Absorption, Bioavailability, and Metabolism of Flavonoids

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Abstract
To unravel mechanisms of action of dietary flavonoids in their potential role in disease prevention, it is crucial to know the factors that determine their release from foods, their extent of absorption, and their fate in the organism. Research on absorption, metabolism, and bioavailability of flavonoids will answer these questions. The subclass, flavonols, with quercetin as the major dietary flavonol, was the first to be studied, and information on other subclasses of flavonoids is emerging. Most flavonoids, except for the subclass of catechins, are present in plants bound to sugars as β-glycosides. This structural feature determines whether the flavonoid can be absorbed from the small intestine or has to go to the colon before absorption can occur. Generally, but exceptions have been described, glucosides are the only glycosides that can be absorbed from the small intestine. Absorption from the small intestine is more efficient than from the colon and will lead to higher plasma values. After absorption from the small intestine, flavonoids are conjugated with glucuronic acid or sulfate or O-methylation may occur. The conjugation reactions, which occur in the small intestine upon absorption, are very efficient. As a result, no free flavonoid aglycones can be found in plasma or urine, except for catechins. Plasma concentrations due to a normal diet will be less than 1 μM. Flavonoids that cannot be absorbed from the small intestine, and absorbed flavonoids secreted with bile, will be degraded in the colon by microorganisms, which will break down the flavonoid ring structure. The resulting phenolic acids have partly been characterised. These phenolic acids can be absorbed and have been measured in plasma and urine. Future research will need to address tissue distribution, cellular uptake, and cellular metabolism.

Keywords: Absorption, bioavailability, flavonoids, glucuronides, glycosides, phenolic acids, polyphenols, metabolism.

Introduction
It is generally recognized that an increased consumption of vegetables and fruits protects against cancer and cardiovascular diseases (CVD) (Ness & Powles, 1997; Research WCRF/AICR, 1997; Ness et al., 1999). An attractive hypothesis is that vegetables and fruits contain bioactive compounds that have a protective effect. Flavonoids, a large group of natural antioxidants ubiquitous in a diet high in plant foods (Kühnau, 1976), may contribute to this protective effect. In addition to their antioxidant properties, flavonoids show a number of effects in animal models and in in vitro systems which might explain their potentially beneficial role (Nijveldt et al., 2001).

Flavonoids are secondary plant metabolites, which together with other plant phenols share a common origin: the amino acid phenylalanine (Parr & Bolwell, 2000). As a result, these phenols are derived from a common building block in their carbon skeleton: the phenylpropanoid unit, C₆–C₃. Biosynthesis according to this pathway produces the large variety of plant phenols: cinnamic acids (C₆–C₃), benzoic acids (C₆–C₃, or C₆–C₃), flavonoids (C₆–C₃–C₆), proanthocyanidins (C₆–C₃–C₆), stilbenes (C₆–C₂–C₆), coumarins (C₆–C₃), lignans (C₆–C₃–C₃–C₆), and lignins (C₆–C₃). Within each family of plant phenols many compounds may exist. Over 4000 different flavonoids (Fig. 1) have been described as occurring in plants (Harborne & Baxter, 1999).

To elucidate the role of dietary flavonoids in human health, it is important to know the concentrations and forms that are present in plasma and tissues after ingestion of these flavonoids with the diet. Therefore, it is essential to study their absorption, metabolism, and bioavailability. The current paper summarizes the current knowledge on human absorption, metabolism, and bioavailability of dietary flavonoids.
Absorption

Before dietary flavonoids can be absorbed from the gut, they must be released from plant foods by chewing, action of the digestive juices in the gastrointestinal tract, and finally the microorganisms of the colon. It can be envisaged that this release from the plant tissues, the so-called food matrix, depends on the type of plant food, its processing conditions, and the presence of other dietary components. The absorption of the flavonoid liberated from the food will depend on its physicochemical properties such as molecular size and configuration, lipophilicity, solubility, and pKa. To date, only fragmentary information is available on the effect of the plant food matrix on absorption. Well-designed studies that addressed this issue have not been reported.

Role of the flavonoid structure: Glycosides and oligomers

Glycosides

Most flavonoids, except catechins, are usually present in the diet as β-glycosides (Fig. 2). Glycosides were considered too hydrophilic for absorption by passive diffusion in the small intestine, thus only aglycones were likely to be absorbed. Studies with germ-free rats showed that large amounts of unchanged glycosides were excreted with feces, whereas only small amounts of glycosides were found in feces of rats with a normal microflora (Griffiths & Barrow, 1972). Thus, it was thought that the glycosylated flavonoids were only marginally absorbed. However, this view on absorption of glycosides had to be revised.

A study with ileostomy subjects who lack a colon with bacteria showed unexpectedly high absorption of quercetin-glucosides (quercetin-4'-glucoside and quercetin-3,4'-bis-glucoside) from onions (52%) (Hollman et al., 1995). These data also suggested that absorption of quercetin glucosides takes place in the small intestine, a novel finding. This was confirmed in a human pharmacokinetic study (Hollman et al., 1997). To explain this remarkable finding that the hydrophilic quercetin glucoside is transported across the small intestine, it was proposed that the intestinal Na⁺-dependent glucose cotransporter (SGLT1) was involved (Hollman et al., 1999). This would imply that intact quercetin glucoside can be transported across the enterocyte and possibly could appear in the plasma. However, intact quercetin-3-glucoside was absent in plasma after supplementation of volunteers with quercetin-3-glucoside, which does not strengthen the SGLT1 hypothesis (Sesink et al., 2001). An alternative mechanism states that quercetin glucosides are hydrolyzed by lactase phloridzin hydrolase (LPH), a β-glucosidase on the outside of the brush border membrane of the small intestine (Day et al., 2000). Subsequently, the liberated aglycone can be absorbed across the small intestine. It was confirmed in an in situ rat perfusion model that LPH is predominantly (>75%) involved in the absorption of quercetin-3-glucoside across the small intestine (Sesink et al., 2003). The substrate specificity of this LPH enzyme varied significantly in a broad range of glycosides (glucosides, galactosides, arabinosides, xylosides, rhamnosides, and galactosides) of flavonols, flavones, flavanones, isoflavones, and anthocyanins (Németh et al., 2003). Only glucosides were efficiently hydrolyzed by LPH, more-or-less independent of the aglycone part of the glucoside.
Figure 2. Structures of two glycosides, quercetin-4′-β-glucoside and quercetin-3-β-rutinoside, and a proanthocyanidin trimer C1.
Noticeable exceptions were the anthocyanin cyanidin-3-glucoside where no hydrolysis was detected, and the isoflavone daidzein-7-glucoside with a low hydrolysis rate.

Glycosides that are not substrates for these two enzymes will be transported toward the colon where bacteria are able to hydrolyze flavonoid glycosides but at the same time will degrade the liberated flavonoid aglycones (Scheline, 1973). Because the absorption capacity of the colon is far less than that of the small intestine, only marginal absorption of these glycosides is to be expected. As an example, the bioavailability of pure quercetin-3-β-rutinoside (no substrate for either LPH or SGLT1) administered to volunteers was only 20% of that of pure quercetin-4’-β-glucoside (Hollman et al., 1999). These data strongly indicate that the sugar moiety of quercetin glycosides is a major determinant of their absorption and bioavailability.

**Oligomers**

In contrast with other flavonoids, catechins occur as aglycones and galloylated forms in foods. Pharmacokinetic data point to absorption from the small intestine of both the aglycones and the galloylated forms (Lee et al., 1995). Human data on the quantity of catechins that are absorbed are lacking. However, besides aglycones, catechins occur in plant foods as oligomers of up to 17 catechin units: the proanthocyanidins (Fig. 2). *In vitro* studies with Caco-2 cells showed that only dimers and trimers were able to pass across monolayers of these cells (Déprez et al., 2001). Indeed, procyanid dimer B2 [epicatechin-(4β→8)-epicatechin] was detected in human plasma after ingestion of a cocoa beverage (Holt et al., 2002). It has been suggested that oligomers can be hydrolyzed to monomers and dimers due to the acidic conditions in the stomach (Spencer et al., 2000). However, sampling of human gastric juice showed that hydrolysis of proanthocyanidins does not occur *in vivo* (Rios et al., 2002). It can be concluded that only proanthocyanidins up to three catechins are absorbable from the colon. Larger molecules will reach the colon where they will be degraded by bacteria.

**Role of other dietary components**

Interaction of proteins with the absorption of polyphenols might be expected, because polyphenols can bind proteins efficiently. It was found in humans that addition of milk to black tea did not change the area under the curve of the plasma concentration-time curves of flavonols and catechins (van het Hof et al., 1998; Hollman et al., 2001). Thus, absorption of flavonols and catechins was independent of the addition of milk. The role of alcohol in the absorption of wine flavonoids has been investigated, because ethanol could increase their absorption by improving the solubility. However, no increase in plasma catechin could be measured (Donovan et al., 1999).

**Bioavailability**

Dietary flavonol glycosides showed very rapid to very slow absorption in man. Times to reach peak concentrations (*T*\(_{\text{max}}\)) were between <0.5 and 9 h (Table 1). The bioavailability of quercetin glucosides from onions was superior. Bioavailability of various quercetin glucosides (β-galactosides and β-xilosides) from apples and of pure quercetin rutinoside was only 30% of that from onions (Hollman et al., 1997). Thus, the sugar moiety of quercetin glycosides seemed to be an important determinant of their bioavailability, which was confirmed when pure quercetin-β-glucoside or pure quercetin-β-rutinoside was administered to healthy human volunteers (Hollman et al., 1999). The peak concentration of quercetin (*C*\(_{\text{max}}\)) in plasma was 20-times higher and reached (*T*\(_{\text{max}}\)) more than 10-times faster after intake of the glucoside than after the rutinoside. These pharmacokinetic data suggest that quercetin glucoside was absorbed from the small intestine, whereas quercetin rutinoside was absorbed from the colon after deglycosylation. Evidently, the sugar moiety played no role in the elimination of quercetin from plasma: elimination half-life was about 20 h for all glycosides (Table 1). This is consistent with the observation that quercetin glucosides do not circulate in the blood (Sesink et al., 2001). Apparently, the sugar part only plays a role upon absorption.

Meanwhile, bioavailability studies have been performed with flavonoids of all subclasses, except for flavones (Table 1). For comparison reasons, *C*\(_{\text{max}}\)/Dose is calculated and shown in this table to give some insight into the relative bioavailability of the flavonoids tested. However, a proper comparison can only be made when areas under the plasma concentration-time curve (AUC) are calculated. The *C*\(_{\text{max}}\) values in this table give insight in the upper levels of flavonoids that will be circulating due to a diet rich in flavonoids. As an example, after ingestion of a solution of 150 mg (325 μmol) pure quercetin-3-glucoside, a plasma concentration of 5 μM quercetin was reached. However, such high quantities of quercetin will never be ingested via an average diet. The average dietary intake of quercetin in The Netherlands is on average only 23 mg (Hertog et al., 1993), which would predict a plasma value of only 1 μM quercetin, assuming that all dietary quercetin is present as quercetin-glucoside, the most bioavailable compound, and is taken as a single dose. Therefore, daily plasma levels of quercetin will be substantially lower than 1 μM.

Catechins are quite rapidly absorbed, suggesting absorption from the small intestine. The galloylated EGCg is not different in this respect. Bioavailability of
Table 1. Plasma concentrations and kinetics after single-dose administration of flavonoids to humans.

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>Source</th>
<th>Dose (μmol)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μM)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/Dose (μM/μmol) × 10&lt;sup&gt;3&lt;/sup&gt;</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>T&lt;sub&gt;half&lt;/sub&gt; (h)</th>
<th>References</th>
</tr>
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<td><strong>Flavonols</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin (Q)</td>
<td>Onions</td>
<td>225</td>
<td>0.74</td>
<td>3.3</td>
<td>0.7</td>
<td>28</td>
<td>Hollman et al. (1997)</td>
</tr>
<tr>
<td></td>
<td>Apples</td>
<td>325</td>
<td>0.30</td>
<td>0.9</td>
<td>2.2</td>
<td>23</td>
<td>Hollman et al. (1997)</td>
</tr>
<tr>
<td></td>
<td>Various foods</td>
<td>288</td>
<td>~0.4</td>
<td>~1.4</td>
<td></td>
<td></td>
<td>Manach et al. (1998)</td>
</tr>
<tr>
<td>Q-3-glucoside</td>
<td>Pure compound</td>
<td>325</td>
<td>5.0</td>
<td>15</td>
<td>0.6</td>
<td>19</td>
<td>Olthof et al. (2000)</td>
</tr>
<tr>
<td>Q-4'-glucoside</td>
<td>Pure compound</td>
<td>331</td>
<td>4.5</td>
<td>14</td>
<td>0.5</td>
<td>19</td>
<td>Olthof et al. (2000)</td>
</tr>
<tr>
<td>Q-3-rutinoside</td>
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<td>311</td>
<td>0.2</td>
<td>0.6</td>
<td>6.0</td>
<td>28</td>
<td>Hollman et al. (1999)</td>
</tr>
<tr>
<td>Pure compound</td>
<td>662</td>
<td>2.0</td>
<td>1.3</td>
<td>7</td>
<td></td>
<td>7</td>
<td>Graefe et al. (2001)</td>
</tr>
<tr>
<td>Black tea</td>
<td>662</td>
<td>1.0</td>
<td>1.5</td>
<td>2</td>
<td></td>
<td>7</td>
<td>Graefe et al. (2001)</td>
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<td><strong>Catechins</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>(+)-Catechin</td>
<td>Red wine</td>
<td>120</td>
<td>0.09</td>
<td>0.75</td>
<td>1.5</td>
<td>3.1</td>
<td>Donovan et al. (1999)</td>
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<tr>
<td>(-)-Epicatechin</td>
<td>Green tea</td>
<td>143</td>
<td>0.43</td>
<td>3.0</td>
<td>1.3</td>
<td>3.0</td>
<td>Richelle et al. (1999)</td>
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<td></td>
<td>Chocolate</td>
<td>565</td>
<td>0.7</td>
<td>1.2</td>
<td></td>
<td>3</td>
<td>Lee et al. (2002)</td>
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<td></td>
<td>EGC</td>
<td>467</td>
<td>0.73</td>
<td>1.6</td>
<td>1.3</td>
<td>1.7</td>
<td>Lee et al. (2002)</td>
</tr>
<tr>
<td></td>
<td>EGCg</td>
<td>395</td>
<td>0.17</td>
<td>0.4</td>
<td>1.6</td>
<td>3.4</td>
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<td></td>
<td>Green tea</td>
<td>230</td>
<td>0.31</td>
<td>1.3</td>
<td>2</td>
<td>—</td>
<td>Unno et al. (1996)</td>
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<tr>
<td>Pure compound</td>
<td>284</td>
<td>0.076</td>
<td>0.27</td>
<td>1.6</td>
<td></td>
<td>3.7</td>
<td>Lee et al. (2002)</td>
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<td><strong>Proanthocyanidins</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimer B2</td>
<td>Chocolate</td>
<td>630</td>
<td>0.08</td>
<td>0.1</td>
<td>2</td>
<td>—</td>
<td>Steinberg et al. (2002)</td>
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<tr>
<td></td>
<td>Chocolate</td>
<td>443</td>
<td>0.04</td>
<td>0.09</td>
<td>2</td>
<td>—</td>
<td>Holt et al. (2002)</td>
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<td><strong>Flavanones</strong></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hesperitin-7-rutinoside</td>
<td>Orange juice</td>
<td>727</td>
<td>1.3</td>
<td>1.8</td>
<td>5.8</td>
<td>—</td>
<td>Manach et al. (2003)</td>
</tr>
<tr>
<td>Naringin-7-rutinoside</td>
<td>Orange juice</td>
<td>166</td>
<td>0.2</td>
<td>1.2</td>
<td>5.0</td>
<td>—</td>
<td>Manach et al. (2003)</td>
</tr>
<tr>
<td><strong>Anthocyanins</strong></td>
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<td></td>
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<tr>
<td>Cyanidin-3-rutinoside</td>
<td>Black currant concentrate</td>
<td>137</td>
<td>0.05</td>
<td>0.3</td>
<td>1.5</td>
<td>3.5</td>
<td>Matsumoto et al. (2001)</td>
</tr>
<tr>
<td>Delphinidin-3-rutinoside</td>
<td>Black currant concentrate</td>
<td>182</td>
<td>0.07</td>
<td>0.4</td>
<td>1.8</td>
<td>3.2</td>
<td>Matsumoto et al. (2001)</td>
</tr>
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<td>Cyanidin-3-glucoside</td>
<td>Black currant concentrate</td>
<td>24.4</td>
<td>0.006</td>
<td>0.2</td>
<td>1.3</td>
<td>1.3</td>
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</tr>
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<td>Delphinidin-3-glucoside</td>
<td>Black currant concentrate</td>
<td>68.6</td>
<td>0.02</td>
<td>0.3</td>
<td>1.5</td>
<td>4.2</td>
<td>Matsumoto et al. (2001)</td>
</tr>
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<td><strong>Isoflavones</strong></td>
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<td>Genistein</td>
<td>Soy milk</td>
<td>70</td>
<td>0.74</td>
<td>10.6</td>
<td>6.5</td>
<td>—</td>
<td>Xu et al. (1994)</td>
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<tr>
<td></td>
<td>Pure compound</td>
<td>186</td>
<td>0.87</td>
<td>4.7</td>
<td>7.4</td>
<td>—</td>
<td>Setchell et al. (2003)</td>
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<td>Genistein-7-glucoside</td>
<td>Pure compound</td>
<td>62</td>
<td>0.40</td>
<td>6.5</td>
<td>4–6</td>
<td>—</td>
<td>Izumi et al. (2000)</td>
</tr>
<tr>
<td>Daidzein</td>
<td>Soy milk</td>
<td>98</td>
<td>0.79</td>
<td>8.1</td>
<td>6.5</td>
<td>—</td>
<td>Xu et al. (1994)</td>
</tr>
<tr>
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<td>Pure compound</td>
<td>196</td>
<td>0.92</td>
<td>4.7</td>
<td>7.2</td>
<td>—</td>
<td>Setchell et al. (2003)</td>
</tr>
<tr>
<td>Daidzein-7-glucoside</td>
<td>Pure compound</td>
<td>55</td>
<td>0.2</td>
<td>3.6</td>
<td>4–6</td>
<td>—</td>
<td>Izumi et al. (2000)</td>
</tr>
</tbody>
</table>

C<sub>max</sub>, peak level; T<sub>max</sub>, time to reach peak level; T<sub>half</sub>, elimination half life; —, data not given; EGCg, (+)-epigallocatechin gallate; EGC, (-)-epigallocatechin; EGCg, (-)epicatechin gallate.

<sup>a</sup>Adapted from Gonthier (2003).

<sup>b</sup>Plasma only sampled at 3, 7, and 20 h after the test meal.
the various catechin monomers seems to be quite similar. However, dimerization reduces bioavailability.

Flavanone rutinosides are slowly absorbed, suggesting a similar role of the attached disaccharide as with flavonols. Isoflavones show the highest bioavailability of all subclasses of flavonoids. Bioavailability does not differ between aglycones and glucosides. Remarkably, the absorption of both the aglycones and the glucosides is quite slow, suggesting absorption from the colon. This fits with the finding that LPH has a weak affinity for daidzein-7-glucoside (Németh et al., 2003), and also would predict a low affinity of LPH for genistein-7-glucoside.

Anthocyanins are quite rapidly absorbed, but their bioavailability seems to be the lowest of all flavonoids. It is not clear yet whether the problematic quantification of anthocyanins in plasma and urine causes these low values. Development of reliable analytical protocols should have a high priority.

The elimination half-lives of flavonols are quite different from those of the other flavonoid subclasses. Catechins and anthocyanins have elimination half-lives that are 5- to 10-fold lower than those of flavonols. No data are available for the other subclasses, but plasma profiles suggest that elimination is comparable with that of catechins and anthocyanins.

**Metabolism**

In the metabolism of flavonoids, two compartments are considered. The first compartment consists of tissues such as the small intestine, liver, and kidneys. The colon constitutes the second compartment (Fig. 3). Flavonoids that are unabsorbable from the small intestine and flavonoids that have been absorbed and then secreted with bile will reach the colon. The significance of biliary flavonoids that have been absorbed and then secreted constitutes the second compartment (Fig. 3). Flavonoids such as the small intestine, liver, and kidneys. The colon is considered. The first compartment consists of tissues that are unabsorbable from the small intestine and flavonoids that are 5- to 10-fold lower than those of flavonols. No data are available for the other subclasses, but plasma profiles suggest that elimination is comparable with that of catechins and anthocyanins.

**Metabolism in tissues: Side groups are attached or detached**

In the first compartment, mainly the small intestine and liver, biotransformation enzymes act upon flavonoids and their colonic metabolites. The kidney also contains enzymes capable of biotransformation of flavonoids. Conjugation of the polar hydroxyl groups with glucuronic acid, sulfate, or glycine has been reported for flavonoids and for their colonic metabolites (Hollman & Katan, 1998). In addition, O-methylation by the enzyme catechol-O-methyltransferase plays an important role in the inactivation of the catechol moiety, that is, the two adjacent (ortho) aromatic hydroxyl groups, of flavonoids and their colonic metabolites. Recently, deglycosylation of glycosides in the brush border membrane of the small intestine was demonstrated (Day et al., 2000).

The conjugation reactions are very efficient in humans, evidenced by the fact that flavonoids predominantly occur in plasma and urine as conjugates, and that it is difficult to detect flavonoid aglycones in plasma, because they are mostly below the limit of detection of the analytical methods used. The presence of flavonoid conjugates in humans, including O-methylated conjugates, is apparent from differential High Performance Liquid Chromatography (HPLC) analyses with and without hydrolysis of the sample with a mixture of β-glucuronidases and sulfatases: flavonols (Manach et al., 1998; Olthof et al., 2000; Graefe et al., 2001; Stahl et al., 2002), flavonones (Shimoi et al., 1998), catechins (Lee et al., 1995; Lee et al., 2002), flavanones (Manach et al., 2003), and anthocyanins (Felgines et al., 2003). In a number of human intervention studies the nature of the conjugates has been identified. Major conjugates of quercetin after onions supplementation were the 3′-sulfate, the 3′-methoxy-3′-glucuronide, and the 3-glucuronide (Day et al., 2001). The 3′-sulfate could not be confirmed with Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (Tandem Mass Spectrometry) (LC-MS/MS) in another study (Wittig et al., 2001). Human studies that identified the circulating plasma conjugates for other flavonoids mainly found glucuronides for isoflavones (Doerge et al., 2000; Setchell et al., 2001; Shelnutt et al., 2002; Zhang et al., 2003), for catechins (Baba et al., 2000; Lee et al., 2002), for flavanones (Manach et al., 2003), and for anthocyanins (Wu et al., 2002; Felgines et al., 2003). Catechins seem to take a separate position in conjugation efficiency: depending on the type of catechin from 10% up to 80% can be present as the aglycone in plasma (Lee et al., 2002). Conjugation of phenolic acids, the colonic metabolites of flavonoids, also seems to occur less efficiently, with conjugation percentages ranging from 13% to 100%, depending on the type of phenolic acid (Olthof et al., 2003).

It also appears that deglycosylation of flavonol glycosides is very efficient, as glycosides were absent in plasma after supplementation of volunteers with quercetin glycosides (Sesink et al., 2001). However, anthocyanins take a different position. Evidence is accumulating that anthocyanidin glycosides are able to at least partly withstand deglycosylation reactions in humans. The appearance of peonidin-3-glucoside, even peonidin-3-sambubioside (sambubioside is a disaccharide!) (Wu et al., 2002) and pelargonidin-3-glucoside (Felgines et al., 2003) in urine has been confirmed with LC-MS.

**Metabolism in the colon: The flavonoid nucleus is split**

Microorganisms degrade the flavonoid molecule in the course of which the heterocyclic oxygen containing ring is split. The subsequent degradation products can
evidently be absorbed because they are found in urine and plasma (Rechner et al., 2002; Olthof et al., 2003). These include a variety of hydroxylated phenyl carboxylic acids. The type of ring fission depends on the type of flavonoid: three schemes have been described based on animal experiments (Hollman & Katan, 1998). Flavonols are degraded to phenylacetic acids and phenylpropionic acids, however, these phenylpropionic acids could not be confirmed in a human study (Olthof et al., 2003). Ring fission of catechins produces valerolactones (a benzene ring with a side chain of five C-atoms), and phenylpropionic acids. Flavones and flavanones follow a scheme producing phenylpropionic acids. These phenylcarboxylic acids are subject to further bacterial degradation and to enzymatic transformations in body tissues. As a result, the phenylpropionic acids will be oxidized to benzoic acids. Recent studies confirmed that this scheme also applies to humans (Rechner et al., 2002; Olthof et al., 2003). There was one exception; in humans as opposed to rodents, only phenylacetic acids were formed after ingestion of quercetin-rutinoside (Olthof et al., 2003). Although about 60 putative phenolic acid metabolites potentially could be identified and quantified, only a limited number of phenolic acids actually were found (Olthof et al., 2003). The glycine ester of benzoic acid, hippuric acid, proved to be a very important metabolite in humans after ingestion of tea, but not after quercetin rutinoside. It was shown that microorganisms in the colon play an essential role in the metabolism of flavonoids into phenolic acids (Olthof et al., 2003).

Apart from degrading the flavonoid ring system, colonic bacteria produce glycosidases, glucuronidases, and sulfatases that can strip flavonoid conjugates of their sugar moieties, glucuronic acids, and sulfates (Scheline, 1973). Human intestinal bacteria are able to hydrolyse O-glycosides (Scheline, 1973) as well as C-glycosides (Hattori et al., 1988).

**Extent of metabolism**

Flavonols were the first to be studied and showed a rather low urinary excretion in humans. Only 0.1% to 3.6% of the ingested dietary quercetin was excreted as quercetin conjugates in urine (Table 2). Urinary excretion will correlate with the amount of intact quercetin in plasma. Because absorption of quercetin glucosides is quite high (up to 50%), whereas excretion of intact quercetin in urine is low, this points to extensive metabolism of quercetin. Additional subclasses have been studied with volunteers, and urinary excretion of metabolites with an intact flavonoid structure have been quantified (Table 2). It is clear that excretion of isoflavones is the highest of all flavonoids. Although the bioavailability of isoflavones is high (Table 1), flavonols glucosides show a higher bioavailability but a smaller urinary excretion. This would imply that the extent of metabolism by which the ring system is modified is lower with isoflavones than with flavonols.
Conclusions

Starting with quercetin, knowledge on bioavailability and metabolism of all subclasses of flavonoids has been increasing steadily during the past 5 years. For a proper evaluation of their potential health effects, this information is essential and still has to be extended. We need more data on the concentrations and metabolic forms that tissues and cells are exposed to after ingestion of flavonoids via the diet. Then the next step can be taken to study the potential biological effects at the tissue and cellular level. New genomic techniques will give tremendous opportunities to explore this field. For this type of research, it is essential to know which metabolites will reach tissues and cells, at what concentrations, and to what extent they are taken up and modified in cells after a flavonoid-rich diet. The high-throughput genomics tools will then be able to increase our understanding on how flavonoids affect metabolic pathways and, as a consequence, affect human health.

References


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Absorption, bioavailability, and metabolism of flavonoids


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