Enteric Disposition and Recycling of Flavonoids and Ginkgo Flavonoids

YONG LIU, Ph.D.,1 YAN LIU, Ph.D.,2 YANG DAI, M.S.,2 LUYING XUN, Ph.D.,1 and MING HU, Ph.D.2

ABSTRACT

Objective: The objective of this study was to determine the intestinal and microbial disposition of flavonoids and how these disposition processes affect their enteric recycling.

Design: Studies were performed using a perfused rat intestinal model or using enrichment cultures and a pure isolate of Enterococcus avium (LY1).

Results: In the rat intestine, aglycones, such as quercetin and apigenin, were as permeable (P*eff > 2) as compounds such as propranolol (100% absorption). However, a significant portion of the absorbed aglycones was conjugated and the metabolites were excreted into the lumen. Flavonoid glycosides, such as isoquercitrin and apigenin-7-O-glucoside, also had high apparent P*eff values (>2) in the upper small intestine because of rapid hydrolysis. However, isoquercitrin was absorbed much slower (P*eff ≤ 0.7, p < 0.05) when hydrolysis was absent or inhibited by 20 mmol gluconolactone. Absorption of other intact glycosides was similar to intact isoquercitrin and was much slower than the corresponding aglycones (P*eff ≤ 0.7, p < 0.05). Intestinal bacteria, such as LY1, hydrolyzed the flavonoid glycosides used in the study. Excreted glycosidases were involved in the hydrolysis of glycosides because glycosides were poorly taken up by LY1. In conclusion, glycosidase-catalyzed hydrolysis is a critical first step in the intestinal and microbial disposition of flavonoid glycosides. Aglycones were not only rapidly absorbed, but also rapidly metabolized into phase II conjugates, which were then excreted back into the lumen. Therefore, intestinal and microbial glycosidases and intestinal phase II enzymes make a significant contribution to the disposition of flavonoids via the proposed enteric and enterohepatic recycling scheme.

INTRODUCTION

The defined ginkgo extract (EGb 761) is derived from the ancient tree Ginkgo biloba, and contains 24% ginkgo flavonoids (mostly flavonol glycosides) and 6% terpenoids (Oken et al., 1998). The flavonoid glycosides in EGB 761 are almost exclusively flavonol-O-glycosides that consist of the flavonols (e.g., quercetin, kaempferol, or isorhamnetin) and sugars (e.g., glucose, galactose) attached to the 3-OH position (Fig. 1) (Jaggy, 1993; Yoshitama, 1997). This standard extract has been used in various clinical trials, mostly in Europe (Oken et al., 1998). A recent meta-analysis of clinical trial data (Oken et al., 1998) strongly supports the

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claim that this extract has clinically significant effects on improving cognitive functions in patients with Alzheimer’s disease (AD). A National Institutes of Health (NIH) supported double-blinded multicenter clinical trial is currently underway using EGB 761 to determine if it is effective in treating mild to moderate dementia.

Despite the assertion that EGB 761 could be “considered equally effective as donepezil, rivastigmine, metrifonate in the treatment of mild to moderate Alzheimer’s dementia (Wettstein, 2000),” few preclinical studies of EGB 761 have been performed due to the complexity of this mixture. A few pharmacokinetic and metabolic studies of ginkgo flavonoids have been performed using radiolabeled EGB 761. Those results indicate that an extensive metabolism of ginkgo flavonoids took place in rats and humans after oral ingestion and bioavailability was generally less than 35% even if one counts the conjugated metabolites as being bioavailable (de Vries et al., 1998; DeFeudis, 1998; Pietta et al., 1995, 1997). However, the absorption mechanisms and metabolic pathways of ginkgo flavonoids in these species have not been clearly defined.

The extensive metabolism of flavonoids has been attributed to the action of intestinal microflora (Kim et al., 1998). Hydrolytic enzymes of intestinal microflora (Macdonald et al., 1983) could convert certain flavonoid glycosides (e.g., rutin) to their corresponding aglycones (e.g., quercetin), which could be further metabolized by intestinal microflora to various single-ring aromatic compounds (Kim et al., 1998; Winter et al., 1989). Recently, however, intestinal hydrolysis of flavone monoglycosides was observed, suggesting that enterocytes might also play an important role in the hydrolysis of glycosides to aglycones (Day et al., 1998; Ioku et al., 1998).

Human intestine and liver may contribute to the extensive metabolism of ginkgo flavonoids because absorbed flavonols could undergo phase I (e.g., oxidation such as hydroxylation) and phase II (e.g., conjugation) metabolisms in these organs. Phase I metabolism commonly breaks down a molecular or attach a hydroxy (OH) group to the molecule so that the compound can be further processed by the body. Phase II metabolism may occur after phase I metabolism or simultaneously as the phase I metabolism. Phase II metabolism typically makes the compound much more soluble so that the metabolites could be eliminated by the urine or via the bile. In the case of flavonoids, phase II metabolism and subsequent metabolite excretion coupled to the repeated shuffling through the same pathways as depicted in the duoenteric and enterohepatic recycling scheme may be used to explain their poor bioavailability (Fig. 2). According to this recycling scheme, flavonol glycosides such as those present in EGB 761 will be metabolized by intestinal and microbial hydrolytic enzymes, taken up by the enterocytes, metabolized by intestinal phase II enzymes and hepatic enzymes, and finally excreted as conjugated metabolites into intestinal lumen or be transported into the systemic circulation (Shali et al., 1991; Walle et al., 2001). The recycling is enabled by the hydrolysis of luminal phase II flavonoid conjugates by microbial hydrolases (e.g., glucuronidases).
DISPOSITION OF FLAVONOIDs VIA RECYCLING

FIG. 2. Proposed recycling of flavonoids through sequential metabolism and/or secretion involving intestinal microflora, intestine, and liver. In this scheme, flavonoids are assumed to be given orally. This recycling scheme involves dual loops: one is the classical enterohepatic recycling and the other is what we called enteric recycling, where phase II metabolites formed and excreted by the small intestine could be reconverted to their aglycones again in the large intestine by the bacteria and reenter the blood via the colon. For ginkgo (Ginkgo biloba) flavonoids and other flavonoids, multiple shuffling through the same loops is expected so that most of the ingested flavonoids are metabolized before reaching the systemic circulation. In this figure, SGLT1 refers to a glucose transporter and MRP refers to multidrug resistant related protein. SGLT1 could participate in the absorptive transport of glycosides (Walgren et al., 2000b), whereas MRP could act as a gatekeeper that prevents the absorption of glycosides (Walgren et al., 2000a).

and sulfatases) to aglycones, which then re-enter the recycling loop (Fig. 2).

We report the intestinal and microbial hydrolysis of selected ginkgo flavonoids, intestinal absorption and metabolism of flavonoid aglycones, and intestinal secretion of phase II metabolites. These results provide additional experimental evidence to support the proposed recycling scheme, which may be used to explain the poor bioavailability of flavonoids in various herbal supplements including EGB 761. Apigenin, apigenin-7-O-glucoside (apigetrin), and isoquercitrin were purchased from Indofine Chemicals (Somerville, NJ). EGB 761 was kindly provided by S.S. Chatterjee, Ph.D., of Dr. Willmar Schwabe GmbH & Co. (Karlsruhe, Germany). Rutin, propranolol, Hank’s balanced salt solution (HBSS, powdered form) and Dulbecco’s phosphate-buffered saline (DPBS, powdered form) were purchased from Sigma Chemical Co. (St. Louis, MO). 14C-PEG4000 and 3H-mannitol were purchased from NEN (Boston, MA). All other materials were analytical grade or higher.

MATERIALS AND METHODS

Materials

Flavonoids such as quercetin, kaempferol, isorhamnetin, apigenin, apigenin-7-O-glucoside (apigetrin), and isoquercitrin were purchased from Indofine Chemicals (Somerville, NJ). EGB 761 was kindly provided by S.S. Chatterjee, Ph.D., of Dr. Willmar Schwabe GmbH & Co. (Karlsruhe, Germany). Rutin, propranolol, Hank’s balanced salt solution (HBSS, powdered form) and Dulbecco’s phosphate-buffered saline (DPBS, powdered form) were purchased from Sigma Chemical Co. (St. Louis, MO). 14C-PEG4000 and 3H-mannitol were purchased from NEN (Boston, MA). All other materials were analytical grade or higher.

Rat intestinal surgery

The procedures described here were approved by the Washington State University Institutional Animal Care and Use Committee.
The anesthesia was induced by intramuscular injection of ketamine (60 mg/kg) and acepromazine (2 mg/kg). After anesthesia was achieved, the rat was put on a warm blanket heater and under a heating lamp to maintain its body temperature throughout the experiment. After the segment was exposed by midline incision of an anesthetized rat, we cannulated a segment of the rat intestine using the same surgical procedures as previously described (Hu et al., 1988, 1998). The perfusate was kept at 37°C by a circulating water bath.

**Rat intestinal perfusion experiments**

The rat perfusion experiment was initiated by starting a syringe pump that delivered a flow rate of 0.382 mL/min. After a 30-minute flush with a perfusate solution containing a flavonoid of choice, EGB 761, or the metabolites of EGB 761 and 14C-PEG4000 (as a water flux maker), four samples were taken at a 10- to 20-minute intervals. The samples are centrifuged at 13,000 rpm for 10 minutes, and high-performance liquid chromatography (HPLC) was used to analyzed the supernatant. A mathematical model for the determination of unbiased permeability has been developed (Hu et al., 1988), and a correlation between this permeability and percent absorption in humans has been published (Amidon et al., 1988). The mathematical principle of this analysis method is well established (Amidon et al., 1988; Hu et al., 1988). This method measures the steady-state uptake of a compound from the perfusate by determining the rate of disappearance from the perfusate, and using the rate of disappearance to calculate dimensionless intestinal permeability (P*eff).

**Bacterial enrichment, isolation and identification procedures**

The anaerobic techniques used for enrichment cultures were essentially those of Hungate (Hungate, 1969) and Bryant (Bryant, 1972). Two anaerobic growth media were used. Medium A and B contained 1.22 g (2 mmol) rutin and 1.22 g EGB761 per liter as sole carbon source, respectively (Yong Liu et al., unpublished data). Medium A was used for the enrichment and isolation of bacteria capable of degrading rutin. Fresh rat fecal materials were used for the enrichment and isolation. Pure cultures were isolated by the roll tube technique (Bryant and Burkey, 1953) in the medium A with 1.5% agar. The isolates were further identified by comparative 16S rDNA gene sequences analysis (Lane, 1991).

**Rutin and ginkgo flavonoid metabolisms by pure cultures**

An isolated pure culture (strain LY1) was grown on medium A and medium B under anaerobic conditions with a 5% inoculum. The metabolites were analyzed by HPLC. The incubation times for rutin and ginkgo flavonoids were 96 and 72 hours at 37°C, respectively.

**Uptake of flavone glycosides and aglycones by bacteria**

Cells of strain LY1 were harvested by centrifugation in sealed centrifuge tubes and washed three times with 20 mmol phosphate-buffered saline (pH 7.0) under anaerobic conditions and the pellet was resuspended in the same buffer to obtain resting cells. The following method was used to estimate the uptake. Rutin and quercetin (10 μmol final concentration) were added into the freshly prepared resting cells and incubated at 37°C, respectively. The time course of substrate uptake was determined by HPLC analysis of samples between 0–10 minutes.

**Analytical methods**

A Hewlett-Packard 1090 HPLC system (Wilmington, DE) equipped with a column C18 with end cap (Aqua 5μ, C-18 200A, 4 × 100 mm, Phenomenex, Torrance, CA) was used to analyze the samples except those for liquid chromatography–mass spectrometry. Mobile phase A and B were 0.01 N phosphoric acid and 100% acetonitrile, respectively. For the detection of the metabolite of rutin, the following elution protocol was used at a flow rate of 1 ml/min: 2% B, 3 minutes; 2–15% B, 2 minute linear gradient; 15%–30% B, 15 minutes linear gradient; 30%–70% B, 10 minutes linear gradient; 70% B, 5 minutes; and 70%–2% B, 5 minutes, linear gradient. For the
detection of flavonoid metabolites of EGb 761, the following running protocol was used at a flow rate of 1 mL/min: 2% B, 3 minutes; 2%–50% B, 32 minutes linear gradient; 50% B, 5 minutes; and 50%–2% B, 1-minute linear gradient. All of the samples were monitored at 258 nm and 375 nm, and the spectra of the peaks were scanned from 220 nm to 450 nm. We selectively determined the concentration of flavonoids by using 375 nm because only compounds with flavonol backbone structure will have UV absorbance at 375 nm. Other known components of EGb 761 (e.g., terpenoids) did not have UV absorbance at this wavelength but can be detected at 258 nm. Therefore, the HPLC profile shown in Figure 2 represents a flavonoid fingerprint of the product. We have internal data to show that ginkgo extracts from different manufacturers have different profiles. This profile can be used to quantify amounts of flavonoids in the perfusate by using peaks that represent the top 13 most enriched flavonoids. It is possible to calculate permeability of these flavonoids because we only needed ratio of the original peak areas and peak areas of these 13 flavonoids following intestinal perfusion to calculate permeability after including an external standard for analytical accuracy.

RESULTS

Intestinal absorption of aglycones

The majority of ginkgo flavonoids are flavonol glycosides and the four major flavonols in EGb 761 are quercetin, kaempferol, isorhamnetin, and myricetin, with the first two being the most prevalent (DeFeudis, 1998). EGb 761 also contained some flavones such as apigenin. We determined the absorption of a flavonol (quercetin) and a flavone (apigenin) in various regions of the intestine. It was found that quercetin and apigenin were rapidly absorbed (Table 1).

Table 1. Regional Absorption of Individual Flavonoids, Flavonoid Mixture in EGb 761, and Model Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Duodenum (P* eff) (Average ± SD)</th>
<th>Jejunum (P* eff) (Average ± SD)</th>
<th>Ileum (P* eff) (Average ± SD)</th>
<th>Colon (P* eff) (Average ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin (Q)</td>
<td>2.67 ± 0.39</td>
<td>2.92 ± 0.33</td>
<td>2.93 ± 0.61</td>
<td>2.83 ± 0.24</td>
</tr>
<tr>
<td>Apigenin (A)</td>
<td>2.54 ± 1.58</td>
<td>2.69 ± 0.20</td>
<td>2.44 ± 1.02</td>
<td>6.33 ± 1.93</td>
</tr>
<tr>
<td>Rutin</td>
<td>0.58 ± 0.07</td>
<td>0.66 ± 0.29</td>
<td>0.71 ± 0.22</td>
<td>0.45 ± 0.05</td>
</tr>
<tr>
<td>Isoquercitrin</td>
<td>4.49 ± 1.31</td>
<td>3.52 ± 1.17</td>
<td>0.53 ± 0.16</td>
<td>0.25 ± 0.09</td>
</tr>
<tr>
<td>A-7-O-glucoside</td>
<td>—</td>
<td>6.17 ± 0.53</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ginkgo flavonoids</td>
<td>0.48 ± 0.15</td>
<td>0.60 ± 0.08</td>
<td>0.50 ± 0.18</td>
<td>0.53 ± 0.14</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.092 ± 0.03</td>
<td>0.14 ± 0.02</td>
<td>0.021 ± 0.01</td>
<td>0.13 ± 0.11</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3.73 ± 0.20</td>
<td>3.49 ± 0.41</td>
<td>1.24 ± 0.32</td>
<td>2.21 ± 0.27</td>
</tr>
</tbody>
</table>

The results, except for apigenin and its glucoside, were from a four-site simultaneously perfused rat intestinal model. Experiments were performed at 37°C and four samples were taken at 10- to 15-minute intervals. Data presented are average of four rats.

SD, standard deviation.
Determining the peak areas of top 13 components before and after perfusion. We found that absorption of EGb 761 was similar to rutin (Table 1), which was somewhat unexpected since EGb 761 contains significant amount of flavonol monoglycosides that are substrates of LPH (Yoshitama, 1997).

Isolation and identification of rutin-degrading bacteria

Pure bacterial culture was isolated from the enrichment cultures derived from the rat fecal materials. The colony was bright yellow with visible precipitations after 24 hours of incubation on rutin. The preliminary identification was done by 16S rDNA gene sequence analysis. The sequence analysis showed 100% identity to Enterococcus avium (data not shown). A typical strain, LY1, was used for further studies.

Metabolism of rutin by strain LY1

The time course of the rutin (2 mmol) metabolism was determined, and the results indicated that 50% of rutin (1 mmol) were consumed anaerobically at 37°C by 24 hours under the defined conditions. HPLC analysis detected two main metabolites eluting at 8.8 and 21.8 minutes, which corresponded to 3,4-dihydroxyphenylacetic acid (3,4-DPA) and quercetin because of their similar UV spectra. The metabolites found in our studies were similar to those previously reported (Bokkenheuser et al., 1987; Winter et al., 1989). Between those two metabolites, quercetin was much more prevalent and formed a yellow precipitate at the bottom of the culture tubes.

Metabolism of flavonoids in EGb 761 by strain LY1

EGb 761 could be used as sole carbon source by strain LY1 under anaerobic conditions. A significant portion of flavonoids in EGb 761 (Fig. 4A) was converted to the main aglycone forms (quercetin and kaempferol) (Fig. 4B) after 36 hours. Using HPLC conditions that generated Figure 4B, aglycones such as quercetin were eluted after 25 minutes, therefore, the two major peaks at 19.2 minutes and 20.7 minutes were likely to be other glycosides present in EGb 761 but not hydrolyzed by strain LY1. At present, the identities of these glycosides remain unknown. When enrichment cultures derived from either rat fecal materials was used, glycosides in EGb 761 were completely consumed but quercetin, kaempferol, and the possible isorhamnetin were only transiently detected during the growth of the bacteria in enrichment cultures. Therefore, bacteria other than strain LY1 are likely to be responsible for releasing other aglycones from glycosides in EGb 761.

Uptake of flavonoids by resting cells of strain LY1

At the end of a 10-minute uptake study, 46% of loaded quercetin was taken up by the resting cells. On the other hand, the diglycoside form of quercetin (i.e., rutin) was not taken into the resting cells (Fig. 5).
Phase II conjugations of gingko flavonoids

We have showed that glycosides were poorly absorbed and that they require activation via intestinal or microbial glycosidases. We also showed that aglycones were rapidly absorbed. The question then was, why does this class of compounds have such poor bioavailabilities? To answer this, we first determined how intestinal metabolism might contribute to the poor bioavailability by determining phase II conjugation of aglycones in the intestinal tract. We found that aglycones such as quercetin and apigenin were rapidly conjugated by the enterocytes into phase II metabolites, which were then efficiently secreted back into the intestinal lumen (Table 2). More phase II conjugates of apigenin were excreted than quercetin (Table 2). Amounts of apigenin metabolites formed were dependent on the segment perfused and were variable (as evidenced by large variations in percent metabolized). We found higher percent metabolized in the duodenum and jejunum than in the terminal ileum and colon. After adding glucuronidase and sulfatase to the perfusate, 50% or more of the quercetin conjugates and nearly 100% of apigenin conjugates could be hydrolyzed into the corresponding aglycones. Small amounts of the metabolites of rutin (<1%) were also detected (Table 2). Addition of glucuronidase and sulfatase to the rutin perfusate did not reconvert these metabolites to rutin. The metabolism of rutin was much slower than quercetin (Table 2). Phase II
conjugates also formed when isoquercitrin was used were quantified, usually between 2.5%–8.5% and only present in the duodenum and jejunum.

**DISCUSSION**

Flavonoids are a major source of antioxidants in our diets and the amount of flavonoids ingested is typically several grams per day (Winter et al., 1989). Flavonoids are also major components of various herbal preparations, such as EGb 761. In nature, flavonoids are mostly present as glycosides. Because glycosides are poorly permeable in the intestine (Walgren et al., 2000), bioactivation of these glycosides through glycosidase-catalyzed hydrolysis is the first step in their intestinal disposition. Presently, there are two bioactivation pathways: one is through the intestinal glycosidases and the other through the microfloral glycosidases.

Our data showed that intestinal glycosidases were primarily active against monoglucosides such as isoquercitrin and apigetrin. This result is consistent with earlier observations by other investigators (Day et al., 1998; Ioku et al., 1998). Intestinal glycosidases were not active against rutin (a diglycoside) or a mixture of flavonoid glycosides in EGb 761, which were bioactivated by microflora bacteria such as LY1. LY1 could completely and rapidly convert all rutin to quercetin and small amounts of ring-fission products. However, it did not convert all of the glycosides in EGb 761 into aglycones. Similar to several rumen bacteria (Cheng et al., 1969; Tsai et al., 1976) and human microflora bacteria (Bokkenheuser et al., 1987; Macdonald et al., 1984; Schneider and Blaut, 2000; Schneider et al., 1999), LY1 also metabolized rutin to quercetin and 3,4-DPA, although the amount of 3,4-DPA formed was minute compared to that of quercetin. Therefore, it is likely that other microflora species also participate in the ring-fission of quercetin to smaller and more hydrophilic metabolites in addition to 3,4-DPA (Schneider et al., 1999; Winter et al., 1989).

Our data demonstrated that bacteria could rapidly hydrolyze glycosides into aglycones. We then performed studies to determine if bacteria-mediated hydrolysis occurred before or after uptake of glycosides. As expected, quercetin was rapidly taken up whereas rutin was not (Fig. 5). Therefore, bioactivation via bacteria requires the action of membrane-bound and/or excreted bacterial enzymes that could rapidly hydrolyze glycosides and make

<table>
<thead>
<tr>
<th>Compound</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin (Q)</td>
<td>3.88 ± 0.46</td>
<td>3.67 ± 0.75</td>
<td>1.94 ± 0.57</td>
<td>3.72 ± 0.97</td>
</tr>
<tr>
<td>Apigenin (A)</td>
<td>9.33 ± 7.48</td>
<td>11.15 ± 4.38</td>
<td>2.84 ± 1.28</td>
<td>0.54 ± 0.64</td>
</tr>
<tr>
<td>Rutin</td>
<td>0.45 ± 0.28</td>
<td>0.79 ± 0.38</td>
<td>0.66 ± 0.28</td>
<td>0.12 ± 0.10</td>
</tr>
<tr>
<td>Isoquercitrin</td>
<td>8.27 ± 2.08</td>
<td>2.69 ± 1.37</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>Ginkgo flavonoids</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
</tr>
</tbody>
</table>

The pH of the perfusate media was pH 7.4, and the flow rate was from 0.191 mL/min (glycosides) to 0.382 (aglycones) mL/min. The segment perfused was approximately 10 cm in length, through which the average residence time of the perfusate was about 5–10 minutes.

BDL stands for below detection limit, which is about 0.1% of original concentration.

SD, standard deviation.
them available for uptake. We are currently conducting studies to determine the identities of enzymes that are capable of cleaving the glycosidic or rhamnosidic bond of the glycosides and α-L-rhamnosidase has been purified in cytoplasmic fraction, which worked on rutin and produce quercetin-3-glucoside as an intermediate (data not shown).

Although glycosides such as isoquercitrin and apigetrin were poorly absorbed in intestinal segments that lack glycosidases, they are often fully bioactivated to aglycones by intestinal or microflora glycosidases. Aglycones were rapidly absorbed (Table 1) but were subject to conjugation via intestinal and liver sulfotransferases and UDP-glucuronosyltransferases (or UGT) (Table 2). The conjugates were excreted into the lumen via intestinal secretion (Table 2) or as a part of bile secretion (Shali et al., 1991; Ueno et al., 1983; Walle et al., 2001). The magnitude of the intestinal metabolism was surprisingly high, in our opinion, considering the fact that the normal small intestinal length of the rat is approximately 80 cm. In our single-pass perfusion study using a short segment of intestine (approximately 10 cm), up to 20% (average approximately 10%) of perfused apigenin were conjugated and then secreted into the duodenum and jejunum (Table 2), and up to 18% (average 14%) of isoquercitrin (Fig.3) were hydrolyzed in jejunum to release quercetin.

In conclusion, these results suggest that flavonoids participate in an enteric and enterohepatic recycling scheme (Fig. 2). As depicted in the scheme, naturally occurring glycosides are bioactivated in the intestine by the enterocytes or microorganisms to aglycones, which are then rapidly absorbed by the intestine. Although microorganisms in the colon may further metabolize certain portions of aglycones, a substantial portion of the aglycones are rapidly absorbed and metabolized via conjugation. Subsequently, a significant portion of the conjugated aglycones is excreted back into the lumen and the rest is transported into the liver, where they may undergo excretion via bile or additional metabolism or both. Because glucuronic acid and sulfate conjugates of flavonoids may be hydrolyzed by bacteria, the “freed” compounds or aglycones could again enter this duo-recycling scheme (Fig. 2). This continuous and repeated shuffling of flavonoids between anaerobic and aerobic conditions may explain the extensive metabolism of flavonoids, which have low bioavailability.

ACKNOWLEDGMENT

This work was supported by grant NIH AT-00182 from the National Institute of Health.

REFERENCES


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