Metabolism of Tea Flavonoids in the Gastrointestinal Tract¹,²

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ABSTRACT There is considerable interest in the bioavailability of flavan-3-ols such as tea catechins and their bioactivity in vivo. Although flavanols such as catechin and epicatechin have long been characterized as powerful antioxidants in vitro, evidence suggests that these compounds undergo significant metabolism and conjugation during absorption in the small intestine and in the colon. In the small intestine these modifications lead primarily to the formation of glucuronide conjugates that are more polar than the parent flavanol and are marked for renal excretion. Other phase II processes lead to the production of O-methylated forms that have reduced antioxidant potential via the methylation of the B-ring catechol. Significant modification of flavanols also occurs in the colon where the resident microflora degrade them to smaller phenolic acids, some of which may be absorbed. Cell, animal and human studies have confirmed such metabolism by the detection of flavanol metabolites in the circulation and tissues. This review will highlight the major sites of flavanol metabolism in the gastrointestinal tract and the processes that give rise to potential bioactive forms of flavan-3-ols in vivo. J. Nutr. 133: 3255S-3261S, 2003.

KEY WORDS: • flavonoid • metabolism • catechin • tea • GI tract

Flavonoids have been the center of huge research interest over the last decade (1,2). They are the most abundant polyphenols in the human diet and are divided into six main classes based on the degree of oxidation of the C-ring, the hydroxylation pattern of the ring-structure and the substitution in the 3-position: flavanols (e.g., epicatechin), flavonols (e.g., quercetin), flavones (e.g., luteolin), flavanones (e.g., naringenin), isoflavones (e.g., genistein) and anthocyanidins (e.g., cyanidin) (3). In both black and green tea the major class of flavonoids are the flavanols, which include catechin, epicatechin, epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG). A large number of in vitro studies has characterized flavanols as powerful antioxidants capable of efficient scavenging of both reactive oxygen and reactive nitrogen species (3–8). The mechanism of their action as radical scavengers involves the donation of a hydrogen atom and/or electron to stabilize the radical species (3). Until recently, the ability of flavanols, and indeed other flavonoids, to act as classical H-donating antioxidants was believed to underlie many of their reported health effects (9–15). However, it is now clear that their ultimate antioxidant potential, and indeed their resulting potential bioactivity, in vivo is dependent on the absorption, metabolism, distribution and excretion of these compounds within the body after ingestion and the reducing properties of the resulting metabolites.

An understanding of the processes involved in the absorption and distribution of tea flavonoids is essential for determining their potential bioactivities in vivo and their overall significance in disease prevention. Much data now exists to support the biotransformation of flavanols and other flavonoids in the small intestine and colon of the gastrointestinal (GI) tract (10,16–22), as well as hepatic metabolism (23–26). This review will attempt to highlight the main sites of biotransformation of tea flavanols within the GI tract, the major metabolites generated in the small and large intestine and the implications of this modification in determining how flavonoids may act in vivo.

Modification of flavanols in the upper GI tract

Effects of saliva. Few studies exist on the ability of saliva and gastric juice to alter the flavonoid structure. Saliva has been found to have little effect on the stability of green tea catechins (27). For example, when mouth rinsing was performed with an aqueous solution of green tea extract (5.0 g/L)
containing eight catechins, it was observed that each catechin was retained at μg/ml levels in saliva for up to 60 min. However, degalloylation of flavanol gallate esters in human saliva has been observed, such as the conversion of EGCG to EGC in the oral cavity with both subsequently being absorbed through the oral mucosa (28). A catechin esterase activity that converts EGCG to EGC has been found in the saliva and is likely of human origin. However, a common human esterase inhibitor did not inhibit the activity. Similar incubation of procyanidin oligomers (dimer-hexamer) in human saliva for up to 30 min does not result in modification of the compounds or their decomposition into smaller oligomeric units (22) suggesting that these compounds remain intact in the mouth and esophagus before entering the stomach.

Another consideration in the upper GI tract is the possible interaction of flavanols and procyanidins with salivary proteins. (+)-Catechin has been observed to have a higher affinity for salivary proline-rich proteins than (−)-epicatechin, which highlights the importance of the stereochemistry of flavan-3-ols on their interaction with proteins (29). Furthermore, procyanidin trimers linked through a C(4)-C(8) interflavan bond had a greater affinity for procyanidin oligomer B2 than those linked C(4)-C(6). In addition, esterification of a galloyl group to the C(3) hydroxyl function of (−)-epicatechin or to the epicatechin moiety of procyanidin dimer B2 had the effect of increasing the binding affinity to proline-rich proteins (29). It is believed that these specific polyphenol-protein interactions in the form of adsorption with high-molecular-weight salivary proteins, bacterial cells and mucous materials may be one explanation for the observed decrease in quercetin mutagenicity after incubation with saliva (30).

Modification in the gastric lumen. Although it seems that monomeric flavan-3-ols are stable in the gastric lumen, flavanol oligomers ranging from a dimer to decamer, such as those isolated from Theobroma cacao, have been observed to be unstable under conditions of low pH similar to that present in the gastric juice of the stomach (31). Upon incubation of the procyanidins with simulated gastric juice (0.1 N HCl) and incubation in murine gastric fluid (pH 2–5), the amount of EGCG decreased 81.6% in only 5 min (37), whereas a similar incubation in murine plasma (pH 7.4) resulted in only a 29.3% decrease in amount. However, the oxidation of EGCG resulted in the formation of dimerized products, which were observed to possess greater superoxide radical scavenging activity than EGCG itself and had powerful iron chelating properties (37). Another factor to consider may be the relative abilities of these polyphenols to bind to proteins in the food matrices in question. In complex food matrices, the pH is likely to be buffered for long periods of time and therefore, oxidation of the flavanols may only occur to a limited extent during intestinal transit. In addition, it has been suggested that ascorbate significantly decreases the stability of flavanols incubated in intestinal fluid (38) and therefore the presence of ascorbate in vivo may stabilize the polyphenols in the neutral or alkaline environment of the small intestine.

Jejunal and ileal transfer and metabolism. Many studies have indicated that significant transfer of ingested flavonoids occurs from the lumen of the small intestine to the mesenteric circulation and that extensive metabolism and conjugation of the flavonoid occurs during this transfer (2,39–46). Although both Caco-2 cell models and isolated preparations of rat small intestine (described below and in Fig. 1) (47) have been utilized to study absorption and metabolism of tea flavonoids in the small intestine, only the latter has provided in-depth information on events occurring in both the jejunum and ileum (40,42,46,48–50). This model allows study of the intestinal transfer of dietary polyphenols (and their glycosides) and can be used to assess the rate of absorption from the lumen. The solute under study appears on the serosal surface in the same form as if it were transferred to the mesenteric circulation and therefore enterocyte metabolism of flavonols and procyanidins, as well as their rate of transfer across specific gut regions, can be studied (42). Tissue viability is assessed by measurement of glucose transfer (47) and viability is confirmed by the finding that fluid transfer continues at a constant rate for the 90-min collection period and that glucose concentra-

**Metabolism and conjugation in the small intestine**

There are many factors that influence the extent and rate of absorption of ingested compounds by the small intestine (34). These include physiochemical factors such as molecular size, lipophilicity, solubility, pKa and biological factors including gastric and intestinal transit time, lumen pH, membrane permeability and first pass metabolism (35,36). Generally flavonoids are present in plants conjugated to sugars and it is these glycosides that are ingested in the diet and enter the GI tract. Flavan-3-ols are the exception to this rule and are almost always present in the diet in the nonglycosylated form (3). Consequently, unlike other dietary flavonoids, there is no initial requirement for β-glucosidase action prior to absorption.

**Effects of intestinal juice.** Upon transfer from the stomach to the jejunum (the top two-fifths of the small intestine) the pH rises from about 2 to 7. It is well known that polyphenolic compounds such as those with catechol structures oxidize in neutral and alkaline pH environments. EGCG has been observed to rapidly oxidize in authentic intestinal fluid (measured pH of 8.5) with the amount of EGCG decreasing 81.6% in only 5 min (37), whereas a similar incubation in murine plasma (pH 7.4) resulted in only a 29.3% decrease in amount. However, the oxidation of EGCG resulted in the formation of dimerized products, which were observed to possess greater superoxide radical scavenging activity than EGCG itself and had powerful iron chelating properties (37). Another factor to consider may be the relative abilities of these polyphenols to bind to proteins in the food matrices in question. In complex food matrices, the pH is likely to be buffered for long periods of time and therefore, oxidation of the flavanols may only occur to a limited extent during intestinal transit. In addition, it has been suggested that ascorbate significantly decreases the stability of flavanols incubated in intestinal fluid (38) and therefore the presence of ascorbate in vivo may stabilize the polyphenols in the neutral or alkaline environment of the small intestine.
tion in the absorbed fluid is over double that initially present in the perfused buffer (42).

Isolated small intestine model. Absorption studies utilizing this model have been performed with a wide range of flavonoids, their glycosides and hydroxycinnamates. These show that there is in almost all cases extensive enteroctyic metabolism of the polyphenol in the enterocyte during transfer from the luminal to the serosal side (42). The extent of glucuronidation in these experiments was dependent on the flavonoid structure, in that the flavonoids with a substituted hydroxyl group on the B-ring (i.e., hesperitin) were less predisposed to glucuronidation, whereas the flavonoids containing a 3',4'-ortho-dihydroxy (or catechol) B-ring were transferred predominantly as glucuronides (42,51). In addition, monophenolic B-ring flavonoids were also extensively glucuronidated, in particular naringenin, which was only detected in serosal fluid as naringenin-7-glucuronide (42). Similar patterns of metabolism have been observed in the ileum, although in general, glucuronidation occurs to a lesser extent most probably due to lower levels of phase I and II enzymes present in the ileum compared with the jejunum. Interestingly, two UDP-glucuronosyltransferase (UGT) isoforms, UGT1A8 and UGT1A10, of human intestinal mucosa, which are absent in liver, have been identified by RT-PCR (39).

Although the major metabolites observed on the serosal side after perfusion of thejejunum with catechin or epicatechinn were always glucuronidated (at the 5- and 7- positions on the A-ring), there were also high levels of both O-methylated and O-methylated-glucuronide forms (Fig. 2) (22,49). 3'-O- and 4'-O-methylated derivatives of the flavonols were detected at high levels in the serosal fluid (~30% of total transferred) and together with O-methyl-glucuronidated forms were the predominant metabolites detected in the serosal fluid (~50%) suggesting that these are the most bioavailable forms in the small intestine (Fig. 2). As with the other flavonoids tested in this model, there was a lower level of metabolism occurring in the ileum although the total amounts of unmetabolised catechin and epicatechin absorbed were significantly higher than in the jejunum (42). The greater susceptibility of flavanols over other flavonoids to methylation in the jejunum may reside in the specificity of catechol-O-methyl-transferase (COMT) for these compounds (52). These data have been supported in a similar model, in which the rat jejunum and ileum were perfused with catechin (41). In this study, catechin was absorbed into intestinal cells and metabolized extensively to a point where no native catechin could be detected in plasma from the mesenteric vein. Mesenteric plasma contained glucuronide conjugates of catechin and 3'-O-methyl catechin, indicating the intestinal origin of these conjugates and the large role the small intestine plays in the biotransformation of flavanols during absorption (41,49). Although many studies have identified flavanol metabolites as being the main forms found entering the hepatic portal vein after absorption from the small intestine, the native flavanols are detected in small amounts (42,49). For example, oral administration of the tea catechins, epicatechin, EGC, ECG and EGCG, to rats led to the detection of all four flavanols in the portal blood (53) clearly indicating that these flavonoids may be absorbed intact to a small degree.

Studies have also shown that catechin and tannic acid may interact with the small intestine but only catechin appears able to traverse the gut (46). This may be due to the binding of tannic acid and catechin by endogenous proteins in the intestinal lumen limiting their absorption in the small intestine. The binding of flavanols to proteins in the small intestine provides one explanation for their relatively low absorption. However, it should also be noted that the protein-binding properties of catechins may be linked to their bactericidal abilities and may play several roles in the digestive tract. In the small intestine, catechins inhibit alpha-amylase activity but do not affect lactic acid bacteria (54). The inclusion of tea catechins in the diet for several weeks had the effect of decreasing putrefactive products and at the same time increased organic acids by lowering pH (54). The high-molecular-weight procyanidins have a high affinity for proteins and their absorption through the gut barrier is most likely limited to lower oligomeric forms and to the metabolites formed by the colonic microflora. Recently, perfusion of isolated small intestine with the procyanidin dimers B2 and B5 extracted from cocoa indicated that both forms of dimer are transferred to the serosal side of enterocytes but only to a very small extent (<1% of the total transferred flavanol-like compounds) (55). Perfusion of dimer mainly resulted in large amounts of unmetabolised/unconjugated epicatechin monomer being detected on the serosal side (~95.8%). Low levels of O-methylated dimer were also detected (~3.2%), but no conjugates and metabolites of epicatechin indicating that metabolism of monomer and dimer is limited during dimer cleavage/translocation.

Caco-2 cell model. Another approach to obtaining a better understanding of the bioavailability of flavonoids and their absorption and metabolism in the small intestine has been in the use of cultured human Caco-2 cells. In recent years studies with the human Caco-2 cell line have helped to unravel the complex processes involved in the absorption and metabolism of dietary polyphenols in humans. These cells were originally derived from human colonic adenocarcinoma cells. However, despite their origin, after culture in DMEM supplemented with fetal calf serum (10%) and glutamate (20 mmol/L) for ~14–21 d (37°C; 5% CO2) these cells more closely resemble enterocytes than colonocytes both morphologically and biochemically. Fully differentiated Caco-2 monolayers also resemble enterocytes in that they express transport systems for sugars, amino acids, bile acids and dipeptides and express many.

**FIGURE 2** The structures of the main small intestinal metabolites of epicatechin produced in the isolated rat small intestine perfusion model. (A) 3’-O-methyl epicatechin; (B) 4’-O-methyl epicatechin; (C) 3’-O-methyl epicatechin-5-glucuronide; (D) epicatechin-5-glucuronide; (E) epicatechin-7-glucuronide.
brush border membrane enzymes, including aminopeptidase, alkaline phosphatase, sucrase and γ-glutamyltranspeptidase. Even so, it is important to consider the full enzymatic profile of the Caco-2 cell model to be used because they may not be identical to normal human small intestinal cells in terms of metabolizing enzymes such as cytochrome P450s.

Absorption studies with flavonols and procyanidins using Caco-2 cells are few (56–58). Interestingly, apical to basolateral transfer of epicatechin across the Caco-2 monolayer has not been detected thus far (56). It is believed that this is due to the action of multidrug resistance-associated protein-2 (MRP2) which acts to rapidly efflux epicatechin and epicatechin metabolites from the cell interior back out to the apical side. Other experiments with radiolabeled procyanidins have shown that flavanol dimers and trimers were transferred to the same extent as epicatechin monomer, whereas oligomers with an average degree of polymerization of 7 were not (23,59). In contrast, we observed very little transfer of the dimer across Caco-2 cells, which was in agreement with our studies in the isolated rat small intestine model (55).

The model has mainly been utilized for the study of the absorption and metabolism of other flavonoids in the small intestine and the data from this work has helped support the general concept of the extentive metabolism of flavonoids in the small intestine. For example, Galijatovic et al. (60,61) observed that chrysosin and quercetin are glucurononated on transfer and also induce UGT in Caco-2 cells. Exposure of the cells to chrysin (50 μmol/L; 2 h) resulted in a 3.8-fold increase in chrysin glucuronidation and a 38% decrease in sulfation in intact cells. Induction of phase II enzymes, such as UGT, may be important for the bioavailability of carcinogens and other toxic chemicals by increasing the ease and rate at which they are excreted from the body. In addition, Wahlgren et al. (62,63) studied the absorption of the predominant dietary form of quercetin, quercetin-4′-β-glucoside. Although quercetin itself was not transferred, they found that the transport of the glucoside involved apical MRP2 suggesting that the transfer of glycosides may occur in the small intestine.

**Colonic metabolism**

Studies have suggested that the extent of absorption of dietary polyphenols in the small intestine is relatively small (10–20%) (42,48,49). The implications of this low absorption in the small intestine is that the majority of ingested polyphenols, including those absorbed and conjugated in the enterocytes and/or the liver before transport back out into the lumen either directly or via the bile (40), will reach the large intestine where they encounter the colonic microflora. The colon contains ~10^{10} microorganisms/cm^3, which have an enormous catalytic and hydrolytic potential, and this enzymatic degradation of flavonoids by the colonic microflora results in a huge array of new metabolites. For example, bacterial enzymes may catalyze many reactions including hydrolysis, dehydroxylation, demethylation, ring cleavage and decarboxylation as well as rapid deconjugation (24). Unlike human enzymes, the microflora catalyze the breakdown of the flavonoid backbone itself to simpler molecules such as phenolic acids. Specific metabolites have been observed in urine after consumption of a variety of phenolics. For example, the glycine conjugate of benzoic acid, hippuric acid, is primarily derived from plant phenolics and aromatic amino acids through the action of intestinal bacteria and, consequently, the level of hippuric acid would be expected to increase in the urine of individuals consuming diets rich in flavanols or polyphenols in general. It must be noted, however, that hippuric acid may possibly derive from other sources such as quinic acid or, in quantitative terms, more importantly from the aromatic amino acids tryptophan, tyrosine and phenylalanine, as well as from the use of benzoic acid as a food preservative. One investigation in humans suggests an association between black tea consumption and excreted amounts of hippuric acid (64). The formation of hippuric acid and hydroxyhippuric acids seems to be a possible central metabolic pathway for dietary flavonoids, in which the colon microflora and the liver are active metabolic sites (24). Other hydroxybenzoic acid glycine derivatives such as 4-hydroxyhippuric acid, vanillylglycine, isoavanglycine might also appear in reasonable amounts in urine after polyphenol consumption in general.

The 5,7,3′,4′-hydroxylation pattern of flavan-3-ols is believed to enhance ring opening after hydrolysis (22,24) and metabolism of flavanols by enzymes of the microflora of the large intestine results in many metabolites: 3,4-dihydroxyphenylactic acid, 3-hydroxyphenylacetic acid, homovanillic acid and their conjugates derived from the B-ring (24) and phenolic acids from the C-ring. Flavanols, because of their structures (no C-4 carbonyl group), can also degrade to the specific metabolites phenylvalerolactones. Phenylpropionic acids (which may undergo further metabolism to benzoic acids) may also be the products of flavanol metabolism in animal studies, which demonstrates fission of the A-ring (24). Only 3.1% of the ingested catechin in rats was extractable from feces, indicating that major absorption and/or degradation of catechin had occurred in the GI tract (65). Such metabolites of flavanols have been detected in human plasma and urine after a single ingestion of green tea (66) which suggests that there may be significant metabolism by gut microbiota in the colon. The two metabolites, (−)-5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone and (−)-5-(3′,4′-dihydroxyphenyl)-γ-valerolactone were identified in urine by both LC-MS/MS and NMR, appearing 7.5–13.5 h after ingestion (after a 3 h lag time), whereas epicatechin and EGC peaked at 2 h. In addition to their late excretion profiles, the amounts of metabolite excreted were 8–25-fold greater than that of epicatechin and EGC and accounted for 6–39% of the epicatechin and EGC ingested. The late excretion and high levels of these metabolites would suggest that they are generated from the precursors epicatechin and EGC by the colonic microorganisms. Previous to this human study, similar observations were made in rats fed with labeled catechin (67). Here catechin glucuronides were observed in the bile after dosing rats with the catechin and m- and p-hydroxyphenylpropionic acid, δ-(3-hydroxyphenyl)-γ-valerolactone and δ-(3,4-dihydroxyphenyl)-γ-valerolactone were identified as metabolites arising due to the action of the colonic microflora (67).

**Action of flavanol metabolites in cell systems**

The action of flavonoid metabolites, in particular the O-methylated flavonoids deriving from small intestinal absorption, are now of great current interest. For example, the ability
of 3'-O-methyl epicatechin and epicatechin glucuronides to protect against apoptotic cell death induced by hydrogen peroxide or oxidized LDL has been investigated (69–71). A mixture of epicatechin-5-O-β-D- and epicatechin-7-O-β-D-glucuronides exhibited no significant protection against peroxide-induced loss in neuronal or fibroblast viability and also failed to prevent peroxide-induced caspase-3 activation in both cell models (71). This lack of activity may be based on the increased polarity of the glucuronide and its reduced ability to partition, which would limit its access to cells. This is consistent with the observation that uptake of epicatechin glucuronide into both cortical neurons and dermal fibroblasts was not detectable (71). Another possibility is that the A-ring is the structurally important feature for cell recognition or biological action within cells and in vivo and presence of a bulky glucuronide on the A-ring limits its activity. In contrast, epicatechin and 3'-O-methyl epicatechin, have been shown to elicit strong cytoprotective effects in fibroblasts and neurons associated with both cell types (69,71,72). Interestingly, the 3'-O-methyl-epicatechin metabolite was as effective as epicatechin at preventing damage and was also equally effective in protecting neurons against oxLDL-induced activation of c-jun N-terminal kinase, c-jun, and procaspase-3 (70). The ability of the O-methylated metabolite to exert protection similar to the native epicatechin is interesting because the H-donating potential of the two compounds is very different, with the O-methylated compound having a reduced capacity to donate electrons from its B-ring. This evidence would suggest that flavonoids might function to protect cells against death induced by oxidants by a mechanism independent of its classical antioxidant properties, a concept which is beginning to receive much attention. However, it is also possible that in vivo demethylation may occur intracellularly by the action of cytochrome P450 enzymes cleaving the O-methylated metabolite to epicatechin.

Additional studies have identified the 5-O-β-D-glucuronide of catechin and epicatechin excreted in the urine of rats postingestion. The metabolism to a glucuronide does not interfere with their antioxidant properties as assessed by their ability to scavenge superoxide (26,73) suggesting that in plasma they may still act as antioxidants. Although glucuronides do not enter cells readily, it is also possible that they might be cleaved by the action of β-glucuronidases located in human tissues such as the liver (74) or by neutrophils that release β-glucuronidases when activated (51,75). For example, various quercetin glucuronides have been shown to be deconjugated by liver cell-free extracts and by pure recombinant human β-glucuronidase indicating that the cleavage of glucuronides to free aglycones may occur in vivo (74). In terms of other possible modes of action, studies suggest that the metabolised flavonoids by phase I and II enzymes in the small intestine may aid detoxification of potential carcinogens. For example, alphanaphthoflavone increases the activity of P450/3A in human jejunal and ileal microsomes (76) and chrysin causes an induction of intestinal UGT in Caco-2 cells (60,77).

There is also a need to assess the role of the colonic microflora in the overall bioavailability and potential bioactivity of dietary flavonoids. The extent of absorption of colonic metabolites is unclear at this time and there is a growing interest in the potential effects of the phenolic acids and their derivatives as potentially beneficial agents. For example, the human intestinal bacteria metabolites of rutin and quercetin, 3,4-dihydroxyphenylacetic acid and 4-hydroxymethyl-phenylacetic acid have been shown to possess a more effective antiplatelet aggregation activity than rutin and quercetin (78). Furthermore, 2,4,6-trihydroxybenzaldehyde and quercetin were more effective than rutin on the cytotoxicity against tumor cell lines. In addition, the effects the phenolics themselves have on the microflora is an emerging field and it is possible that a flavanol-induced change in the rich colonic bacterial population may have an influence on the overall health of an individual, the so called prebiotic concept.

**Conclusions**

Over the recent years we have gained a greater knowledge of the bioavailable metabolites of dietary flavonoids and it is now essential to fully evaluate the role of these conjugates and metabolites in disease prevention (Fig. 3). It is clear that the GI tract plays a very significant role in the metabolism and conjugation of these polyphenols before the liver is reached. In the jejunum and ileum of the small intestine there is efficient glucuronidation of flavanols by the action of UGT enzymes and extensive O-methylation by the action of COMT. Unabsorbed flavanols, and those taken up, metabolized in the small intestine and liver and transported back into the intestinal lumen, will reach the large intestine where they are further metabolized by the gut microflora into smaller phenolic acids and valerolactones. The extent to which these phenolic acids are absorbed in the colon is presently unclear. However, they are detected in plasma and are often further conjugated and metabolized in the liver. Remaining compounds derived from flavonoid intake pass out in the feces. It is now important to assess whether the observed metabolism aids entry into cells and/or renders them better or worse at providing protection against different stresses, such as oxidative or nitritative stress.

New data in the field is already beginning to suggest that flavonoids may act to protect cells by more complex mechanisms than was once thought (70). Eventually it is hoped that

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**FIGURE 3** Summary of the formation of metabolites and conjugates of flavonoids in humans. Cleavage of procyanidins may occur in the stomach in environments of low pH. All classes of flavonoids undergo extensive metabolism in the jejunum and ileum of the small intestine and the resulting metabolites enter the portal vein and undergo further metabolism in the liver. Colonic microflora degrade flavonoids into smaller phenolic acids, which may also be absorbed. The fate of most of these metabolites is renal excretion, however, the extent to which these compounds enter cells and tissues is unknown.
these studies will enable specific dietary recommendations to be made which will increase general health in the population.

LITERATURE CITED


