Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies[1,2,3]

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Abstract

Polyphenols are abundant micronutrients in our diet, and evidence for their role in the prevention of degenerative diseases is emerging. Bioavailability differs greatly from one polyphenol to another, so that the most abundant polyphenols in our diet are not necessarily those leading to the highest concentrations of active metabolites in target tissues. Mean values for the maximal plasma concentration, the time to reach the maximal plasma concentration, the area under the plasma concentration-time curve, the elimination half-life, and the relative urinary excretion were calculated for 18 major polyphenols. We used data from 97 studies that investigated the kinetics and extent of polyphenol absorption among adults, after ingestion of a single dose of polyphenol provided as pure compound, plant extract, or whole food/beverage. The metabolites present in blood, resulting from digestive and hepatic activity, usually differ from the native compounds. The nature of the known metabolites is described when data are available. The plasma concentrations of total metabolites ranged from 0 to 4 μmol/L with an intake of 50 mg aglycone equivalents, and the relative urinary excretion ranged from 0.3% to 43% of the ingested dose, depending on the polyphenol. Gallic acid and isoflavones are the most well-absorbed polyphenols, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least well-absorbed polyphenols are the proanthocyanidins, the galloylated tea catechins, and the anthocyanins. Data are still too limited for assessment of hydroxycinnamic acids and other polyphenols. These data may be useful for the design and interpretation of intervention studies investigating the health effects of polyphenols.

Polyphenols   flavonoids   isoflavones   flavonols   flavanones   hydroxycinnamic acids   hydroxybenzoic acids   anthocyanins   proanthocyanidins   catechins   bioavailability   metabolism   pharmacokinetics   elimination half-life   humans

INTRODUCTION

Epidemiologic studies have clearly shown that diets rich in plant foods protect humans against degenerative diseases such as cancer and cardiovascular diseases. Plant foods contain fiber, vitamins, phytosterols, sulfur compounds, carotenoids, and organic acids, which contribute to the health effects, but they also contain a variety of polyphenols, which are increasingly regarded as effective protective agents.

Polyphenols represent a wide variety of compounds, which are divided into several classes, ie, hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, proanthocyanidins, flavonols, flavones, flavanols, flavanones, isoflavones, stilbenes, and lignans. The chemical structures and the food contents of the various polyphenols have been reviewed elsewhere (1). One of the main objectives of bioavailability studies is to determine, among the hundreds of dietary polyphenols, which are better absorbed and which lead to the formation of active metabolites.
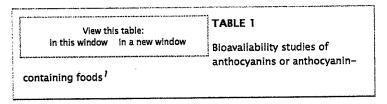
Many researchers have investigated the kinetics and extent of polyphenol

absorption by measuring plasma concentrations and/or urinary excretion among adults after the ingestion of a single dose of polyphenol, provided as pure compound, plant extract, or whole food/beverage. We have reviewed 97 studies of various classes of polyphenols, namely, anthocyanins, flavonols, flavanones, flavanol monomers, proanthocyanidins, isoflavones, hydroxycinnamic acids, and hydroxybenzoic acids. We have compiled the data from the most relevant studies, ie, those using well-described polyphenol sources and accurate methods of analysis, to calculate mean values for several bioavailability measures, including the maximal plasma concentration (C_{max}), time to reach C_{max}, area under the plasma concentration-time curve, elimination half-life, and relative urinary excretion. The results clearly show wide variability in the bioavailability of the different polyphenols.

ANTHOCYANINS

Anthocyanins are present in very large amounts in some diets. Servings of 200 g of aubergine or black grapes can provide up to 1500 mg anthocyanins and servings of 100 g of berries up to 500 mg. Therefore, an intake of several hundred milligrams would not be considered exceptional. The mean dietary intake in Finland has been estimated to be 82 mg/d, with the main sources being berries, red wine, juices, and the coloring agent E163 (M Heinonen, personal communication, 2001).

The results of a literature survey on the bioavailability of anthocyanins among humans are presented in **Table 1**. Single doses of 150 mg to 2 g total anthocyanins were given to the volunteers, generally in the form of berries, berry extracts, or concentrates. After such intakes, concentrations of anthocyanins measured in plasma were very low, on the order of 10-50 nmol/L. The mean time to reach C_{max} was 1.5 h (range: 0.75-4 h) for plasma and 2.5 h for urine. Most studies reported low relative urinary excretions, ranging from 0.004% to 0.1% of the intake, although Lapidot et al (11) and Felgines et al (14) measured higher levels of anthocyanin excretion (up to 5%) after red wine or strawberry consumption. The time course of absorption was consistent with absorption in the stomach, as described for animals (15, 16). The most striking features of the survey were thus that anthocyanins are very rapidly absorbed and eliminated and that they are absorbed with poor efficiency.

| View this table: | TABLE 1 |
| In this window   In a new window | Bioavailability studies of anthocyanins or anthocyanin-containing foods[1] |

Although anthocyanin bioavailability appears low, it could have been underestimated, for 2 main reasons, ie, some important metabolites might have been ignored or the methods used might need to be optimized for the analysis of anthocyanin metabolites. It is well known that different chemical forms of anthocyanins are present in equilibrium, depending on the pH. In most studies, analyses were performed with ultraviolet-visible light detection, on the basis of complete conversion of all of the chemical forms of anthocyanins into a colored flavylium cation with acidification. However, it is possible that some forms existing at neutral pH would not be converted into the flavylium form, because of putative binding to or chemical reactions with other components of the plasma or urine, for example. It would be very useful to have labeled anthocyanins for identification of all of the metabolites generated from these polyphenols.

With our current knowledge, there seem to be important differences in the metabolism of anthocyanins, compared with other polyphenols. Whereas flavonoids are generally recovered in plasma and urine as glucuronidated and/or sulfated derivatives, with no or only trace amounts of native forms, unchanged glycosides were the only metabolites identified for anthocyanins in most studies. However, glucuronides and sulfates of anthocyanins were recently identified in human urine with HPLC-mass spectrometry/mass spectrometry analyses (6, 14). In the study conducted by Felgines et al (14), monoglucuronides accounted for >80% of the total metabolites when analyses were performed immediately after urine collection. The authors also showed that all of the metabolites of the
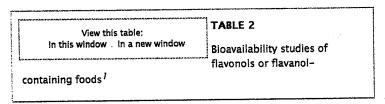
strawberry anthocyanins, except for the native glucoside, were very unstable and were extensively degraded when acidified urine samples were frozen for storage. This probably explains why such metabolites were not observed in previous studies. Therefore, it seems crucial to reconsider anthocyanin bioavailability, with methods that allow preservation of all of the metabolites in frozen samples.

Other metabolites that have not yet been considered but could contribute to the biological effects of anthocyanins are the metabolites produced by the intestinal microflora. However, studies performed in the 1970s showed that degradation of anthocyanins by the microflora occurs to a much more limited extent than with other flavonoids (17). Protocatechuic acid was identified as an abundant metabolite of cyanidin-3-O-glucoside in rats, but it was also formed in vitro with simple incubation of cyanidin with rat plasma in the absence of colonic bacteria (18). Identification of all of the microbial metabolites in humans should be reinvestigated with pure anthocyanins and not only berry extracts, which contain other polyphenols as well as anthocyanins.

FLAVONOLS

Flavonols, especially quercetin, have been extensively studied, mainly because they are widely distributed in dietary plants. However, their content in the diet is generally quite low. The daily intake of flavonols has been estimated as only 20–35 mg/d (19-22).

Twenty years after Gugler et al (23, 24) failed to find quercetin in plasma or urine from volunteers challenged with 4 g pure aglycone, the team of Hollman et al (23, 24) showed that quercetin was indeed absorbed in humans. They demonstrated that glucosides of quercetin were more efficiently absorbed than quercetin itself, whereas the rhamnoglucoside (rutin) was less efficiently and less rapidly absorbed (**Table 2$**). This difference in absorption rates was confirmed by others (33, 34). When pure compounds were given, the bioavailability of rutin was ~20% that of quercetin glucosides, on the basis of area under the plasma concentration–time curve values and relative urinary excretions (30, 34). The biochemical explanation for the better absorption of quercetin glucosides has been discussed elsewhere (1). It is clear that, for quercetin, bioavailability differs among food sources, depending on the type of glycosides they contain. For example, onions, which contain glucosides, are better sources of bioavailable quercetin than are apples and tea, which contain rutin and other glycosides.

View this table: In this window . In a new window	**TABLE 2** Bioavailability studies of flavonols or flavanol-containing foods[1]

The presence of intact glycosides of quercetin in plasma was debated a few years ago, but it is now accepted that such compounds are absent from plasma after nutritional doses (34, 37-40). Quercetin is not present as an aglycone and occurs only in conjugated forms. Generally, ~20-40% of quercetin is methylated in the 3'-position, yielding isorhamnetin (31, 34, 38). The exact nature of the metabolites present in plasma after the ingestion of onions was determined by Day et al (38). They identified quercetin-3'-O-glucuronide, 3'-O-methylquercetin-3-O-glucu-ronide, and quercetin-3'-O-sulfate as the major conjugates.
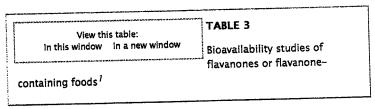
Some phenolic and aromatic acids can also be produced from flavonols by the microflora. Quercetin degradation produces mainly 3,4-dihydroxyphenylacetic, 3-methoxy-4-hydroxyphenylacetic (homovanillic acid), and 3-hydroxyphenylacetic acid (17, 41-43). The total urinary excretion of microbial metabolites accounted for as much as 50% of the ingested dose among volunteers challenged with 75 mg rutin (44).

One characteristic feature of quercetin bioavailability is that the elimination of quercetin metabolites is quite slow, with reported half-lives ranging from 11 to 28 h. This could favor accumulation in plasma with repeated intakes. A few authors investigated the bioavailability of quercetin after several days or weeks of supplementation. Baseline quercetin concentrations, measured after overnight

fasting, were generally ~50-80 nmol/L, and values were even lower when a low-polyphenol diet was given to the volunteers before a test meal (45, 46). The baseline concentration slightly increased (165 nmol/L) after 6-wk supplementation with 500 mg/d pure rutin (32). The increase was more pronounced in 2 other studies; plasma concentrations reached 1.5 μmol/L after 28 d of supplementation with a high dose of quercetin (>1 g/d) (47) and 0.63 μmol/L after supplementation with 80 mg/d quercetin equivalents for 1 wk (37). It should be noted that very high interindividual variability was observed in the latter study and in others (27, 34, 37). Some individuals could be better absorbers than others, possibly because of particular polymorphisms for intestinal enzymes or transporters. Quantitative data are still lacking for other flavonols and flavones.

FLAVANONES

Flavanones represent a small group of compounds, including glycosides of hesperetin present in oranges and glycosides of naringenin present in grapefruit. The bioavailability of the glycosides of eriodictyol, present in lemons, has never been studied in humans. The C_{max} values for flavanone metabolites were measured ~5 h after the ingestion of citrus fruits (Table 3⇓). This is the time required for hydrolysis of the rhamnoglycosides hesperidin, naringin, and narirutin by the microflora, before absorption of the released aglycones in the colon. Aglycones are absorbed more rapidly; Bugianesi et al (50) showed that C_{max} was reached as early as 2 h after the ingestion of tomato paste, which contains naringenin aglycone. However, natural foods rarely contain significant amounts of flavanones in the aglycone form.

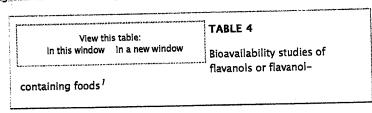| View this table: In this window In a new window	TABLE 3 Bioavailability studies of flavanones or flavanone-containing foods[1]

Plasma metabolites of flavanones have not yet been identified. Monoglucuronides of hesperetin were shown to be the major forms present in plasma after ingestion of orange juice, but the positions of glucuronidation are still not known (48). Microbial metabolites such as p-hydroxyphenylpropionic acid, p-coumaric acid, p-hydroxybenzoic acid, and phenylpropionic acid were produced with in vitro incubation of naringenin with human microflora (17, 55, 56). They were also detected in rat urine (57). The same types of microbial metabolites were detected for hesperetin (58, 59). Therefore, microbial metabolites may also be present in human plasma.

The total urinary excretion of conjugated flavanones accounted for 8.6% of the intake for hesperidin and 8.8% for naringin (Table 3⇑). Plasma concentrations reached 1.3-2.2 μmol/L hesperetin metabolites with an intake of 130-220 mg given as orange juice (48, 49) and up to 6 μmol/L naringenin metabolites with 200 mg ingested as grapefruit juice (49). However, data are still scarce, with only 3 studies having investigated the bioavailability of flavanones in plasma.

CATECHINS

The daily intake of catechin and proanthocyanidin dimers and trimers has been estimated to be 18-50 mg/d, with the main sources being tea, chocolate, apples, pears, grapes, and red wine (60, 61). Although they are present in many fruits and in red wine, the bioavailability of catechins has been studied mainly after ingestion of cocoa or tea (Table 4⇓).

View this table: In this window In a new window	TABLE 4 Bioavailability studies of flavanols or flavanol-containing foods[1]

Bioavailability differs markedly among catechins. By giving pure catechins

individually, van Amelsvoort et al (78) demonstrated that galloylation of catechins reduces their absorption. They found that only epigallocatechin was methylated and that 4'-O-methyl-epigallocatechin accounted for 30–40% of the total metabolites of epigallocatechin. In another study, the 4'-O-methyl-epigallocatechin concentration was 5 times higher than that of epigallocatechin in plasma and 3 times higher than that in urine (84). Meng et al (74) recently showed that epigallocatechin gallate (EGCG) was also methylated into 4',4"-di-O-methyl-EGCG. The concentration of this metabolite was ~15% that of EGCG in human plasma. Catechin was also methylated but preferentially in the 3-position (68). Only unchanged catechins were measured in most studies, whereas the methylated metabolites were not analyzed. Therefore, the mean bioavailability parameters calculated in this review for catechins are probably underestimated.

EGCG is the only known polyphenol present in plasma in large proportion (77–90%) in a free form (73–76). The other catechins are highly conjugated with glucuronic acid and/or sulfate groups. The exact nature of the major circulating metabolites of epicatechin has been elucidated, ie, epicatechin-3'-O-glucuronide, 4'-O-methylepicatechin-3'-O-glucuronide, 4'-O-methylepicatechin-5- or 7-O-glucuronide, and the aglycones epicatechin and 4'-O-methylepicatechin (89).

Microbial metabolites, namely, 5-(3',4',5'-trihydroxyphenyl)valerolactone, 5-(3',4'-dihydroxyphenyl)valerolactone, and 5-(3',5'-dihydroxyphenyl)valerolactone, mostly in conjugated forms, were also identified in plasma and urine of volunteers after ingestion of green tea (74). These metabolites accounted for 6–39% of the ingested epigallocatechin and epicatechin, 8–25 times the levels measured for the unchanged compounds (90). Because they appear later than catechins in plasma and have long half-lives, these compounds could prolong the actions of catechins (75). They probably exert some interesting antioxidant activity, because of their di-/trihydroxyphenyl groups.

Catechins are rapidly eliminated. Galloylated catechins were never recovered in urine (75, 76, 78). This is explained not by degalloylation, which has been shown to be a minor process in humans, but rather by preferential excretion of these compounds in bile (78). Extensive biliary excretion of EGCG was previously reported in rats (91).

PROANTHOCYANIDINS

Because of the lack of accurate data on the proanthocyanidin contents of foods, we are not yet able to provide a good estimation of the mean daily intake of these compounds. However, nearly one-half of 88 tested foods derived from plants were found to be dietary sources of proanthocyanidins, which suggests that these are among the most abundant polyphenols in our diet (92).

Polymeric proanthocyanidins are not absorbed as such. The detection of proanthocyanidin dimers B1 and B2 in human plasma was reported in only 2 studies (62, 93) (Table 5⬇). The absorption of these dimers was minor, ~100-fold lower than that of the flavanol monomers in the study by Holt et al (62). In vitro and animal studies confirmed that polymerization greatly impairs intestinal absorption (94–96).

View this table: In this window In a new window	TABLE 5 Bioavailability studies of proanthocyanidins or proanthocyanidin-containing foods[1]

However, health effects of proanthocyanidins may not require efficient absorption through the gut. Indeed, these compounds may have direct effects on the intestinal mucosa and protect it against oxidative stress or the actions of carcinogens. In addition, the consumption of proanthocyanidin-rich foods, such as cocoa, red wine, or grape seed extracts, has been shown to increase the plasma antioxidant capacity, to have positive effects on vascular function, and to reduce platelet activity in humans (97). These procyanidin-rich sources always contain 5–25% monomers or other polyphenols, which leaves doubts about
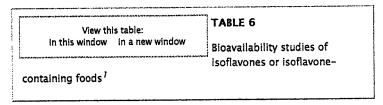
whether proanthocyanidins are actually the active compounds in these sources. If they are, then they may have effects through interactions with other components, such as lipids or iron, in the gut.

Biological effects may be attributable not to direct actions of proanthocyanidins themselves but to actions of some of their metabolites that can be more readily absorbed. On the basis of in vitro experiments, Spencer et al (98) suggested that polymers could be degraded into monomers during their transit in the stomach. However, Rios et al (99) clearly demonstrated that this does not occur in humans, probably because the food bolus has a buffering effect, making the acidic conditions milder than required for proanthocyanidin hydrolysis.

Proanthocyanidins are degraded into various aromatic acids by the microflora. The incubation of purified, ^{14}C-labeled, proanthocyanidin oligomers with human colonic microflora led to the formation of m-hydroxyphenylpropionic acid, m-hydroxyphenylacetic acid, and their p-hydroxy isomers, m-hydroxyphenylvaleric acid, phenylpropionic acid, phenylacetic acid, and benzoic acid (100). Some of these compounds, namely, m-hydroxyphenylpropionic acid and m-hydroxyphenylacetic acid, as well as m-hydroxybenzoic acid, were shown to increase in human urine after consumption of procyanidin-rich chocolate (101). However, the microbial metabolism of proanthocyanidins has never been studied in humans after consumption of purified proanthocyanidin polymers. By feeding rats with purified catechin, dimer B3, trimer C2, or procyanidin polymers, Gonthier et al (102) showed that the extent of degradation into aromatic acids decreased as the degree of polymerization increased; it was 21 times lower for polymers than for the catechin monomer, probably because of the antimicrobial properties and protein-binding capacity frequently described for proanthocyanidins. Therefore, the quantitative importance of the degradation of proanthocyanidins into microbial metabolites must be further evaluated in humans.

ISOFLAVONES

Isoflavones are provided only by soybean-derived products. They can be present as aglycones or glycosides, depending on the soy preparation. Some authors investigated the differences in bioavailability between aglycones and glycosides by using pure molecules. Contradictory results have been obtained (**Table 6⇓**). Setchell et al (112) found greater bioavailability of glucosides, as measured from the areas under the plasma concentration-time curves. Izumi et al (110) found greater bioavailability of aglycones, on the basis of C_{max}, but they did not measure isoflavone concentrations between 6 and 24 h, whereas Setchell et al (112) reported that the mean time to reach C_{max} was prolonged to 9 h after glycoside ingestion. Two other studies found no significant differences in the absorption efficiency for aglycones and glycosides (117, 118).

View this table: In this window In a new window	TABLE 6 Bioavailability studies of isoflavones or isoflavone-
containing foods[1]	

In contrast, equol production was significantly higher after ingestion of daidzin than after ingestion of daidzein (112, 117). Equol is a bacterial metabolite that has been shown to be more estrogenic than its precursor daidzein in many in vitro studies and in animal models (119). There is great interindividual variability in the capacity to produce equol, and only 30–40% of the Western population are "equol producers." Equol producers may gain more benefits from soy consumption than do nonproducers (119, 120). Therefore, it would be interesting to find a way to make nonproducers become producers. To date, no clear correlations between dietary habits or microflora composition and the capacity to produce equol have been reported. It would be interesting to separate volunteers into equol producers and nonproducers in future intervention studies designed to investigate the effects of soy isoflavones. C_{max} values for equol were measured 12–24 h after isoflavone ingestion (112, 117).

It has long been thought that the greater urinary excretion of daidzein reflects

greater bioavailability of this isoflavone, compared with genistein ([103]). The explanation is that a greater fraction of genistein is eliminated in bile, as observed in rats ([121]). Plasma kinetic curves often showed a first peak followed ~3 h later by a second peak, reflecting enterohepatic cycling ([112], [117]). By using ^{13}C-labeled daidzein and genistein, Setchell et al ([116]) recently showed that the systemic bioavailability and C_{max} were significantly higher for genistein than for daidzein. The limited data for glycitein indicate greater bioavailability than for the other isoflavones ([107], [114]).
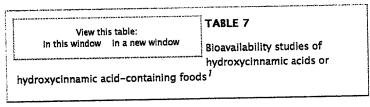
The nature of isoflavone metabolites was the same after glycoside or aglycone ingestion. Glycosides are hydrolyzed before absorption and are not recovered as such in plasma ([122]). Aglycones have been recovered in small proportions, generally <5% of the total metabolites ([111]–[113], [123]). The main metabolites are 7-O-glucuronides and 4'-O-glucuronides, with small proportions of sulfate esters ([111], [123], [124]). Additional metabolites have been identified in human plasma or urine, including dihydrodaidzein, dihydrogenistein, dihydroequol, O-desmethylangolensin, and 6-hydroxy-O-desmethylangolensin ([125]–[127]).

Elimination of isoflavones is quite slow, with half-life values of 6–8 h (Table 6⇑). After ingestion of daidzein or genistein at 0.4 or 0.8 mg/kg body weight, baseline concentrations of isoflavones in plasma were regained only after ~48 h ([116]). Plasma concentrations should therefore increase with repeated ingestion of soy products. However, Lu et al ([128]) reported that relative urinary excretion of isoflavones and elimination half-lives progressively decreased during 4 wk of daily soymilk ingestion. Lampe et al ([129]) did not observe any effect on urinary excretion of 1-mo supplementation with isoflavones.

Another point worth noting is the evidence that high concentrations of isoflavones can be found in breast tissue of premenopausal women and in prostate glands of men ([130]–[132]). These are the only available data on polyphenol concentrations in tissues.

HYDROXYCINNAMIC ACIDS

Intake of chlorogenic acid varies widely but may be very high, up to 800 mg/d among coffee drinkers ([133], [134]). Nevertheless, very few studies have addressed the bioavailability of this hydroxycinnamic acid, in comparison with other polyphenols (**Table 7⇓**).
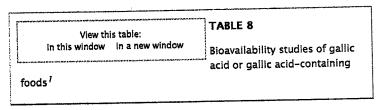
View this table: In this window In a new window	TABLE 7 Bioavailability studies of hydroxycinnamic acids or hydroxycinnamic acid–containing foods[1]

Olthof et al ([138]) showed that the esterification of caffeic acid, as in chlorogenic acid, markedly reduced its absorption. This was also observed in rats ([145], [146]). In fact, the absorption of chlorogenic acid occurs mainly in the colon, after hydrolysis by microbial esterases. It is not clear whether chlorogenic acid is present, as such or in a conjugated form, in human plasma. Nardini et al ([135]) found only caffeic acid in plasma after the ingestion of coffee. We observed, however, that the preparation of β-glucuronidase from *Helix pomatia* that is generally used to hydrolyze samples also contains esterases that are able to degrade chlorogenic acid into caffeic acid. Therefore, the possibility that chlorogenic acid is present in plasma but is hydrolyzed during sample treatment cannot be excluded. Intact chlorogenic acid has been detected at low concentrations in nonhydrolyzed urine samples ([138], [147]). Metabolites other than caffeic acid have been identified after ingestion of chlorogenic or caffeic acid, namely, ferulic acid, isoferulic acid, dihydroferulic acid, vanillic acid, 3,4-dihydroxyphenylpropionic acid, 3-hydroxyhippuric acid, and hippuric acid ([139], [140], [147]). Their quantitative importance remains to be investigated.

Ferulic acid is another abundant hydroxycinnamic acid. When present in free form in tomatoes or beer, it is efficiently absorbed ([143], [144]). However, ferulic acid is also the main polyphenol present in cereals, in which it is esterified to the arabinoxylans of the grain cell walls. This binding has been reported to hamper the absorption of ferulic acid in rats ([148], [149]). In humans, Kern et al ([142])

measured the urinary excretion and plasma concentrations of ferulic acid metabolites after ingestion of breakfast cereals. They deduced from the kinetic data that absorption of ferulic acid from cereals takes place mainly in the small intestine, from the soluble fraction present in cereals. Only a minor amount of ferulic acid linked to arabinoxylans was absorbed after hydrolysis in the large intestine.
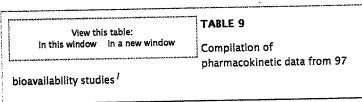
HYDROXYBENZOIC ACIDS

Very little is known about the absorption and metabolism of hydroxybenzoic acids (150). Their limited distribution in food has resulted in limited interest by nutritionists. However, the few studies addressing the bioavailability of gallic acid in humans revealed that this compound is extremely well absorbed, compared with other polyphenols (Table 8↓). Plasma concentrations of free and glucuronidated forms of gallic acid and its main metabolite 4-O-methylgallic acid reached 4 μmol/L after ingestion of 50 mg pure gallic acid. Such intake is not inconceivable, because red wine usually contains 10–60 mg/L gallic acid. However, gallic acid exists in different forms in fruits, nuts, tea, and red wine, ie, the free form, esterified to glucose (as in hydrolyzable tannins), or esterified to catechins or proanthocyanidins (92, 154). It would be interesting to compare the bioavailability of the different forms of gallic acid.

| View this table: | TABLE 8 |
| In this window   In a new window | Bioavailability studies of gallic acid or gallic acid-containing foods[1] |

COMPARATIVE BIOAVAILABILITY OF POLYPHENOLS

Mean values for C_{max}, time to reach C_{max}, area under the plasma concentration-time curve, elimination half-life, and relative urinary excretion (related to the ingested dose) were calculated for the different polyphenols (Table 9↓), on the basis of the data compiled in Tables 1↑–8↑. Only data from studies using a single dose of a well-characterized polyphenol source were taken into account. To facilitate comparisons between polyphenols, data were converted to correspond to the same supply of polyphenols, a single 50-mg dose of aglycone equivalent. For this, we assumed that the bioavailability parameters increase linearly with the dose, which has been demonstrated in humans only for EGCG (73). When several doses were investigated in the same study, only a mean value for the whole study was considered.

| View this table: | TABLE 9 |
| In this window   In a new window | Compilation of pharmacokinetic data from 97 bioavailability studies[1] |

The most striking result of this survey was that gallic acid is far better absorbed than the other polyphenols. The C_{max} values for its metabolites reached 4 μmol/L with a 50-mg intake, and the relative urinary excretion was 38%. Next are isoflavones, which are the most well-absorbed flavonoids, with C_{max} values of ~2 μmol/L after a 50-mg intake and mean relative urinary excretions of 42% for daidzin and 15.6% for genistin. Proanthocyanidins and anthocyanins are very poorly absorbed but, in the case of anthocyanins, all of the metabolites might not have been identified, resulting in underestimation of their bioavailability. Values for catechins are certainly underestimated, because methylated metabolites were not taken into account in some studies. Data are still scarce for hydroxycinnamic acids, and the calculated mean values are probably not very reliable.

The mean area under the plasma concentration-time curve, C_{max}, and urinary excretion values clearly show the lower absorption of rutin, compared with quercetin glucosides. Another observation is that galloylation of epigallocatechin markedly reduces its absorption. Gallic acid, quercetin glucosides, catechins, free hydroxycinnamic acids, and anthocyanins, which are absorbed in the small

intestine or the stomach, reached C_{max} at ~1.5 h, whereas rutin and the flavanones hesperidin and naringin, which are absorbed after release of the aglycones by the microflora, reached C_{max} at ~5.5 h. The mean time to reach C_{max} for chlorogenic acid is surprising, because this compound also must be hydrolyzed by the microflora before absorption. In the sole study considered, however, chlorogenic acid was provided as a liquid (coffee) to fasted volunteers, which might have accelerated the absorption kinetics.

Relative urinary excretion is currently used to estimate the minimal absorption rate but, when polyphenols are highly excreted in bile, as for EGCG and genistein, absorption is underestimated. For most polyphenols, the urinary excretion values were consistent with the plasma kinetic data. Values ranged from 0.3% to 43% of the intake, which demonstrates the great variability in the bioavailability of the different polyphenols.

With respect to the elimination half-lives, it appears that catechins, gallic acid, and flavanones have no chance to accumulate in plasma with repeated ingestion. Some of their metabolites may have longer half-lives, however, and quercetin, with a longer half-life, could accumulate in plasma with repeated ingestion.

Extensive variability was observed among the studies. Ten-fold variations in the C_{max} values were observed for most compounds. Several factors may explain the variability, such as the food matrix or background diet. Interindividual variations are also important, and some people might have different levels of metabolizing enzymes or transporters, enabling more efficient absorption of polyphenols.

It is important to realize that the mode of calculation and representation used in this review does not take into account the mean dietary intake of each polyphenol. For example, even if isoflavones are efficiently absorbed, they are usually not the major circulating polyphenols in Western populations, because the isoflavone intake is far lower than 50 mg/d for these populations. In contrast, a single glass of orange juice easily provides 50 mg hesperidin.

CONCLUSIONS

Bioavailability varies widely among polyphenols and, for some of compounds, among dietary sources, depending on the forms they contain. The plasma concentrations of total metabolites range from 0 to 4 μmol/L with an intake of 50 mg aglycone equivalents. The polyphenols that are most well absorbed in humans are isoflavones and gallic acid, followed by catechins, flavanones, and quercetin glucosides, with different kinetics. The least well-absorbed polyphenols are the proanthocyanidins, the galloylated tea catechins, and the anthocyanins. Data for other polyphenols are still too limited. The plasma kinetics also differ among polyphenol classes, with C_{max} being reached after ~1.5 h or ~5.5 h, depending on the site of intestinal absorption. This information should be useful for the design and interpretation of intervention studies investigating the health effects of polyphenols.

Footnotes

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