blood plasma.[169] No explanation was offered, but it could be speculated that the ability of tartaric acid to form complexes with divalent minerals,[170] which could otherwise complex and precipitate polyphenols, may play a role.

As tea and coffee provide considerable daily amounts of polyphenols, the addition of milk and other creamers to such beverages has attracted interest (see also the section "Proteins"). In one study, the addition of milk to black tea did not appear to have a major impact on various plasma parameters (AUC, C_{max}, T_{max}, or $T_{1/2}$), compared with black tea alone,[171] whereas in another study, a 20% reduction in AUC was found. However, plasma concentrations were only monitored for 3 hours,[172] and the milk may have delayed peak absorption to some extent. Mixed effects or only small reductions in bioavailability were also found for coffee polyphenols when consumed with coffee and milk or dairy creamer. While no effect of milk was noticed, dairy creamer with sugar and rich in casein increased T_{max} and reduced C_{max} significantly in a human study,[173] with no effect on AUC, suggesting that the type of protein fraction, or other factors such as viscosity, could impact polyphenol absorption kinetics.

Most polyphenols consumed are obtained from solid foods. Although solid, more complex food matrices (see following sections) may delay the availability of polyphenols, they may also stabilize certain compounds or offer protection against further reactions until the site of absorption is reached. For example, when raspberry extract was digested in vitro with foodstuffs, i.e., bread, breakfast cereals, ice cream, and cooked minced beef, higher proportions of anthocyanins were recovered in the bioaccessible phase than when raspberry extract was digested alone, suggesting anthocyanins were transiently bound to the food matrix, which was able to protect them against degradation.[174] This effect was especially pronounced in minced meat, in which the bioaccessible fraction of anthocyanins was twice as high (8.4% vs 3.5%).

Dosing

The amount of polyphenols consumed, at least for nonglycosylated polyphenols, generally does not appear to have a significant effect on fractional absorption, something that may be expected for compounds taken up primarily or entirely by passive diffusion, i.e., nonsaturable processes. This was demonstrated when a product rich in green tea EGCG containing 400, 800, or 1,200 mg was consumed; no reduction in fractional absorption as measured by the plasma AUC was determined in humans.[161] A linear relationship between dose and uptake, pointing

toward passive diffusion, was also suggested for chlorogenic acid on the basis of pig mucosa experiments.[175] However, if metabolism prior to absorption or the participation of active transport systems or transporters (facilitated uptake) is involved, this relationship may change. For several polyphenols, high dosing has resulted in decreased fractional absorption, although typically, low and medium doses appear to be taken up in a rather linear fashion. For example, for isoflavonoid glycosides, absorption appeared to be linear up to an intake of 35 mg, while doses above 30–40 mg resulted in decreased fractional absorption.[105] It was suggested that, at lower concentrations, the rate-determining step in absorption is the transfer of isoflavonoids to the cell wall, constituting a rather nonsaturable process,[176] while at higher doses, other, saturable mechanisms, presumably the cleavage of glycosides into aglycons by brush-border enzymes such as LPH, may play a role.[66] Daayf and Lattanzio[177] summarized human anthocyanin studies in which different doses ranging between approximately 55 and 3,600 mg were administered and found a nonlinear dose relationship to be evident, suggesting a saturable mechanism for these glucosides. Thus, it can be hypothesized that polyphenols in amounts usually consumed within a meal may not be significantly compromised by saturation processes that limit their uptake; however, intake of supplements or other concentrated forms of polyphenols may limit uptake.

INFLUENCE OF MACROCONSTITUENTS ON POLYPHENOL BIOAVAILABILITY

Dietary fiber

A large proportion of polyphenols is associated with dietary fiber. Extractable polyphenols should be differentiated from nonextractable (or insoluble-bound) polyphenols (NEPPs), which are mostly attached to the cell wall. In general, fiber-polyphenol complexes may be present as soluble polymers, as insoluble macromolecular assemblies, or as swollen, hydrated networks.[178] While many of the low-weight polyphenols, such as phenolic acids, are easily extractable with common solvents (methanol, water) and are also usually released during digestion in the gastric phase or in the small intestine, higher-molecular-weight compounds, such as tannins and proanthocyanidins, which are the major fractions constituting NEPPs, are typically covalently bound to dietary fiber or proteins and can only be extracted under more drastic conditions, such as after enzymatic cleavage or hydrolysis with sulfuric acid; in vivo, NEPPs would be expected to reach the colon.[19] The amount of NEPPs in foods varies considerably between food items, ranging from over 50% in grains such as wheat, barley, and brown rice[179] to 80–90% in some frequently consumed fruits such as apples, peaches, and nectarines[180] to over 95% in some fiber-rich foods,[19] and NEPP intake in a Spanish population was shown to be up to four times higher than the intake of extractable polyphenols.[181]

In a recent review of dietary fiber as a carrier of antioxidants,[182] it is suggested that, although NEPPs may not be available in the small intestine, they may be released into the colon by microbiological fermentation. In a human study by Cerda et al.,[183] hydrolyzable tannins yielded metabolites of ellagic acid in the colon. These metabolites are absorbable and may result in health benefits in the colon epithelium.[184] In general, NEPPs associated with dietary fiber include a variety of polyphenols, encompassing polymeric tannins and hydrolyzable polyphenols as well as ferulic acid, caffeic acid, hesperidin, naringin, catechin, epicatechin, ellagic acid, gallic acid derivatives, protocatechin, and p-hydroxybenzoic acid,[181] which are typically linked to polysaccharides via hydrogen bonds, hydrophobic interactions, and covalent bonds (e.g., ester).

The activity of polyphenols released later in the gut may be different from that of more rapidly absorbable polyphenols, and additional metabolites with altered properties may be formed.[185] In fact, the kinetics of NEPPs differs from that of extractable polyphenols, with NEPPs having a somewhat delayed absorption[185] that ranges up to over 50 hours postprandial. In a rat experiment with NEPPs, ferulic acid from bread showed a markedly prolonged presence in plasma, up to 24 hours, versus only 4 hours for the free form,[186] which also correlated with a higher bioavailability as estimated by AUC. A prolonged presence in plasma – up to 24 hours postprandial – of NEPPs from grape seeds and peels compared with free polyphenols was also suggested in a human study by Pérez-Jiménez et al.[187]

The addition of separate forms of dietary fiber (free of polyphenols) is expected to have a less pronounced effect on polyphenol absorption, as this fiber is not expected to increase the pool of NEPPs. However, a general entrapment of polyphenols by added fiber may occur during digestion,[178] similar to the negative impact of fibers such as pectin on carotenoid bioavailability.[57] The addition of dietary fiber (40 g) to a meal containing 15 g wheat fiber decreased the plasma appearance of the isoflavonoid genistein by 55% in humans,[188] supposedly due to hydrophobic interactions, though it did not affect plasma levels of the somewhat more hydrophilic daidzein. In a study on mice, the addition of dietary fiber in the form of 5% hemicellulose to a diet already containing 5% cellulose was shown to decrease the availability of daidzein slightly but significantly, as shown by plasma concentrations. Moreover, the concentration of equol, a major microbial product of daidzein, was slightly but

nonsignificantly reduced, either via reducing available daidzein or via binding and/or entrapment,[189] as the binding of several phytoestrogens, including isoflavonoids, to fiber has been reported.[188]

A positive (or at least a less negative) effect on polyphenol bioavailability may be attributable to fermentable fibers, which may also act as prebiotics. It has been suggested that fermentable fibers such as fructo-oligosaccharides, inulin, and resistant starches increase the microbiota fermentation of some polyphenols, such as isoflavones in rats and in humans, enhancing the bioavailability of aglycons and/or gut metabolites (partly via increasing rates of deglycosylation) but reducing the bioavailability of native polyphenols.[190–192] A similar effect was found in a study by Tamura et al.,[193] where pectin enhanced the absorption of quercetin originating from rutin in mice, presumably by altering the metabolic activity of the microbiota.

Dietary fiber can also affect gastrointestinal transit time. While both insoluble (e.g., cellulose) and soluble (e.g., pectin) fiber increase the intestinal bulk, insoluble fiber typically reduces transit time, while soluble fiber increases it.[194] It is not fully understood how this may affect polyphenol uptake, but a larger bulk together with a shorter transit time can be expected to reduce the amount and number of colonic metabolites and to limit small intestinal uptake. In this respect, it has been speculated that high amounts of nondigestible proteins and carbohydrates may limit the availability and fermentation of polyphenols and the formation of microbiota metabolites through complexation.[195] While no systematic studies exist on polyphenols, reduced gastrointestinal transit time has been shown to decrease the bioavailability of various drugs.[196]

In summary, while only limited information is available on the effect of added fiber on polyphenol absorption in humans, it is speculated that fiber decreases available polyphenols, mainly due to factors such as physical entrapment, increased viscosity, and increased bulk. A stronger negative impact is expected when NEPPs are consumed, and, while fermentable fiber may not necessarily result in a reduced bioavailability of polyphenols, it may alter the profile of metabolites.

Dietary lipids

Surprisingly, not many studies have investigated the effect of dietary lipids on polyphenol absorption. As the majority of polyphenols are water soluble and transported via the portal vein, dietary lipids have been estimated to have a limited influence on the more hydrophilic polyphenols. This may be different with the more hydrophobic constituents, such as curcumin and xanthones, or even some of the flavonoid aglycons. For example, it has been shown that mixed micelles consisting of oleate and taurocholate in the apical part of a Caco-2 cell model enhanced transepithelial transport of α-mangostin from mangosteen juice,[197] and it has been suggested in an in vivo study that the comparably high absorption of approximately 2% of xanthones was due to the high lipid content of test meals.[59]

Conversely, polyphenols may bind to digestive proteins, limiting the amount of lipids and carbohydrates that may be physiologically available,[19] as shown, for example, by the ability of green tea and coffee polyphenols to limit lipolysis.[198] In turn, this would increase gastrointestinal bulk and may also reduce the availability of the native polyphenols, at least in the small intestine.

Dietary fats also increase gastrointestinal passage time and may alter the kinetics of polyphenol absorption. When strawberries were consumed with cream in a human trial, a delayed (in the first 2 hours) but not altered total bioavailability (as AUC in plasma) of anthocyanins was recognized[199] over a 24-hour period.

Ortega et al.[200] found a much higher fractional bioaccessibility of procyanidins – but not of phenolic acids and flavones – from lipid-rich cacao liquor (45% fat) than from cacao powder (15% fat) in an in vitro digestion model, which is in line with the theory that the more apolar polyphenols are, at least in part, micellarized and that lipids from the food matrix aid in the stabilization/solubilization of mixed micelles. A similar conclusion, i.e., improved micellarization, absorption, and a more pronounced enterohepatic circulation, may be drawn from a study by Lesser et al.,[201] where bioavailability of quercetin in pigs was influenced by dietary fat content. While the quercetin (as conjugated quercetin) AUC of a 17% fat diet was approximately 57% higher than that of a 3% fat diet, no further increase was seen with a 32% fat diet. To date, the single existing human study, with 9 subjects, investigated quercetin bioavailability of an aglycon supplement (1 g) taken with a fat-rich (15 g) breakfast versus a fat-free breakfast. It was found that the AUC in plasma was approximately 45% higher in subjects who consumed the fat-rich breakfast.[202]

Interestingly, even for comparatively polar compounds such as tyrosol and hydroxytyrosol, absorption from a lipid-rich matrix such as olive oil was shown to be approximately 25% greater than that from an aqueous solution in a rat model,[203] although protection by other antioxidants present in the olive oil could have also contributed to this effect.

Proteins

Some polyphenols, especially those with a high number of hydroxyl groups, i.e., polyhydroxyl phenols, have a comparably high affinity for proteins. For tannins, apparently,

at least three flavonol subunits are required for effective protein precipitation.[204] Similarly, tannins with over 12 hydroxyl groups have been reported to strongly bind to proteins such as albumins, not only from the food matrix but also from saliva, resulting in complexes that reduce polyphenol absorption (especially those containing proline), while polyphenols with a smaller mass and fewer hydroxyl substitutions may be less influenced, as found for quercetin.[205] Complexes may also be formed with brush-border membrane proteins, including SGLT1 or other gut wall proteins, as shown for tannic acid,[206] perhaps partially explaining carbohydrate uptake inhibition by polyphenols. It is not too surprising that some polyphenols, especially tannins, were therefore regarded as antinutrients in the past, shown to result in stunted growth, at least in animals.[207]

Complexes may be further formed postabsorption with plasma proteins. This formation is to some extent reversible, with low pH fostering complexation and high pH favoring cleavage of the complex,[208] suggesting that binding occurs in part via the formation of hydrogen bonds, such as between the phenolic groups and the carbonyl groups of peptides. However, intermolecular bonds have also been suggested due to the strong affinity of some polyphenols, such as EGCG, to fibronectin in plasma.[209,210]

The opposite effect, i.e., the effect of proteins on polyphenol availability, is more difficult to judge, and only indirect indications of protein-polyphenol interactions are available. In a study by Mullen et al.,[211] cacao consumed with milk resulted in lower plasma AUC and higher urinary flavan-3-ol (and metabolites) concentrations (approx. 25% and 50%, respectively), which was speculated to result from a decreased uptake from the gut due to protein-polyphenol interactions. In a study by Urpi-Sarda et al.,[212] cacao powder was dissolved in either milk or water, and the concentration of polyphenols in plasma was measured. In particular, higher amounts of the phenolic acids vanillic acid and phenylacetic acid from the milk were found, perhaps indicating the liberation and metabolism of phenolic acids into vanillic acid by the microbiota. However, for most polyphenols, absorption from cacao dissolved in water was superior. Similarly, concentrations of caffeic acid and ferulic acid in human plasma following blueberry consumption were higher when blueberries were consumed with water instead of milk.[213] In another human study, the availability of phenolic acids from orange juice consumed with or without yogurt was reduced when yogurt was consumed with orange juice.[214] Not all studies, however, showed a negative effect of milk or milk-protein-containing foods on polyphenol absorption. In a human study by Keogh et al.,[215] subjects consumed 2 g of chocolate polyphenols with or without 2.5 g of milk protein, and no negative effect on polyphenol levels in plasma was observed, perhaps because the ratio of polyphenols to proteins was quite high. In another study, by Roura et al.,[216] 21 subjects consumed 40 g of cacao powder containing at least 60 mg of polyphenols in 250 mL of either water or whole milk. After 2 hours, plasma concentrations of ECG were slightly, but not significantly, lower in subjects who consumed cacao with milk versus cacao with water, 274 nmol/L versus 330 nmol/L.

These effects may suggest negative interactions between proteins and polyphenols, though additional effects of matrix components such as lipids or carbohydrates cannot be excluded. For example, in a study by Langley-Evans,[217] it was shown that high-fat milk digested in vitro with black tea had a significantly more pronounced negative impact on antioxidant capacity (ferric-reducing antioxidant power [FRAP], employed as a marker of total phenolic compounds) than low-fat milk. However, levels of individual polyphenols were not determined. It was argued that longer peptide chains, the formation of which is apparently associated with increasing fat content, could have resulted in increased polyphenol complexation,[213] perhaps similar to the interactions described between β-lactoglobulins and phenolic acids.[218] In contrast, in an in vitro study by Ryan and Petit,[219] antioxidant activity in black tea was measured after the addition of either skimmed, semi-skimmed, or whole milk. It was found that skimmed milk had the most drastic effect in reducing antioxidant activity (as determined by FRAP), although, compared with water, all milk types decreased antioxidant capacity. It is possible that other antioxidant compounds present in tea, such as theaflavins and thearubigin, were overlayering the results. In summary, further studies on protein-polyphenol interactions are warranted, and although negative effects of proteins on polyphenol bioavailability appear plausible, the effect may depend largely on the type of protein and polyphenols involved.

Digestible carbohydrates

Similar to that of lipids and proteins, the digestion of carbohydrates is also affected by polyphenols, with starch digestion reduced in some studies by up to 50%, possibly via amylase inhibition.[42] In addition, several polyphenols have been reported to inhibit glucose uptake transporters, including MCTs, SGLT1, and glucose transporters (GLUTs).[220] Predicting the opposite effect, i.e., reduction of polyphenol uptake by sugar-rich ingredients, is more challenging, as far fewer studies have examined the impact of carbohydrates on polyphenol uptake than the impact of polyphenols on carbohydrate metabolism. In a study by Schramm et al.,[221] the addition of carbohydrates, in the form of either sugar, bread, or milk, all significantly

enhanced the plasma AUC of cacao flavanols in humans by up to 40%, while meals comprised mainly of proteins (steak) and lipids (butter) barely had any impact. The reasons remained unexplained but could include the activation of transporters also involved in polyphenol glycoside uptake, such as SGLT1. Similarly, in a human study by Bitsch et al.,[222] a synergistic effect of glucose and anthocyanins from red grape juice was proposed, as intestinal anthocyanin uptake from red grape juice was superior by approximately 70% compared with that from red wine, as measured by plasma AUC (3 hours) and urinary excretion (7 hours). More studies on the effect of sugars on polyphenol absorption are needed to support the hypothesis that polyphenol glycoside uptake may be enhanced by sugars.

INFLUENCE OF MINOR CONSTITUENTS ON POLYPHENOL BIOAVAILABILITY

Minerals and trace elements

Several polyphenols, including phenolic acids and flavonoids, have been shown to reduce the absorption of a number of minerals and trace elements, including iron, zinc, and copper, as well as sodium,[19] most likely due to chelation by, e.g., galloyl and catechol groups. In particular, the negative impact of polyphenols such as EGCG and other gallates on iron[223] and zinc uptake[224] in Caco-2 cells and in humans[225] has been well documented, although the effect on zinc is more controversial.[226] Conversely, the effect of mineral intake on polyphenol bioavailability has never been studied systematically. It is known that the strength of polyphenol chelation depends on the type of mineral. For example, for phytic acid complexes, the strength generally decreases in the sequence Cu>Zn >Mn>Fe>Ca,[227] with Mg assumed to be a weaker chelator that forms more soluble complexes, while monovalent ions such as Na and K are very weak chelators and would not be expected to form unavailable complexes. As Ca in particular plays a significant role in terms of a high dietary intake, consumption of high amounts of Ca (e.g., in form of supplements) might reduce the availability of polyphenols in the small intestine, although microbiota activity may result in the release of polyphenols in the colon. The study by Matsumoto et al.[228] may provide rather indirect proof of a potential negative effect on polyphenol absorption. In this rat and human study, animals and subjects received black currant anthocyanins with or without phytic acid (1% solutions), and the plasma and urine concentrations of anthocyanins were markedly improved (up to approx. 15-fold) when phytic acid was given. As phytic acid is a strong chelator of divalent minerals, it may have prevented the formation of mineral-polyphenol complexes. However, the duration of gastrointestinal passage was also longer with phytic acid, which could have altered absorption kinetics.

Other micronutrients

Few studies have investigated interactions between polyphenols and other micronutrients, such as lipophilic vitamins or carotenoids. In a study by Reboul et al.,[229] it was shown that naringenin, a comparatively lipophilic polyphenol, inhibited the uptake of various carotenoids and of tocopherols into Caco-2 cells,[230] perhaps due to the effects of polyphenols on the carotenoid uptake transporter scavenger receptor class B type I or by affecting the invagination of lipid raft domains containing lutein receptors. However, whether carotenoids or vitamin E may in turn affect polyphenol uptake is not known and is perhaps less likely, as concentrations of polyphenols in the gut are typically higher by one order of magnitude. Thus far, carotenoids and vitamin E have not been reported to interfere with any of the transporters involved in polyphenol epithelial uptake. However, for the lipophilic polyphenols in particular, it cannot be excluded that high amounts of compounds competing for micellarization may have negative effects on their bioaccessibility. In a study by Shishikura et al.,[231] in vitro digestion of the green tea polyphenols EGC and EGCG together with olive oil resulted in a significantly enlarged lipid droplet size (from 1 μm to over 25 or 50 μm, at 1 and 0.1 mg/mL), possibly due to interactions between phosphatidylcholine and polyphenols, as well as the incorporation of polyphenols into the outer sphere of emulsion droplets, suggesting possible interactions between the micellarization of polyphenols and other micronutrients.

The presence of other antioxidants that may prevent oxidation of polyphenols has been suggested to enhance polyphenol bioavailability. Many polyphenols, such as EGC and EGCG, are prone to autoxidation, especially in the comparably high pH of the small intestine.[102] Some beverages made from tea extracts also contain ascorbic acid, which has been found to prevent oxidation reactions, increasing the recovery of EGCG and EGC from 12% to 72% and from 4% to 54%, respectively, in the intestinal phase of a digestion model,[232] and similar effects were also found for teas that contained citrus fruit juices rich in vitamin C. This was also shown in vivo, where a 2.5- to 3-fold higher rate of absorption of EGC and EGCG was found with intake of green tea products containing sugar and ascorbic acid versus intake of green tea only in a rat model,[233] and even in humans, although EGCG absorption increased only by 14% or 27% when green tea extracts were combined with nutrient-rich mixtures containing, respectively, ascorbic acid or additional grapes.[234]

Other polyphenols

Interestingly, it has been reported that several phytochemicals, including carotenoids and di- and triterpenes, as well as some polyphenols, including quercetin, hypericin, and kaempferol, were able to inhibit P-glycoprotein efflux transporters of ritonavir, an HIV drug, at least in Caco-2 cell models overexpressing these transporters,[235] indicating that intracellular polyphenol concentrations in the enterocytes may be enhanced following digestion of foods rich in phytochemicals, as these may be re-excreted back into the gut lumen by P-glycoprotein. This has also been suggested for another efflux transporter by Brand et al.,[236] who speculated that quercetin would be better available when consumed with a BCRP inhibitor such as apigenin, hesperitin, or naringenin. The blocking of BCRP in mice resulted in an increased uptake of quercetin metabolites and higher plasma levels.[237] In another study, Brand et al.[238] demonstrated that transport of the flavanone hesperetin toward the basolateral side of Caco-2 cells was increased (up to 100%) in the presence of other flavonoids (isoflavones, flavones, and flavonols, but not rutinosides or flavanols, suggesting that 2,3-double bonds in ring C and the ring B attached at position 2 are important for inhibiting BCRP), likewise connoting that the efflux back to the apical side via MCTs and BCRP may have been compromised. In an earlier study investigating the effect of various flavonoids (apigenin, biochanin A, chrysin, genistein, kaempferol, hesperetin, naringenin, and silymarin) on BCRP transport in MCF-7 breast cancer cells, it was suggested that the various flavonoids have an additive effect.[239] Possible reasons for the transporter inhibition likely included BCRP-associated inhibition of ATPase activity as well as competitive effects. In another study, tea polyphenols, even though they were not likely substrates for MCTs, showed inhibitory effects on these transporters, also suggesting they may enhance the bioavailability of other polyphenols.[82]

Phenolic acids have also been reported to have positive effects on polyphenol uptake. Rosmarinic acid uptake into Caco-2 cells was significantly higher when apigenin and luteolin were simultaneously present at 90 μM, as uptake expressed as permeation increased from approximately 33% to 90%. Interestingly, lower concentrations of flavonoids, i.e., those below 50 μM, slightly decreased uptake. It was speculated that, at low concentrations, uptake transporters were more likely to be blocked, while at higher concentrations, transporters responsible for the efflux into the lumen were blocked more predominantly.[240] In contrast, limiting efflux transporter activity toward the basolateral side, as shown in mice not expressing MRP3 and having low resveratrol availability,[241] would certainly decrease bioavailability, but no food component has been clearly shown to affect this or other MRP transporters so far.

Another way that micronutrients and phytochemicals may affect polyphenol bioavailability is by influencing phase I and II enzyme systems, which would normally result in a rapid production of metabolites, thereby reducing the bioavailability of the original polyphenol. It is well understood that naringin and its aglycon naringenin, as present in grapefruit juice, can inhibit cytochrome oxygenases (i.e., CP3A4), thereby enhancing the potency of various drugs.[242] Similar effects have been shown for polyphenol metabolism. For example, biochanin A, a flavonoid, was found to be much more bioavailable in rats (expressed as AUC) when administered together with quercetin and EGCG, a result attributed to reduced conjugation (reduced UGT and SULT activity).[243] Several flavonoids, including tangeritin and silybin, have been shown to inhibit UGTs (in vitro at concentrations below 1 μM [IC_{50} values]), and others, such as quercetin, myricetin, chrysin, kaempferol, apigenin, and genistein, have been shown to reduce SULTs, but it remains unclear whether this translates into measurable effects in vivo.[117] Another effect, also suggested to be linked to altered phase II metabolism, is the increased uptake of curcumin in animals and humans (up to 20-fold) observed after being coadministered with piperine,[244] possibly due to decreased glucuronidation in the intestine and liver. Likewise, piperine has been shown to enhance the absorption of EGCG in mice.[245]

The reverse action, i.e., the induction of phase I and phase II enzymes, which reduces polyphenol bioavailability, should also be possible, but less is known about the food compounds that induce these enzymes. Some herbs, such as St. John's wort, rich in flavonoids, phenylpropanes, and naphthodianthrones, as well as other herbs and garlic have been shown to enhance some of the cytochrome P450 enzymes, which may or may not reduce polyphenol bioavailability.[117]

Even prior to absorption, polyphenol uptake in the intestine may be influenced by coingested phytochemicals. It has been suggested that some polymeric polyphenols, without being taken up themselves, may enhance the cellular uptake of monomeric and dimeric polyphenols from the gut, presumably by increasing tight junction permeability,[83,220] which enhances the paracellular uptake of lower-molecular-weight polyphenols. This has been shown in several rat studies, which reported enhanced uptake of procyanidin B2 by tetramer proanthocyanidins[94] as well as increased absorption of apple procyanidin oligomers, which was enhanced by high-weight polymeric procyandins.[208] It cannot be excluded, however, that these high-molecular-weight polyphenols bind preferentially to mucosal proteins in the gut, thereby allowing the monomeric and

Table 3 **Overview of dietary factors affecting aspects of polyphenol bioavailability.**

Food aspect	Food aspect/compound	Polyphenols implicated	Type of interaction	Type of studies providing evidence	Effect and strength of effect	Examples of references
Matrix	Solid vs liquid	All types	Protection of anthocyanins by solid food matrix	In vitro	2× higher from minced meat than from juice	McDougall et al.[174]
	Fasting vs fed	Tea PPs	Reduced absorption in fasting state	Human	⅔ reduction of absorption in fed state	Chow et al.[161]
	Whole plant cell material	Chlorogenic acid	Entrapment of PPs by solid plant material	Human	Higher colonic availability of PPs from smoothie	Hagl et al.[165]
Dosing	All	Aglycons	Possibly no effect	Human, in vitro	NA	Chow et al.,[161] Erk et al.[72]
Dosing	All	Glycosides	Reduced fractional absorption with higher doses	Human, in vitro, cell models	Reduced absorption >35 mg doses	Daayf & Lattanzio,[177] Bohn[105]
Macromolecules	Proteins	Polar PPs, esp. with multiple OH groups	Binding of PPs via hydrogen bonds	Human	50% reduction in AUC with milk vs water	Roowi et al.,[214] Serafini et al.,[213] Mullen et al.,[211] Urpi-Sarda et al.,[212] Ryan & Petit[219]
	Lipids, emulsifiers	Apolar PPs: xanthones, quercetin, procyanidins,	Enhancement of bioaccessibility	In vitro, Caco-2 cells, animal	6-fold enhancement of xanthones by bile salts; dietary lipids enhance uptake of procyanidins, quercetin	Bumrungpert et al.,[197] Chitchumroonchokchai et al.,[59] Ortega et al.,[200] Lesser et al.,[201] Tuck et al.[203]
	Carbohydrates	Cacao glycoside flavanols anthocyanins	Enhancement of cellular uptake (SGLT1↑), glucose-anthocyanins	Human	Up to 40% enhanced absorption suggested, 70% higher uptake from juice than from wine	Schramm et al.[221] Bitsch et al.[222]
	Nonfermentable dietary fiber	All types	Delayed availability due to either entrapped PPs or PPs bound as NEPPs, increased metabolism	Animal, human	Severalfold higher AUC from bran than from free form, reduced native PPs	Saura-Calixto,[182] Saura-Calixto et al.,[185] Tew et al.,[188] Rondini et al.,[186] Pérez-Jiménez et al.[187]
	Fermentable dietary fiber (prebiotics)	All types	Enhanced fermentation and altered PP metabolism, enhanced deglycosylation	Human	Suggestive	Larkin et al.,[190] Piazza et al.,[192] Tew et al.[188]
Micronutrients	Minerals, trace elements	Various	Complexation by divalent minerals, decreased absorption	Cell model,, human	Speculative, indirect	Ma et al.,[223] Hurrell et al.,[225] Matsumoto et al.[228]
	Vitamin C (AA)	Various	Prevention of PP oxidation	In vitro, animal, human,	With AA: >5× concentration of green tea PPs in intestine, 2.5–3× higher absorption of EGC/EGCG	Green et al.,[232] Peters et al.,[233] Gawande et al.[234]
Phytochemicals	Other PPs	High-weight polymers	Enhanced tight-junction permeability, preferred binding to mucosal proteins	Rat, Caco-2 cells	Increased absorption of PPs	Appeldoorn et al.,[94] Shoji et al.,[208] Shimizu[220]
		Phenolic acids, flavonoids	Reduced efflux (MCTs↓, BCRP↓) to basolateral side	Rat, Caco-2 cells	Enhanced uptake (up to 100%) of other PPs	Sesink et al.,[237] Moon & Morris,[243] Brand et al.,[238] Zhang et al.,[239] Fale et al.[240]
		Flavonoids	Reduced phase I and phase II metabolism	Rat, cell models	Reduced biochanin absorption by quercetin and EGCG, 20× higher curcumin absorption	Moon & Morris,[243] Scheepens et al.[117] Shoba et al.,[244] Lambert et al.[245]
Food treatment/ processing	Plant ripeness	Phenolic acids, anthocyanins	Reduction during ripening increases during ripening	In situ	Various	D'Archivio et al.[136]
	Plant stress	All types	Increased PP concentration when grown organically or exposed to environment	In situ	Various; average of 12% higher in organically grown plants	Manach et al.,[1] Brandt et al.[135]
	Storage time	All types, anthocyanins	Enzymatic degradation	In situ	Higher anthocyanins, general reduction in PPs	D'Archivio et al.[136]
	Reduced particle size/grinding	All types	Enhanced bioaccessibility	Cell models, rat	2× enhancement for reduction from 20 µm to 3 µm	Maeda-Yamamoto et al.,[144] Li et al.[145]
	Drying	All types	Enzymatic degradation during cell destruction	In situ	<80% losses, lowest with vacuum methods and microwave	Shofian et al.,[140] Hii et al.,[142] Mejia-Meza et al.[141]
	Heat treatment	Selected tomato PPs	Enhanced bioaccessibility due to softening of cell walls	Human	Severalfold enhancement of absorption	Bugianesi et al.[146]
		All types, different matrices, esp. juices	Increased heat-related degradation of PPs	In situ (matrices)	≥2× reduction	Xu & Chang,[153] Hernandez et al.,[149] Shivashankara & Acharya[148]
	(Micro-)encapsulation e.g., by liposomes or cyclodextrins	Lipid soluble, e.g., curcumin, but also green tea PPs, quercetin, isoflavones	Enhanced solubility, protection from negative influences during digestion	Rat, in vitro	5× enhancement of absorption	Takahashi et al.,[246] Fang et al.,[247] Barras et al.,[159] Lee et al.[248]

Abbreviations: AA, ascorbic acid; AUC, area under plasma-time curve; BCRP, breast cancer resistance protein; EGC, epigallocatechin; EGCG, epigallocatechin gallate; MCTs, monocarboxylic acid transporters; NA, not applicable; NEPPs, nonextractable polyphenols; OH, hydroxyl; PPs, polyphenols; SGLT1,sodium-glucose linked transporter 1.

dimeric polyphenols to be absorbed and their interaction with proteins to be minimized.

Taken together, the majority of studies suggest that polyphenols may have greater bioavailability when they are ingested in combination with other polyphenols than when taken alone, such as in a supplement.

CONCLUSION

Polyphenol bioavailability appears to depend on a variety of factors related to diet and the food matrix, summarized in Table 3.[209–248] Bioaccessibility appears to be favorably affected by 1) physiological dose, 2) smaller particle size and heating, both of which improve release from the matrix, and 3) the presence of a certain amount of lipids as well as low levels of proteins and indigestible carbohydrates in the matrix. The simultaneous intake of antioxidant micronutrients such as vitamins C and E may, to some extent, reduce gastrointestinal degradation of polyphenols, while the presence of additional polyphenols may enhance polyphenol availability by influencing efflux transporters. A largely neglected factor appears to be the potential effect of nutrients and non-nutrients on polyphenol biodistribution and excretion.

Thus, in view of the potential relationship between polyphenols and the reduction of chronic diseases on one hand, and the risk of micronutrient deficiencies such as zinc and iron with elevated polyphenol intake on the other, as well as the plethora of dietary supplements on the market, more research in this domain is warranted. The combination of food science and technological knowledge to tailor these aspects and steer the bioavailability of polyphenols by optimally combining various ingredients is desired to guarantee optimal nutrition.

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