Food Content, Processing, Absorption and Metabolism of Onion Flavonoids

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The question as to how far the development of chronic diseases in humans depends on diet still remains open. Simultaneously, epidemiological studies suggest the consumption of a flavonoids rich diet might decrease the risk of degenerative changes and certain diseases. The intake of this group of compounds as to quality and quantity depends on dietary habits and a widespread presence of quercetin in the diet makes this compound one of the key factors. Onion, one of the richest and most common quercetin sources, was particularly often studied in different aspects. Quercetin is present in onion mainly as glycosides, of which the distribution within the onion bulb changes in onion processing, and biological activities attracted a lot of attention. Especially antioxidative activity demonstrated in vitro was initially associated with most of the beneficial effects of quercetin on the human body. However, after ingestion quercetin undergoes extensive metabolism and microbial action resulting in its altered or degraded structure; therefore, most of the effects shown in in vitro experiments with the pure compound cannot be directly extrapolated to in vivo systems. Yet, this does not mean that quercetin simultaneously loses its positive impact on consumer health. Even after being metabolized it may still affect the redox balance by inducing antioxidative and detoxifying enzymes or compounds which may be involved in sustaining homeostasis.

Keywords onion, quercetin, processing, bioavailability, plasma, metabolism

ABBREVIATIONS

- SGLT1: sodium-dependent glucose transporter
- LPH: lactase-phlorizin hydrolase
- UGT: UDP-glucuronyltransferase
- COMT: catechol O-methyltransferase
- Q: quercetin
- b.w.: body weight

INTRODUCTION

Flavonoids are polyphenolic compounds occurring in a variety of foods and beverages of plant origin. Over 6,500 flavonoids have been described so far and classified into several subclasses. They play important roles in plant development and in the protection of the plant against UV radiation, pathogens, and herbivores (Harborne and Williams, 2000; Ross and Kasum, 2002). Flavonoids are secondary plant metabolites contributing substantially to the non-energetic part of the human diet (Noteborn et al., 1997). Apart from some fermented foods such as wine, tempeh (Klus and Barz, 1995), or tea, where flavonoid aglycones are present, most of the dietary flavonoids are β-O-glycosides, mainly with D-glucose (Hermann, 1988) and in this form are ingested. Glycosylation increases the polarity of the flavonoid molecule, which is necessary for storage in plant cell vacuoles (Aherne and O’Brien, 2002).

The flavonoids of dietary significance can be divided into six main classes: flavones, flavonols, flavanones, isoflavones, flavanols (including catechins and tannins), and anthocyanins. Flavan-3,4-diols are also referred to as leucoanthocyanidins. Polymeric structures based on the flavan-3,4-diols and flavan-3-ols make up the procyanidins (condensed tannins) (Harborne and Williams, 2000; Spanos and Wrolstad, 1992).

There is an increasing awareness of the role of flavonoids as epidemiological studies suggest that consumption of flavonol- and isoflavone-rich diets might decrease the risk of developing coronary heart disease and certain cancers (Formica and Regelson, 1995; Arai et al., 2000). Five out of seven studies showed a negative correlation between flavonol intake and the
development of cardiovascular disease and the protective effect of flavonols seems to be rather systemic than local (Hollman, 2001). When considering systemic action, cellular uptake of flavonoids metabolites needs full understanding, especially the transport mechanisms through cells membranes (Walle, 2004).

In this paper we focused on onion flavonoids as the onion is one of the richest and commonly consumed sources of dietary flavonoids. The subsequent sections of this paper are structured to follow the sources of flavonoids, their food content, impact of processing on them, and their intake. Next, we follow the flavonoids ingested with food through the gastrointestinal tract, from entering the mouth through proceeding to the stomach, the small and large intestines along with intestinal absorption, metabolism, and distribution in the body.

**MAJOR SOURCES AND DAILY INTAKE OF FLAVONOIDS**

Sources of dietary polyphenols are fruits, vegetables, beverages, and dietary supplements. In foods, flavonoids contribute to flavor and color characteristics. Pure procyanidins display both bitterness and astringency and the balance between these sensations depends on the molecular weight. Tetrameric procyanidins have been shown to be the most bitter, while the more polymeric ones are more astringent on an equivalent weight basis. Bitterness is caused by an interaction between polar molecules and the lipid portion of the taste papillae membrane. Astringency results from nonspecific and to some extent irreversible hydrogen binding between o-diphenol and proline-rich proteins in the mouth (Spanos and Wrolstad, 1992).

Polyphenol intake is different in particular countries and depends on preferences as to quality as well as quantity. Flavonoids (including catechins, proanthocyanidins, anthocyanins, and their oxidation products) account for approximately two-thirds of the total plant phenols, and phenolic acids for one-third (Scalbert and Williamson, 2000). As a rough estimate, the total daily intake of polyphenols is between 150 and 1000 mg (Kühnau, 1976; Aherne and O’Brien, 2002). However, the wide range of results is due to the diversity of dietary habits and the methodology of estimation applied. The mean flavonol intake by German population was calculated to be 11.5 mg per day, mainly derived from fruits and vegetables, but also from black tea and red wine (Böhm et al., 1999; Ly et al., 2005) (Fig. 1). The flavonoids present in the peel are mainly aglycones due to flavonol glucoside hydrolysis for the Dutch population not representing total flavonoid intake, only that of three flavonol-type flavonoids (quercetin, myricetin, and kaempferol) and two flavone-type flavonoids (luteolin, apigenin), was estimated to be 23–25 mg per capita, with quercetin (16 mg/day) as the mostly consumed out of these five flavonoids (Hertog et al., 1993; Hertog et al., 1995). According to the US Department of Health and Human Services, the average human daily intake of quercetin alone is 25 mg (Stavric, 1994). Also in the “Seven Countries Study” (Hertog et al., 1995) quercetin was reported to account for a significant percentage of total daily flavonoid intake.

The highest concentrations of quercetin expressed as aglycone were found in onions (284–486 mg/kg fresh edible part), kale (110 mg/kg), apples (217–72 mg/kg), tea infusions (10–25 mg/L), red wine (4–16 mg/L) (Hertog et al., 1992; Hertog et al., 1993), cherry tomatoes (17–203 mg/kg) (Crozier et al., 1997), broccoli (30 mg/kg), green beans (39 mg/kg) (Hertog et al., 1992) or in asparagus spears (142 mg/kg) (Makris and Rossiter, 2001). In yellow onions Makris and Rossiter (2001) found ~300 mg/kg of quercetin, while Tsushida and Suzuki (1996) reported 227 mg/kg and as much as 793 mg/kg in red onion. In comparison, Price and Rhodes (1997) found higher levels of quercetin in pink, yellow, and red onion varieties (Table 1) ranging ~719–927 mg/kg. In red onions consumed by the Brazilian population up to 1000 mg/kg were reported (Arabbi et al., 2004). Lower quercetin levels (67–121.5 mg/kg) were found in edible parts of Hungarian onions (Lugasi and Hovari, 2000) or white onions (Tsushida and Suzuki, 1996; Price and Rhodes, 1997). Surprisingly Crozier and co-workers (Crozier et al., 1997) found only 201 mg/kg of quercetin in edible parts of red onion but much higher quercetin amount in white onions (185–634 mg/kg). It was also reported that the total quercetin content in long-day cultivars was higher than in short-day cultivars and this does not depend on the growing origin (Okamoto et al., 2006; Lombard et al., 2004).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Q3′,4′-Glc</th>
<th>Q4′-Glc</th>
<th>Q3′Glc</th>
<th>IR4′-Glc</th>
<th>Q</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>626.51</td>
<td>464.38</td>
<td>464.38</td>
<td>478.40</td>
<td>302.23</td>
<td>Tsushida and Suzuki (1996)</td>
</tr>
<tr>
<td>Red onion</td>
<td>1.03</td>
<td>0.08</td>
<td>0.125</td>
<td></td>
<td>0.03</td>
<td>Price and Rhodes (1997)</td>
</tr>
<tr>
<td>Red onion</td>
<td>2.19</td>
<td>0.85</td>
<td></td>
<td></td>
<td>0.005–0.013</td>
<td>Makris and Rossiter (2001)</td>
</tr>
<tr>
<td>Yellow onion</td>
<td>0.47–0.49</td>
<td>0.45–0.48</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Tsushida and Suzuki (1996)</td>
</tr>
<tr>
<td>Yellow onion</td>
<td>0.27</td>
<td>0.40</td>
<td>0.02</td>
<td>0.061</td>
<td>–</td>
<td>Price and Rhodes (1997)</td>
</tr>
<tr>
<td>Pink onion</td>
<td>1.68</td>
<td>0.65</td>
<td></td>
<td></td>
<td>0.05</td>
<td>Price and Rhodes (1997)</td>
</tr>
<tr>
<td>White onion</td>
<td>≤0.08</td>
<td>≤0.08</td>
<td></td>
<td></td>
<td>≤0.01</td>
<td>Tsushida and Suzuki (1996); Price and Rhodes (1997)</td>
</tr>
</tbody>
</table>

Note: Q = quercetin; IR = isorhamnetin; Glc = glucoside; MW = molecular weight.
Flavonoids are generally found at higher concentrations in outer layers of fruits and vegetables (Tsushida and Suzuki, 1996), therefore peeling results in their great loss. After home-like peeling, red onions contained 79% of the original total flavonoids compared to those of garlic (Allium sativum) and leek (Allium porrum) (Fattorusso et al., 2002). Although quercetin derivatives are the most abundant flavonoids in vegetables, kaempferol glycosides can be prevalent or even be the only flavonol type present, e.g. in endive and leek (Böhme et al., 1998). Leek has an exceptional position within the Allium genus as its flavonoid content is made up almost entirely from kaempferol derivatives. Fattorusso and co-workers (2001) identified two kaempferol related compounds in leek: kaempferol-3-O-[-2-O-(trans-3-methoxy-4-hydroxycinnamoyl)-β-D-galactopyranosyl]-1→4-O-β-D-glucopyranoside and kaempferol-3-O-[2-O-(trans-3-methoxy-4-hydroxycinnamoyl)-β-D-glucopyranosyl]-1→6-O-β-D-glucopyranoside. Shallot, belonging to the Aggregatum group of the Allium cepa L. (Le-Guen-Le Saos et al., 2002), also known as Allium ascalonicum Hort., grows in clusters of bulbs and was reported to have 940 mg/kg fresh weight of total flavonols (Fattorusso et al., 2002), the highest concentration among onion varieties.

**ONION PROCESSING**

Flavonoids are generally found at higher concentrations in outer layers of fruits and vegetables (Tsushida and Suzuki, 1996), therefore peeling results in their great loss. After home-like peeling, red onions contained 79% of the original total content of quercetin-4′-glucoside and only 27% of the anthocyanins (Gennaro et al., 2002). Quercetin-3,4′-diglucoside and quercetin-4′-glucoside (Q3,4′-dIGlc, Q4′Glc) were unaffected by chopping of onions, whereas the rutin content in asparagus was decreased by 18.5% in 60 min. This decline was not accompanied by an increase in free quercetin, therefore the authors speculated that the hydrolysis of rutin was possibly followed by an immediate oxidative cleavage of quercetin (Makris and Rossiter, 2001).
Usual food preparation conditions did not lead to complete loss of the two major glucosides in onions and the food contained a mixture of the two glycosides (Q3,4′diGlc, Q4′Glc) and a variable amount of the quercetin aglycone. However, quercetin-3,4′-diglucoside was rapidly degraded in macerated tissues with a 50% loss after 5h resulting in the production of quercetin monoglucoside and aglycone (Price and Rhodes, 1997), which could be explained by the activity of onion flavonol glucosidases (Tsushida and Suzuki, 1996).

Quercetin glycosides were not degraded when the onion was cooked but transferred into the cooking water, turning the onion soup into a good source of flavonoids (Nemeth et al., 2004; Takenaka et al., 2004). The total flavonoid content of onion remained unaltered during frying with oil and butter for 40 min; however, the composition pattern of quercetin derivatives after frying was left unmentioned (Ioku et al., 2001). Microwave heating for 1 min resulted in 50% increase of total quercetin content, but probably this apparent increase observed was due to their better extractability (Ioku et al., 2001). Such apparent increase in the quercetin content was also observed during onion baking and sautéing (7–25%), but boiling was reported to result in 18% loss in quercetin as compared to raw onion (Lombard et al., 2005). The process of cooking was shown to be a diminishing factor of onion and other vegetables’ antioxidative activity and as well led to the disappearance of antihypertensive activity of onion in rats (Agostini et al., 2004; Kawamoto et al., 2004). Nevertheless, despite the decrease of antioxidative activity of onion extracts after heating, their chain-breaking activity was reported to increase (Benkebila, 2005).

Shredding of leaf with the subsequent exposure to light for 48 hours resulted in dramatic flavonoid decline ranging 6–94% depending on the lettuce variety (DuPont et al., 2000). Technological processing increased the amount of quercetin in sweet cherries, whereas freezing and canning halved the flavonoid levels in processed foods compared to those in fresh products (Hertog et al., 1992). Also, a significant increase of both free and total quercetin concentrations was shown after irradiation of onions (Patil, 2004). This process was shown as an effective tool for the decontamination of onion flakes from spore forming microorganisms with a parallel enhancement of total concentration of volatile compounds (Pezzuti et al., 2005; Gyawali et al., 2006). On the whole, processing decreases the amount of flavonoids by removing them from the food, although deglycosylation does not necessarily occur unless enzymatic activity is present.

During onion processing several reactions can lead to the deteriorating of onion quality through changes in its color. Drying and storage often results in non-enzymatic browning and it strongly depends on the kind of process (Kaymak-Ertekin and Gedik, 2005; Kumar et al., 2005). Onion and garlic processing is also accompanied by the formation of pink or green-blue pigments (Kubec et al., 2004; Imai et al., 2006).

Due to the antioxidative potential of quercetin abundant in onion, the onion extract or onion flesh is used as a food additive to provide other foodstuffs with protection against oxidation. Also, onion green leaves water extracts exhibits protective effects against reactive oxygen and nitrogen species (Wang et al., 2006). It was shown that onion powder added to extruded corn or chicken meat before cooking improved their shelf-life (Camire et al., 2005; Karastogiannioud, 1999) as well as onion extract added to turkey breast rolls (Tang and Cronin, 2007). Onion extract through its ability to inhibit polyphenol oxidase is also effective in preventing from enzymatic browning (Kim et al., 2005). Recently an extract from red onion peel was shown in vitro to be a strong inhibitor of phosphodiesterase 5A, which is considered important for the treatment of erectile dysfunction. However, this phenomenon was not directly associated with free radical scavenging activity (Lines and Ono, 2006). In any case, the addition of onion or onion products to foodstuff also enriches its health beneficial polyphenols.

**ABSORPTION METABOLISM AND ELIMINATION**

There are several factors affecting flavonoid absorption, like the presence or absence of glycosylation on hydroxyl groups, the position of glycosylation, the quality of sugar moiety attached, plant/food matrix, and interactions with proteins, micelles, and emulsifiers (Piskula, 2000; Lesser et al., 2004; Cermak et al., 2003).

Hollman et al. (1997) reported that the bioavailability of quercetin from apples and of pure quercetin rutinoside was 30% of that from onions. Maximum plasma levels of quercetin (Q) were <0.7 h after ingestion of onions (225 ± 43 µmol = 68 ± 13 mg Q) (Table 2), 2.5 h after ingestion of apples supplied as applesauce plus apple peel (325±7 µmol Q) and 9 h after ingestion of rutinoside in a capsule (331 µmol Q-3-O-β-rutinoside). Apples contain a variety of quercetin glycosides: galactosides, arabinosides, rhamnosides, xylosides, and glucosides—resulting in an intermediate absorption rate (compared with onion and Q rutinoside). On the other hand the food matrix could also have contributed to the differences in the absorption rates (Goldberg et al., 2003).

After ingestion of 311 µmol quercetin–4′-glucoside the peak concentration of quercetin in plasma ($C_{\text{max}} = 3.5 ± 0.6 \, \mu M$) was reached at $T_{\text{max}} < 0.5 \, h$ which is a time interval similar to that for D-glucose (Hollman and Katan, 1999). In contrast, the maximum quercetin plasma concentration ($C_{\text{max}} = 0.18 ± 0.4 \, \mu M$), after ingestion of the same molar amount (311 µmol) of quercetin-3-rutinoside was reached at $T_{\text{max}} = 6.0 ± 1.2 \, h$. The results were confirmed by Graefe et al. (2001) who compared the influence of the sugar moiety or food matrix on bioavailability and pharmacokinetics of quercetin and in humans. Based on these findings the authors speculated that quercetin-4′-glucoside could be absorbed from the small intestine, while quercetin-3-rutinoside from the colon, and even that to a lesser extent. The lower absorption in the colon probably owes to microbial degradation, as discussed below in the Colon section.

A similar experiment was conducted by Morand and coworkers (2000) on rats, when they also studied the effect of the quality of the sugar on the absorption of the glycosides supplying
black or green tea did not affect the plasma antioxidant activity sumed with or without milk. Similarly, the addition of milk to (quercetin and kaempferol) absorption when black tea was con-
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habit flavonoid absorption as they bind polyphenols effectively. However, Hollman et al. (2001) found no change in flavonol (quercetin and kaempferol) absorption when black tea was consumed with or without milk. Similarly, the addition of milk to black or green tea did not affect the plasma antioxidant activity (Leenen et al., 2000).

<table>
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<th>Type of processing</th>
<th>Dose of onion</th>
<th>Supplemented with</th>
<th>Q amount supplied</th>
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</tr>
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<tbody>
<tr>
<td>Janssen et al., 1998</td>
<td>Microwaved</td>
<td>220 g</td>
<td>400 g bouillon</td>
<td>377 μ mol</td>
<td>1.5 μ mol/L (mean level)</td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>800 g complex meal</td>
<td>288 μ mol</td>
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</tr>
<tr>
<td>Hollman et al., 1999b</td>
<td>Fried</td>
<td>150 g</td>
<td>–</td>
<td>288 μ mol</td>
<td>0.63 μ mol/L (peak after 2.9 h)</td>
</tr>
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<td>Hollman et al., 1997</td>
<td>Fried</td>
<td>–</td>
<td>Breakfast</td>
<td>225 μ mol</td>
<td>0.74 μ mol/L (peak after 0.7 h)</td>
</tr>
<tr>
<td>Hollman et al., 1996</td>
<td>Fried with margarine, ketchup, Italian herbs</td>
<td>to 215 g raw onion</td>
<td>Breakfast low in proteins</td>
<td>212 μ mol</td>
<td>0.65 μ mol/L (peak after 2.9 h)</td>
</tr>
<tr>
<td>McAnlis et al., 1999</td>
<td>Fried</td>
<td>225 g</td>
<td>–</td>
<td>167 μ mol</td>
<td>0.82 μ mol/L (peak after 2h)</td>
</tr>
<tr>
<td>Day et al., 2001</td>
<td>Fried with butter</td>
<td>200 g cooked weight</td>
<td>Bread and coffee</td>
<td>262 μ mol</td>
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</tr>
<tr>
<td>Noroozi et al., 2000</td>
<td>Fried in olive oil</td>
<td>400 g onion</td>
<td>Meals and tea</td>
<td>189 μ mol/d; for 14 days</td>
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Human studies with onion supplementation as a source of quercetin (Q)

The oral cavity is the first section of the alimentary tract, where the digestion of polysaccharides (by α-amylase) and dietary lipids (by lingual lipase) starts. The food is masticated and mixed with saliva to facilitate swallowing (Johnson, 1991; DeSesso and Jacobson, 2001). Proline-rich proteins in saliva have strong affinity for polyphenols (e.g. catechins), resulting in their complexation and development of astringent response in the palate (Haslam et al., 1999).

The hydrolysis of flavonoid glycosides could be catalyzed by human enzymes in the mouth or by those of microbial origin. Hirota et al. (2001) reported that the appearance of free quercetin in the human saliva after consumption of onion soup results from the glucosidase activity coming from detached oral cavity epithelial cells. Also, after incubation of quercetin-4′-glucoside with human saliva, free quercetin appeared within minutes but not when rutin or quercerin were treated the same way. The appearance of free quercetin in the oral cavity can contribute to the prevention of oral cancer since it effectively inhibits proliferation of human oral squamous carcinoma SCC-9 cells (Walle et al., 2005; Browning et al., 2005). Phenolics can also undergo oxidation in the mouth, reported subsequent decrease of free quercetin in the saliva was attributed to its oxidation by peroxidase, therefore it was suggested that quercetin can donate electrons to peroxidase in the saliva in the oral cavity to scavenger H₂O₂ (Hirota et al., 2001; Takahama et al., 2002; Stahl et al., 2002).

The ingested material is transferred from the mouth to the stomach through the pharynx and esophagus. In the stomach, the masticated food is mixed with secreted enzymes to form a chyme (DeSesso and Jacobson, 2001). The non-enzymatic deglycosylation of flavonoids, such as gastric acid hydrolysis was not found (Gee et al., 1998).

Crespy and co-workers (2002) reported a rapid absorption of quercetin aglycone from rat stomach after its in situ absorption and metabolism of onion flavonoids

Table 2

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administered (15 µmol/L for 30 min) and recovery in bile 20 min following administration at concentration level of ~4 µmol/L. Related flavonols, rutin and quercetin-3-O-glucoside, were neither deglycosylated nor absorbed in the stomach. The same phenomena were demonstrated earlier on isoflavones. Piskula et al. (1999) have shown that daidzein and genistein but not their glucuronides were absorbed from the rat stomach.

In contrast, partial flavonoid deglycosylation was reported to occur in the rat stomach after flavonoid glycosides (of quercetin, kaempferol,isorhamnetin, apigenin, luteolin, and chrysoeriol) were administered in an aqueous suspension, extracted from parsley. The glycosides could have been hydrolyzed by β-glucosidases of microbes colonizing the rat stomach. Some flavonoid derivatives were also detected in the stomach wall and reported to be glycosides (Pforte et al., 1999). As these compounds were identified using UV spectra and comparison of retention times of standards, it can not be ruled out, that the putative glycosides were glucuronides. Indeed, it was shown that gastric mucosa possess uridine 5′-diphosphate glucuronosyltransferase activity capable for quercetin glucuronides formation and a number of quercetin metabolites were found in stomach tissues (Murota and Terao, 2005; Graf et al., 2006).

Small Intestine

The stomach content is emptied into the small intestine, divided into three segments: duodenum, jejunum, and ileum. The intestinal lumen can be considered as the continuation of the external environment, therefore its epithelium functions as a crucial barrier; the substances absorbed from the lumen must first cross the epithelium to reach systemic circulation. Apart from the regulation of absorptive and secretory processes, the epithelium can also modify the substances traversing it (Johnson, 1991). The chief organ in phenol metabolism being the liver was questioned by Powell et al. already in 1974 by showing that the intestinal barrier was able to detoxicate phenol and that phenol entered the portal blood in conjugated form (Powell et al., 1974).

Deglycosylation has been shown as the first step of metabolism of some flavonoid glucosides occurring in the small intestinal lumen (Day et al., 2000; Nemeth et al., 2003). The epithelial cells of the gastrointestinal tract are the only cells of the body in contact with flavonoid glucosides; the other cells are reached only by flavonoid metabolites and degradation products (Depeint et al., 2002).

Flavonoids passing into the small intestine as glycosides can undergo either luminal deglycosylation catalyzed by membrane-bound enzymes (Day et al., 2000; Depeint et al., 2002) or enter the enterocytes in the form of glycosides requiring active transport (Hollman et al., 1995; Arts et al., 2002) followed by intracellular hydrolysis by e.g. broad-specificity cytosolic β-glucosidase (EC 3.2.1.21) (Day et al., 1998). Flavonoids liberated in the lumen can pass into enterocytes via passive diffusion where they are subject to Phase II metabolism.

Quercetin glucuronides were shown to interact with the sodium-dependent glucose transport receptors in the rat mucosal epithelium. In an experiment with everted rings and sacs of rat, quercetin-3-glucoside was found to be absorbed via stimulated counter-transport of the pre-loaded sugars (Gee et al., 1998). As for the ratio of quercetin absorbed, Crespy and co-workers (1999) showed a rapid and extensive transfer of quercetin into intestinal wall in rats after in situ perfusion of jejunum and ileum (Crespy et al., 1999). Although the transfer of quercetin aglycone accounted for 66.7% of the amount perfused, this was not the case of rutin (Crespy et al., 1999).

Quercetin aglycone was significantly absorbed and metabolized by the human intestinal cell line Caco-2 whereas its glucosides (3′-, 4′-, 3,4′-) were poorly absorbed. Among the glucosides tested, quercetin-4′-glucoside was absorbed relatively more efficiently than the others owing to its higher lipophilicity (Murota et al., 2000). The transport across the intestinal enterocytes depends on the quality of the flavonoid aglycone moiety and the nature and position of the attached sugar. The mechanism of absorption of quercetin-4′-glucoside was shown to involve both interaction with the sodium-dependent glucose transporter (SGLT1) and luminal hydrolysis by LPH, whereas quercetin-3-glucoside was absorbed only following deglycosylation by LPH (Day et al., 2003). Human lactase-phlorizin hydrolase (LPH; EC 3.2.1.23/62), localized to the apical membrane of the enterocytes, has been reported to hydrolyse a range of flavonoid glucosides (Day et al., 2000). The fact that Caco-2 cells have significantly lower LPH activity (Sun et al., 2002) could have contributed to the low absorption of quercetin glucosides.

Also in the Caco-2 cells model it was demonstrated that there is a mechanism removing 4′-O-β-quercetin glucoside from enterocytes back to the intestine lumen with the involvement of multidrug resistance-associated protein (MRP2) from ABC (ATP-Binding Cassette) transporters family (Walgren et al., 2000) and this was also confirmed in the case of (-)-epicatechin gallate (Vaidyanathan and Walle, 2003).

β-Glucosidase activity of rat jejunum was the highest compared to the duodenum and the ileum and the hydrolytic activity toward quercetin-4′-glucoside was about twice as high as that toward quercetin-7-glucoside or quercetin-3-glucoside (Ioku et al., 1998).

After passage into enterocytes, flavonoid glucosides are susceptible to hydrolysis by intracellular β-glucosidases, e.g. broad-specificity cytosolic β-glucosidase (Berrin et al., 2002). Day and co-workers have shown that quercetin-4′-glucoside, naringenin-7-glucoside, apigenin-7-glucoside, genistein-7-glucoside, and daidzein-7-glucoside were rapidly deglycosylated by human small intestine and liver cell-free extracts, while quercetin-3,4′-glucoside, quercetin-3-glucoside, kaempferol-3-glucoside, quercetin-3-rhamnoglucoside and naringenin-7-rhamnoglucoside were not hydrolyzed (Day et al., 1998). Similarly, the need for deglycosylation prior to absorption was reported for isoflavone glucosides (Setchell et al., 2002; Wilkinson et al., 2003). After absorption, polyphenols are conjugated to glucuronide, sulphate, and/or methyl
groups in the intestinal mucosa and inner tissues (Scalbert et al., 2002). Xenobiotics are detoxified mainly in the liver but apart from it, Phase II reactions—conjugation reactions such as glucuronidation after deglycosylation, and methylation can occur in the jejunal and the ileal part of the small intestine (Crespy et al., 1999; Manach et al., 1998; Spencer et al., 1999; Kuhnle et al., 2000).

UDP-glucuronyltransferases (UGTs; EC 2.4.1.17) are membrane-bound enzymes, situated in the endoplasmic reticulum, expressed primarily in the liver but also present in the intestinal epithelium, stomach mucosa, kidney, brain, and skin (Murota and Terao, 2005; Radominska-Pandya et al., 1998). For comparison, glucuronidation in microsomes from rabbit small intestinal mucosa was 70–100% of hepatic activities, whereas that in the rat only 5–15% (Vargas and Franklin, 1997). The major sites for quercetin and luteolin glucuronidation were the 7-, 3-, 3′-, or 4′-hydroxyl moieties using microsomal incubations of the substrates. However, the pattern was dependent on the isoenzymes of UGTs involved. In the human liver, especially UGT1A9 and, in the intestine, UGT1A1 and UGT1A8 are involved in the glucuronidation of quercetin and luteolin (Boersma et al., 2002). Glucuronidation, the first detoxification step of (-)-epicatechin, occurs in the intestinal mucosa of rats. (-)-Epicatechin, entirely in the form of glucuronides, is transported to the liver with portal blood where they are sulfated (Piskula and Terao, 1998).

Major products of rat small intestinal cell metabolism ex vivo are quercetin-3- and quercetin-7-glucuronides (Gee et al., 2000). It has also been shown in animal models that after the metabolism of quercetin, epithelial cells are capable of resecreting glucuronides from their apical surfaces back to the intestinal lumen (Crespy et al., 2001). Quercetin-3- and quercetin-7-glucuronides were shown to be further processed using the HepG2 hepatic cell model. One pathway seems to be the methylation of the catechol moiety of both quercetin glucuronides resulting in 3′-methylquercetin- and 4′-methylquercetin-glucuronides. The other way is deglucuronidation with subsequent sulfation in 3′-position (O’Leary et al., 2003).

Catechol O-methyltransferases (COMT; EC 2.1.1.3) transfer a methyl group from S-adenosyl-L-methionine to the catechol substrate in the presence of magnesium. Kuhnle and co-workers demonstrated the activity of COMTs in the metabolism of catechin and epicatechin using a rat small intestine perfusion model (Kuhnle et al., 2000). These flavanols were glucuronidated (~45% of total flavanols identified), methylated to 3′-O-methyl- and 4′-O-methyl-compounds (~30%), and O-methyl-glucuronidated (~20% of total flavanols identified) during transfer across the jejunal enterocytes to the serosal side.

**Colon**

Continuing absorption of water, electrolytes, and nutrients occurs in this part of the gastrointestinal tract. The colon is heavily colonized by microorganisms (~10^{12}/mL) with a strong catalytic and hydrolytic potential (Scalbert and Williamson, 2000) against compounds of exogenous (dietary) and endogenous origin. Microbiota also function as a conservator of nitrogen that would otherwise be excreted as urea. In exchange, the flora competes directly with the host tissues for nutrients ingested in the diet (Savage, 1986; Cermak et al., 2006).

Flavonoids neither absorbed in the stomach nor in the small intestine are propelled to the colon. Reaching the colon, they are subject to deglycosylation (Price and Rhodes, 1997) and deconjugation by colonic bacteria, and are cleaved giving rise to ring fission products.

Prior to absorption, the rutin must undergo deglycosylation, what cannot be achieved by the small intestinal enzymatic system, and is possible by colon microflora. As this flora cleaves the aglycone as well, the absorption of rutin is less efficient compared to that of quercetin. Kim and co-workers reported on flavonoid glycosides metabolized to phenolic acids via aglycones by human intestinal microflora (Kim et al., 1998). Rutin, hesperidin, naringin, and poncirin were transformed to their aglycones by the bacteria producing a-rhamnosidase and β-glucosidase or endo-β-glucosidase. Baicalin, puerrarin, and daidzin were transformed to their aglycones by the bacteria producing β-glucuronidase, C-glycosidase, and β-glucosidase, respectively.

The type of ring fission depends on the type of flavonoids. Flavonols are degraded to phenylacetic acids and phenylpropionic acids. Flavones and flavanones are cleaved to phenylpropionic acids. Ring fission of catechins gives rise to valerolactones (a benzene ring with a side chain of 5 C-atoms), and phenylpropionic acids which are finally oxidized (beta-oxidation) to benzoic acids (Hollman and Katan, 1998; Aura et al., 2002). These low molecular microbial metabolites of flavonoids exhibit several important biological activities. Anti-platelet activity and cytotoxicity for tumor cell lines were more effective than those of the parental compounds. 4-Dihydroxyphenylacetic acid and 4-hydroxy-phenylacetic acid were more effective than rutin and quercetin on anti-platelet aggregation activity. 2,4,6-Trihydroxybenzaldehyde and quercetin were more effective than rutin on the cytotoxicity (Kim et al., 1998). *Eubacterium ramulus* was identified in human large bowel to cleave quercetin-3-glucoside resulting in phloroglucinol as intermediate, 3,4-dihydroxyphenylacetic acid, acetate, butyrate, and CO2. However, *E. ramulus* was found hardly capable of degrading the aglycone quercetin, or further degrading 3,4-dihydroxyphenylacetic acid. The number of these bacteria able to use quercetin-3-glucoside was estimated to be 10^7–10^9/g of fecal dry mass (Schneider et al., 1999) and the consumption of flavonoids (quercetin, rutin) was reported to increase the relative proportion of *E. ramulus* from 0.2% (on day 1) to 6.9% (on day 8) of the total flora after supplementation (Simmering et al., 2002).

The arising cleavage products are absorbed from the colon or further metabolized. 3,4-Dihydroxyphenylpropionic acid is degraded in the colon to phenylpropionic, 3-hydroxypropionic, and 4-hydroxypropionic acid, which are further metabolized by the liver giving rise to hippuric, 3-hydroxyhippuric, and 4-hydroxyhippuric acids (Rechner et al., 2002).
Liver

Compounds absorbed from intestines enter the liver via the portal vein. Once in the liver, the absorbed substances are removed from the blood by the liver parenchymal cells and biotransformed (DeSesso and Jacobson, 2001).

The metabolism of xenobiotics is a process in which the compound first undergoes a reaction of oxidation, reduction, or hydrolysis (Phase I), which introduces or discloses within its structure a functional group (e.g. –OH, –NH2) suitable for linkage with glucuronic or sulfuric acid in the second step called conjugation (Phase II). Compounds with a suitable group can undergo conjugation directly. Xenobiotics can covalently bind to biological molecules as blood or cellular (glyco)proteins, forming xenobiotic-macromolecule adducts with immunological properties (Testa, 1995).

Phase I reactions take place in the smooth endoplasmatic reticulum of hepatocytes. Many of the oxidative reactions are catalyzed by cytochrome P450 systems. The Phase I biotransformation reactions of flavonoids introduce or expose polar groups. Hydroxylation of flavonols and flavones occurs, unless there are two or more hydroxyl groups on the B-ring (Williamson, 2000). Kaempferol, having a single (4′)-hydroxy group on B-ring, was extensively hydroxylated to quercetin by rat liver microsomal monooxygenases (Nielson et al., 1997). Exposure of hydroxyl groups can occur when P450 enzymes demethylate the methyl group in the 4′ position (Williamson et al., 2000). Conjugation of the polar hydroxy groups with glucuronic acid, sulfuric acid, glycine (Hollman and Katan, 1998), or possibly glutathione (Spencer et al., 2003) are Phase II reactions. The arising water-soluble conjugates can be excreted into the urine. Moreover, their molecular weight increases, which promotes secretion into the bile. Finally, O-methylation plays an important role in the inactivation of B-ring catechol moiety, the two ortho-hydroxyl groups in some flavonoids (i.e. quercetin, catechin) (Griffiths, 1983).

Enzymes of the Phase II reactions are transferases. Glucuronidation is catalyzed by glucuronosyltransferases (EC 2.4.1.17), yielding O- and N-glucuronides. The coenzyme involved is the “active glucuronate”, the uridine diphosphate derivative of glucuronic acid (UDP-GlcUA). Similarly, sulfate esters are synthesized with the help of the “active sulfate”, phosphoadenosinephosphosulfate (PAPS), catalyzed by phenolsulfo-transferase (PST) (EC 2.8.2.1).

Conjugates are eliminated either from the liver with bile—the gallbladder squirts the bile into duodenum, or renally, i.e., via the urine. One of the factors determining whether a compound/conjugate will undergo biliary excretion is minimum molecular weight. The molecular weight threshold, depending on particular species, in humans was reported to be around 500–600 Da (Hackett, 1986).

Human small intestinal microsomes were shown to hydrolyze quercetin glucuronides in vitro. However, this deconjugating activity was related to microsomal β-glucuronidase and thus deglucuronidation can occur provided the flavonoid conjugate reaches the same cellular compartment (O’Leary et al., 2001). As yet no transport of glucuronides has been shown across the cell wall which would make them accessible for intracellular β-glucuronidases. Neither has deglucuronidation been reported in the gastrointestinal lumen due to other than microbial activity. However, deglucuronidation of flavonoids can occur during inflammation. β-Glucuronidase released from stimulated neutrophils or certain injured cells can hydrolyze luteolin monoglucuronide to free luteolin possessing anti-inflammatory activities (Shimoi et al., 2000; Shimoi et al., 2001).

Sakamoto and co-workers reported high microbial β-glucuronidase activity in rat cecum content (Sakamoto et al., 2002). In rats, the cecum, which is a primary site of microbial digestion, accounts for approximately 26% of the length of the colon, whereas only for 5% of the human large intestine (DeSesso and Jacobson, 2001). Deconjugation of flavonoid metabolites originating from biliary clearance is thus possible to occur—although to a lesser extent—in humans as well. Moreover, flavonoid glucuronide and/or sulfate metabolites secreted with bile or in any other way into the small intestine could be hydrolyzed and the liberated aglycones would then pass into enteroocytes passively, reabsorbed again, and metabolized—forming an enterohepatic cycling (Crespy et al., 1999).

Urine

Water and water-soluble substances like salts, metabolic wastes, and foreign substances that have to be excreted from the body are released into the urine in the kidneys. Several papers report elimination of flavonoid metabolites by the urinary pathway (Nielsen et al., 1997; Zhu et al., 1994; Clarke et al., 2002; Nielsen et al., 2002; Rasmussen and Breinholt, 2003).

After oral administration, the quercetin is absorbed from the intestine, undergoes detoxification, and is excreted in the urine in the form of glucuronide/sulfate. Interestingly, after a large-dose intraperitoneal administration of quercetin to hamsters (165 μmol/kg), a major portion of quercetin was excreted with the urine in a methylated form. In a first 24 h urinary diethyl ether extract, 97% of quercetin was 3′-methylated and 2% non-methylated. Moreover, 34% of the total urinary flavonoid content was only O-methylated without sulfation or glucuronidation. The rapid O-methylation of the catechol moieties is a suggested reason for the previously observed lack of carcinogenicity of this quercetin metabolite despite free quercetin mutagenic activity in bacterial test systems (Zhu et al., 1994). In urine, quercetin-4′-O-methylated, tamarixetin was found at concentrations comparable to that of quercetin (Manach et al., 1996).

Plasma

Polyphenols in plasma are in the conjugated form; reactions leading to conjugate formation facilitate the excretion of polyphenols and decrease their potential toxicity (Scalbert et al.,
supplements are summarized in Table 2. In human plasma 1.5 hr post meal (Mullen et al., 2002), quercetin variations were noted. After consumption of fried onions five different glucuronides of quercetin were detected in human plasma samples by means of HPLC-UV-MS/MS. Selective determination of the target compounds was achieved by simultaneous UV (254 nm) and MS/MS detection with selected reaction monitoring experiments using positive mode electrospray ionization. After the administration of synthesized [2-14C]quercetin-4″-glucoside to rats followed by analysis with HPLC-radiocounting and tandem mass spectrometry, eighteen quercetin metabolites were detected in rat plasma with varying degrees of glucuronidation, methylation, and/or sulfation (Moon et al., 2002).

The results of some human intervention studies with onion supplements are summarized in Table 2. In human plasma 1.5 hr after onion consumption Day and co-workers have detected Q-3-glucuronide, 3′-methyl-Q-3-glucuronide and Q-3′-sulphate as major conjugates (Day et al., 2001). A further quercetin conjugate found in human plasma was characterized as quercetin-4″-glucuronide (Moon et al., 2001). Moon and co-workers (2000) found free quercetin only in glucuronidase-sulfatase-treated plasma suggesting that all quercetin in human plasma circulated in the form of conjugates. This was observed after 1-wk supplementation with onion (223.67–309.70 µmol Q/day), where the concentration of quercetin in plasma increased from 0.04 ± 0.04 µmol/L to 0.63 ± 0.72 µmol/L.

Quercetin-3-glucuronide was shown as an antioxidative metabolite accumulating in rat plasma after oral administration of quercetin (827.2 µmol/kg b.w.) with a substantial antioxidative effect on copper ion-induced oxidation of human plasma LDL as well as 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity (Moon et al., 2001). Quercetin metabolites have a lower but still significant inhibitory effect on lipid peroxidation and other biological activities as compared to the aglycone and these properties depend on the conjugation pattern (Shirai et al., 2001; Janisch et al., 2004; Williamson et al., 2005).

When Hollman and co-workers (1996) studied the time course of the plasma quercetin concentration in humans supplemented with 150 g fried onions (∼212 µmol Q), the maximum plasma levels of 650 mmol/L Q in hydrolyzed plasma were reached after 2.9 h with a half-life of absorption of 0.87 h and a half-life of elimination of 17 h. It has to be mentioned here that the authors did not measure the methylated quercetin, one of the metabolites of quercetin.

Onion consumption raised the mean plasma quercetin concentrations to 1.5 µmol/L when volunteers were offered 220 g onions/day (microwave-cooked yellow onion added to 400 g bouillon) providing ∼377 µmol Q/day). This in vivo concentration did not have anti-aggregatory effects (Janssen et al., 1998).

Manach and co-workers (1998) determined the plasma concentration of quercetin in 10 individuals 2 h before and 3, 7, and 20 h after consumption of a complex meal rich in plant products containing ∼288 µmol of quercetin (amount similar to that in (Hollman et al., 1995)). Again, quercetin was found in plasma in conjugated forms only. The rapid absorption of quercetin indicates that it probably takes place in the proximal part of the intestine (Manach et al., 1998; Hollman and Katan, 1997).

Major quercetin metabolites (91.5%) in plasma of rats supplemented with a diet containing 0.2% quercetin were glucurono-sulf conjugates of both isorhamnetin and quercetin. Glucuronides of quercetin and its methylated forms were minor circulating quercetin metabolites (8.5%) (Morand et al., 1998). Another study showed isorhamnetin and quercetin metabolites in molar ratio of about 5 in plasma of rats fed 0.25% quercetin diet for 14 days (101 ± 13 µmol/L and 19 ± 3 µmol/L, resp.) (Manach et al., 1996). When rats were administered synthetic [2-14C]quercetin-4″-glucoside, the circulating metabolites were glucuronides, methylates, and/or sulfates of (methyl)quercetin, quercetin aglycone could not be detected (Mullen et al., 2002).

Due to aromatic nucleus and hydroxyl substituents, flavonoids have a great affinity for proteins, particularly for albumin. The binding of quercetin to human albumin was 70–80% (Lembre et al., 1994). Manach and co-workers (1995) have shown quercetin bound to albumin by demonstrating the bathochromic effect—a shift of its maximal absorption to longer wavelength (+33 nm) which was increased in parallel to the albumin/flavonoid molar ratio. The presence of the unsaturated C2-C3 bond of the C-ring of flavonoids is crucial for this effect. The magnitude of the effect is reinforced by the presence of hydroxyl groups on the B-ring. Circulating metabolites of quercetin retained the property to strongly bind to albumin, with a bathochromic effect comparable to that of native quercetin (Manach et al., 1996; Manach et al., 1995; Kaldis et al., 2005; Mishra et al., 2005). Albumin-bound quercetin conjugates retained the antioxidative property with the following order of efficacy: quercetin-3′-sulfate > quercetin-7-glucuronide > quercetin-3-glucuronide > quercetin-4″-glucuronide = isorhamnetin-3-glucuronide (Janisch et al., 2004).
after orally administered [2-14C]quercetin-4′-glucoside to rats, almost 94% of the recovered radioactivity was still in the pool of the stomach, and the small and large intestines with their contents (denoted as intestine pool). To a small extent, radioactivity was recovered in plasma (2.8%), liver (1.2%), muscle tissues (1.4%), and kidneys (0.8%). The major metabolites in the intestine pool were quercetin-3-glucuronide, quercetin glucuronide sulfate, methyl-quercetin glucuronide, probably originating from biliary clearance, and quercetin. The major metabolite detected in the kidneys was methyl-quercetin glucuronide (Mullen et al., 2002). Direct evidence of quercetin distribution was presented in rats and pigs after feeding them with large dose of 500–800 mg quercetin/(kg b.w. · day). In the 11 weeks study in rats the highest concentration of quercetin and its metabolites was found in the lung, testes, and kidney while in the 3-days study in pigs high concentrations of quercetin metabolites did not appear in tissues other than liver and kidney (de Boer et al., 2005). An explanation of the high concentration of quercetin metabolites in the rat lung tissue was proposed by Murota and Terao (2005) whose recent finding showing the presence of quercetin in the rat thoracic lymph may provide a potential mechanism of this phenomenon.

CONCLUSION

Flavonoids are the main factors in the hypothesis that the consumption of a diet rich in vegetables and fruits may be protective for human health. In particular, when the etiology of coronary heart disease and certain cancers was associated with imbalance in the redox system of an organism, the antioxidative properties of flavonoids demonstrated in vitro become a key issue. Moreover, intensive research on a wide array of the biological activities of flavonoids conducted in in vitro tests with pure aglycones supported this hypothesis.

Out of different dietary sources of flavonoids, onions are amongst the richest ones with a substantial load of quercetin derivatives, mainly glucosides. Processing may decrease the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit. On the other hand it can increase the extractability from the matrix resulting in a higher apparent age from the vegetable/fruit. On the other hand it can increase the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit. On the other hand it can increase the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit. On the other hand it can increase the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit. On the other hand it can increase the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit. On the other hand it can increase the flavonoid content as a consequence of preparation and/or leakage from the vegetable/fruit.

As presented above, flavonoids undergo extensive metabolism after ingestion resulting in their altered structure. They were found in systemic circulation in the form of (methylated)glucuronide and/or sulfate conjugates, whereby the hydroxyl groups are not available. Therefore, most of the effects shown in in vitro experiments with aglycones can not be directly extrapolated to in vivo systems apart from the digestive tract where the possibility of direct interactions is obvious. This also concerns the antioxidant properties of flavonoids, which are significantly reduced or even lost. However, it does not mean that they simultaneously lose their positive impact on consumer health. Even after being metabolized they may act locally or indirectly influence redox balance by inducing antioxidative enzymes, detoxifying enzymes, or compounds which may be involved in sustaining homeostasis.

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