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Bioavailability of Quercetin in Humans with a Focus on Interindividual Variation

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Abstract: After consumption of plant-derived foods or beverages, dietary polyphenols such as quercetin are absorbed in the small intestine and metabolized by the body, or they are subject to catabolism by the gut microbiota followed by absorption of the resulting products by the colon. The resulting compounds are bioavailable, circulate in the blood as conjugates with glucuronide, methyl, or sulfate groups attached, and they are eventually excreted in the urine. In this review, the various conjugates from different intervention studies are summarized and discussed. In addition, the substantial variation between different individuals in the measured quercetin bioavailability parameters is assessed in detail by examining published human intervention studies where sources of quercetin have been consumed in the form of food, beverages, or supplements. It is apparent that most reported studies have examined quercetin and/or metabolites in urine and plasma from a relatively small number of volunteers. Despite this limitation, it is evident that there is less interindividual variation in metabolites which are derived from absorption in the small intestine compared to catabolites derived from the action of microbiota in the colon. There is also some evidence that a high absorber of intact quercetin conjugates could be a low absorber of microbiota-catalyzed phenolics, and vice versa. From the studies reported so far, the reasons or causes of the interindividual differences are not clear, but, based on the known metabolic pathways, it is predicted that dietary history, genetic polymorphisms, and variations in gut microbiota metabolism would play significant roles. In conclusion, quercetin bioavailability is subject to substantial variation between individuals, and further work is required to establish if this contributes to interindividual differences in biological responses.

Keywords: ADME, interindividual, metabolism, quercetin

Introduction

Quercetin is a polyphenolic compound of the flavonoid class (subclass flavonol) and is regularly consumed in the diet. Rich sources are kale, onion, various berries, apples, black tea, and red grapes (Perez-Jimenez et al., 2011; Perez-Jimenez, Neveu, Vos, & Scalbert, 2010), and also certain commercially available food supplements (Serra et al., 2012). Quercetin safety has been critically reviewed (Harwood et al., 2007; Okamoto, 2005) and high-purity quercetin was given *Generally Recognized As Safe* (GRAS) status in 2010 (FDA, 2010). Over the last few decades, many biological studies on quercetin have been published, reporting a wide range of biological effects *in vitro* and *in vivo* including anti-inflammatory and neuroprotective activities (Boots, Haenen, & Bast, 2008; Dajas, 2012; Gibellini et al., 2011; Harwood et al., 2007; Kawabata, Mukai, & Ishisaka, 2015; Kerimi & Williamson, 2017; Okamoto, 2005; Russo, Spagnuolo, Tedesco, Bilotto, & Russo, 2012).

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Quercetin Metabolism after Consumption in Humans

The pathways of quercetin absorption in the gastrointestinal tract of humans and other mammals are quite well understood (Crozier, Del Rio, & Clifford, 2010; Del Rio et al., 2013). Only a minor proportion of quercetin is absorbed in the stomach (Crespy et al., 2002), and the primary site of absorption is the small intestine (Ader, Wessmann, & Wolffram, 2000; Erlund et al., 2000; Graefe, Derendorf, & Veit, 1999). In plants, quercetin is found attached to sugars, since the aglycone is highly reactive and relatively insoluble in aqueous media (Azuma, Ippoushi, Ito, Higashio, & Terao, 2002; Smith, Kavuru, Wojtas, Zaworotko, & Shytle, 2011). The absorbed "unit" of quercetin is the aglycone itself, and before absorption into the enterocyte, any attached chemical groups such as sugars must be removed. This is achieved by brush border enzymes such as lactase phloridzin hydrolase (LPH), which remove glucose groups from flavonols (Day et al.,

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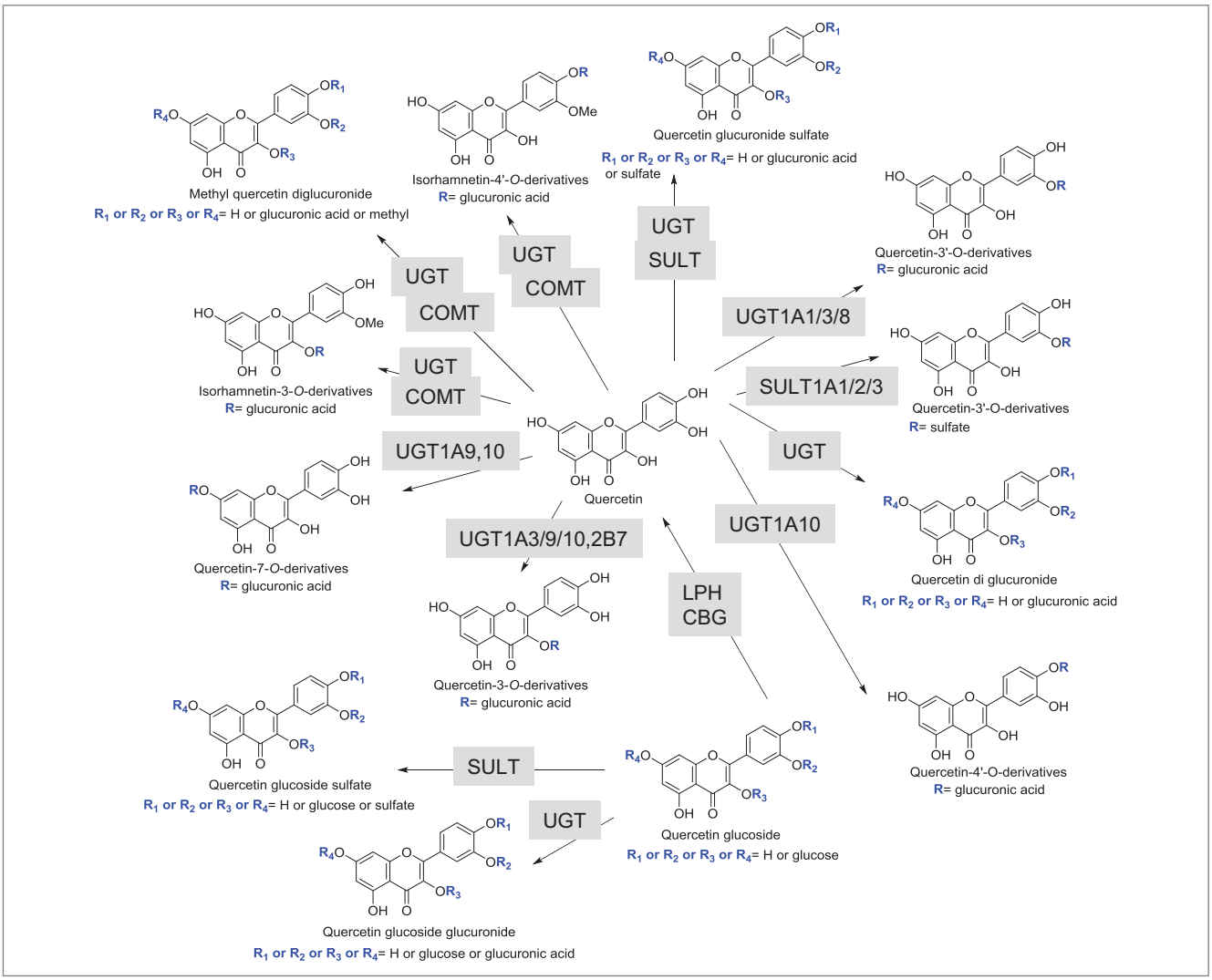

Figure 1–Metabolism of quercetin to form conjugates. Where information on the involvement of a specific enzyme is published (Boersma et al., 2002), then only the most active isoforms are indicated in the figure. When the specific form is unknown, then the general notation of UGT (UDP-glucuronosyltransferase) or SULT (sulfotransferase) is used. For COMT (catechol-O-methyl transferase), LPH (lactase phloridzin hydrolase), and CBG (cytosolic β-glucosidase), only one form of the enzyme exists in humans. Information for this figure is a compilation from several publications including (Day et al., 2001; Day et al., 2000; Del Rio et al., 2013; Govind, Suiko, Sakakibara, & Ming, 2001; Hong & Mitchell, 2004).

2000). Paradoxically, quercetin glycosides are generally more bioavailable than the aglycone since the latter is more insoluble in the lumen of the gut (Hollman, Devries, Vanleeuwen, Mengelers, & Katan, 1995; Hollman et al., 1996; Hollman et al., 1997). Since the brush border enzymes are specific for glucose, quercetin glucosides are absorbed more quickly than other types of glycosides, for example, rutin (quercetin-3-*O*-rutinoside), which can only be deglycosylated to quercetin aglycone by enzymes from the gut microbiota (Arts, Sesink, Faassen-Peters, & Hollman, 2004; Cermak, Landgraf, & Wolffram, 2003; Reinboth, Wolffram, Abraham, Ungemach, & Cermak, 2010; Russo et al., 2012). The importance of solubility is apparent from studies on the bioavailability of quercetin in pigs, rats, and humans, which can be enhanced when administered in combination with a high-fat (17%) diet (Guo et al., 2013; Lesser, Cermak, & Wolffram, 2004), alcohol (Dragoni, Gee, Bennett, Valoti, & Sgaragli, 2006), or with nondigestible oligosaccharides (Matsukawa et al., 2009). After absorption by enterocytes, quercetin is glucuronidated by UDP-glucuronosyl transferases (UGTs), sulfated by sulfotransferases (SULTs), and/or methylated by catechol-*O*-methyl transferase (COMT) present in intestinal and hepatic cells (Figure 1). These biotransformation reactions are also observed in rat or human hepatocytes *in vitro* (Vacek et al., 2012). Once absorbed, quercetin enters the bloodstream and appears as various different chemical species, including methylated forms. In plasma, 78% to 79% was estimated as conjugates of quercetin, 10% to 13% as tamarixetin (4′-*O*-methyl-quercetin), and 8.5% to 11% as isorhamnetin (3′-*O*-methyl-quercetin) conjugates (Cermak et al., 2003; Lesser et al., 2004; Reinboth et al., 2010). A significant proportion of conjugated flavonoids is excreted back into the intestinal lumen by enterocytes *via* multidrug resistance-associated protein 2 (MRP2 (ABCC2)) or breast cancer resistance protein (BCRP (ABCG2); Cermak & Wolffram, 2006). Quercetin glucuronides serve as a more stable form of quercetin for transport in the bloodstream, but they may be deconjugated, for example, in vascular smooth muscle cells (Galindo et al., 2012; Menendez et al., 2011) and at sites of inflammation (Menendez et al., 2011; Perez et al., 2014; Shimoi et al., 2001; Yoshichika Kawai, 2014). The conjugates themselves

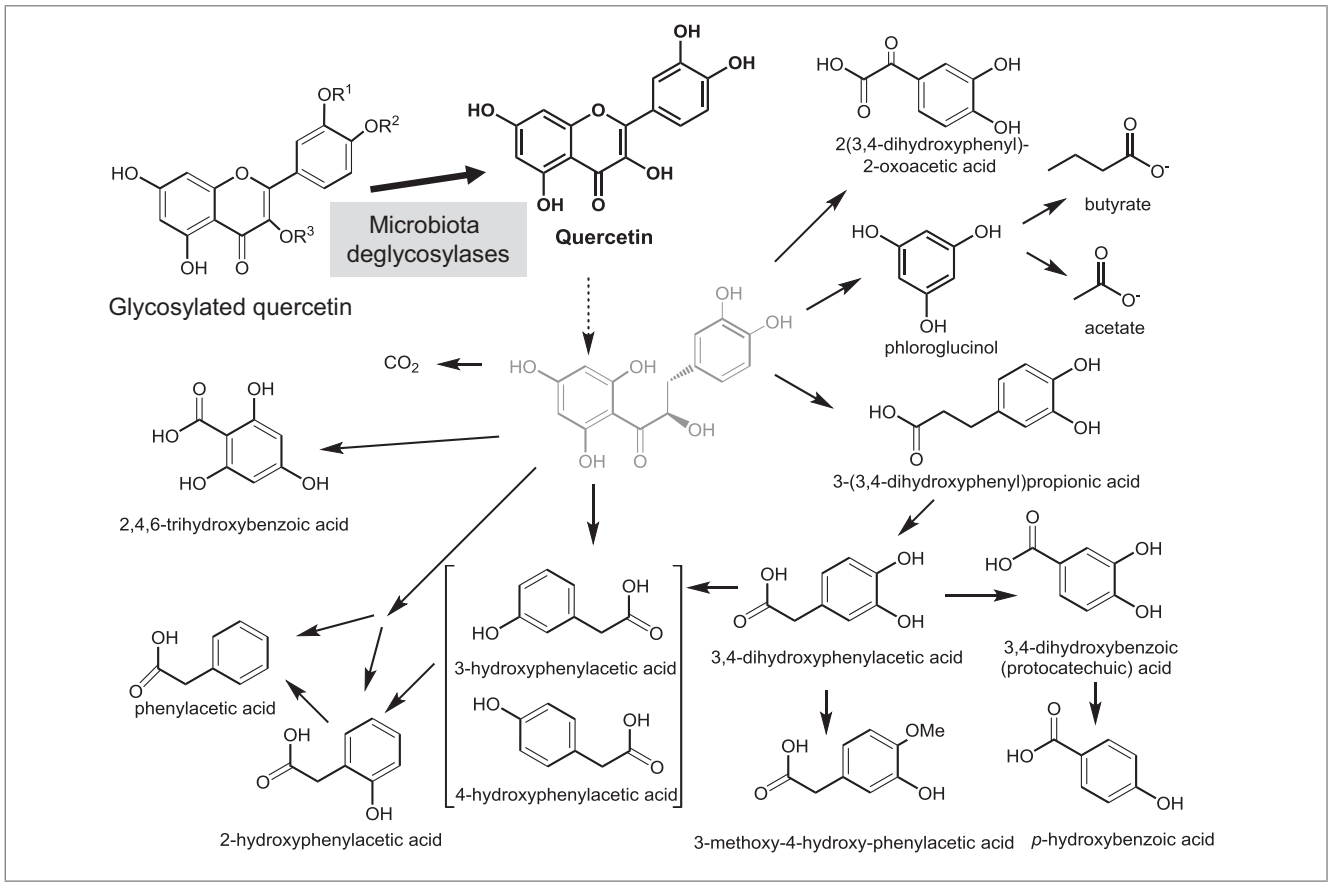

Figure 2–Schematic representation of quercetin metabolism by gut microbiota Information is taken from (Harwood et al., 2007; Lu et al., 2013; Ramesova et al., 2012; Schneider, Schwiertz, Collins, & Blaut, 1999; Serra et al., 2012; Vacek et al., 2012; Valentová et al., 2014; Walle, 2004); the speculative proposed intermediate where the C-ring is opened is shown in grey. R1, R2, and R3 represent substitution positions of sugars. The microbial conjugates from polyphenols are mostly found conjugated with sulfate, or sometimes glucuronide groups (Clifford, van der Hooft, & Crozier, 2013; Pimpao, Ventura, Ferreira, Williamson, & Santos, 2015).

generally have diminished biological activity compared to the aglycone, but there are exceptions to this, and sometimes conjugated and/or methylated metabolites display biological activity distinct from that of the parent compound (Araujo, Costa, Pazini, Valadares, & de Oliveira, 2013; Beekmann et al., 2012; Lodi et al., 2009; Tribolo et al., 2008; Williamson, Barron, Shimoi, & Terao, 2005). Quercetin derivatives, such as rutin, which are not absorbed in the small intestine, pass to the colon, where they undergo deglycosylation by α-rhamnosidases and β-glucosidases produced by the gut microbiota. The resulting aglycone is then absorbed by the colonocytes and passed into the circulation, or it is subjected to catabolic reactions to form lower-molecular-weight phenolic species, as outlined in Figure 2. Quercetin was transformed by certain strains of *Pediococcus spp.*, *Streptococcus spp.*, *Lactobacillus spp.*, *Bifidobacterium spp.*, and *Bacteroides spp.* to various phenolic (3-hydroxybenzoic, 3,4-dihydroxybenzoic, and 3,4-dihydroxyphenylacetic) acids (Cermak, Breves, Lupke, & Wolffram, 2006). Quercetin was also metabolized by porcine hindgut contents *in vitro* (Cermak et al., 2006). After quercetin *in vitro* colonic fermentation with rat feces for 48 h, the main product was protocatechuic acid with lower amounts of homovanilic, phenylacetic, and *p*-hydroxybenzoic acids (Serra et al., 2012). Similar degradation products were observed when quercetin was exposed to exhaustive electrochemical hydrolysis (Ramesova et al., 2012; Sokolova et al., 2011, 2012). Degradation of quercetin by the rat gut microbiota therefore involves C-ring fission, formation of 3-(3,4-dihydroxyphenyl)propionic acid, and subsequent transformation to 3,4-dihydroxyphenylacetic acid. Further transformation leads to protocatechuic acid and then to 4-hydroxybenzoic acid. 3,4-Dihydroxyphenylacetic acid can also be dehydroxylated to *m*- or *p*-hydroxyphenylacetic and phenylacetic acids (Figure 2; Serra et al., 2012). These compounds are further degraded into various simpler products and finally to carbon dioxide (Walle, 2004; Walle, Walle, & Halushka, 2001).

The main pathways of metabolism of quercetin depend on conjugating enzymes, most of which have known genetic polymorphisms, but are also inducible by drugs, food, and the environment. Quercetin catabolism is also affected by the microbiota composition, which is influenced by multiple factors. It is not surprising, therefore, that there is substantial interindividual variation in absorption and metabolism of quercetin between individuals. This has been observed for other groups of polyphenols. For example, the metabolism of ellagitannins in humans shows several metabolizing phenotypes, or "metabotypes" (Gonzalez-Sarrias et al., 2017). These phenotypes are determined by the concentration and activity of intestinal carriers and postabsorptive phase I and phase II metabolizing enzymes, and also by the composition and activities of the gut microbiota, many of which will be influenced by the genotype of the subject (Yousri et al., 2014). Pharmacogenomic studies have demonstrated that, for some drugs, individuals

can be categorized into poor, intermediate, or extensive absorbers or metabolizers, and dosing has to be adapted clinically (Kaddurah-Daouk, Weinshilboum, & Pharmacometabolomics Research Network, 2014). Plant food phytochemicals are absorbed and metabolized through the same polymorphic carriers and enzymatic systems as drugs, and so their pharmacokinetics are also likely to depend on the same determinants.

In this review, we have examined interindividual variation in quercetin bioavailability by systematically assessing published human studies dealing directly or indirectly with this subject. Bioavailability has several definitions, but it is generally regarded as representing the amount of a substance that reaches a given site of action. For polyphenols, this is usually considered as the amount which appears in plasma. The minimum bioavailability can also be estimated as a percentage of dose based on urinary measurement of the compound and its metabolites (Hollman & Katan, 1999; Pérez-Jiménez et al., 2010). A comparable term is ADME (absorption, metabolism, disposition, and excretion), which can be applied to polyphenols but is more often used in the pharmaceutical area (Prot et al., 2014). Here, the term bioavailability is used for convenience but is used in a relative sense so that different sources and different derivatives can be compared (Rescigno, Thakur, & Marzo, 1994; Schlemmer, 1995).

Assessment of the Literature for Studies on Quercetin Bioavailability

In order to find as many papers as possible and remove any bias, we performed a systematic search for papers on flavonol bioavailability in humans, and then further refined it by examining each paper for data on interindividual variation. The search was conducted using Web of Science and PubMed to include all original research articles written in English, published between January 1990 and March 2015, on the relationship between interindividual variation and quercetin ADME in humans. The search strategies were as follows: "(quercetin OR kaempferol) AND human AND (bioavailability OR absorption) AND (in vivo OR clinical OR intervention OR volunteer) NOT review" and 298 abstracts were retrieved. Updated searches were performed in March 2016 and July 2017 and there retrieved 20 and 25 additional abstracts, respectively. Kaempferol was originally included as it is also a flavonol, but since no relevant papers on interindividual variation in absorption were ultimately found, it was not considered further in this review. In phase 1, all studies identified by the search strategy were randomly split within reviewers. Based on the title and abstract, only studies that were associated with ADME parameters from human intervention studies with quercetin or quercetin food sources were kept for phase 2 of the data collection process. *In vitro*, animal studies, and human intervention studies that evaluated the impact of quercetin on the pharmacokinetics of other compounds were excluded. In phase 2, the remaining studies, based on their abstracts, were again randomly split and distributed to authors and data from the papers were summarized in a tabulated form. In order to standardize reporting of differences between individuals in the various studies, the data presented was further processed and made more consistent where necessary and possible. The literature search of human intervention studies in phase 1 on quercetin and quercetin-rich foods resulted in a total of 343 potential publications for inclusion. A review of titles and abstracts reduced the number of relevant publications to 97, and, after screening the full publications according to predefined criteria, 55 articles met the inclusion criteria and were included in this review (Figure 3).

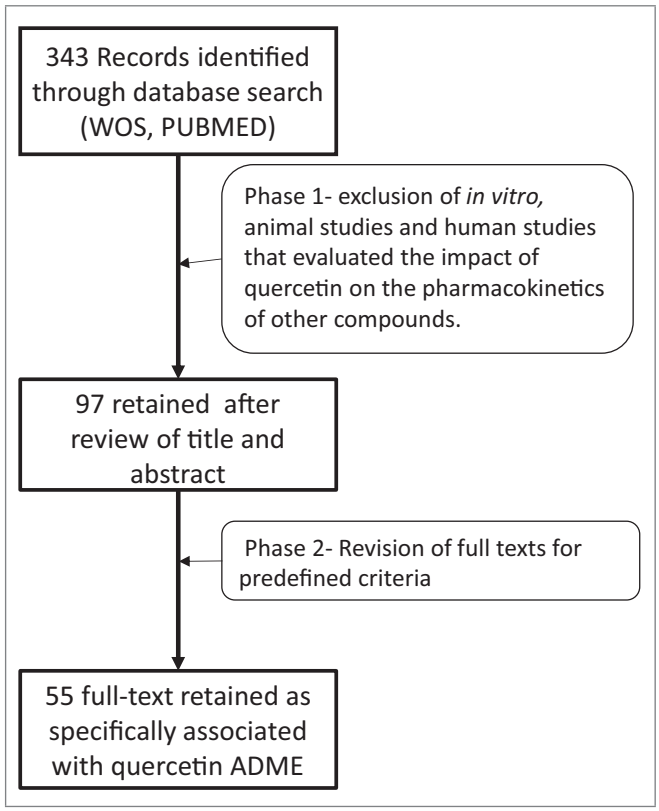

Figure 3–Scheme showing the literature search and revision process.

Design of Human Intervention Studies Examining Quercetin Bioavailability

Papers on the absorption by volunteers of quercetin from raw foods, processed foods, and food extracts, or from quercetin in solution, powder, tablet, or capsule form, were included. Studies were divided by source of quercetin as follows: food (29 studies, Table 1), pure quercetin or its glycosides (17 studies, Table 2), mixed matrix of food with pure compounds (six studies, Table 3), or food extracts (three studies (data not shown); Correa et al., 2014; Schulz, Schurer, Bassler, & Weiser, 2005; Wojcicki et al., 1995). In general, bioavailability was estimated by measuring quercetin derivatives or catabolites in blood or urine. Since quercetin is mostly found in several conjugated forms *in vivo* (Figure 1), then the analytical procedure followed by most authors is to either attempt to measure as many of the conjugated forms as possible, or to hydrolyze the samples to give quercetin and/or methylated quercetin in the aglycone form, and then measure just the resulting aglycone forms. Thirty-five studies estimated quercetin absorption by measuring quercetin aglycone after hydrolysis, 12 studies estimated quercetin conjugates, and five studies reported measuring both conjugates and aglycone after hydrolysis in urine and/or plasma. The number of subjects, however, was usually relatively small (<10).

Interindividual Variations in Quercetin Bioavailability in Studies without Explicit Individual Data

Most studies on quercetin bioavailability present the data as concentrations in plasma or urine. The data, over time, are then used to estimate pharmacokinetic parameters such as c_{max} (the maximum concentration reached), T_{max} (the time at which c_{max} is

Table 1–Characterization of intervention studies using food as quercetin source.

Food matrix (raw/processed)	Study design			Nº of subjects (gender)	Analysis		References
	Total time	Frequency (single dose/repeated, cross-over)	Dose		Type of sample	Sample treatment	
Lightly fried onions and fresh cherry tomato	4 weeks	Single dose, cross-over: 1 week wash-out → Phase 1 → 2 weeks wash-out → Phase 2	Phase 1: 200 g onions Phase 2: 200 g onions + 100 g tomatoes	6 (F)	Plasma	Hydrolysis and native	(Boyle et al., 2000)
Red grape juice and fried onions	1 day	Single dose, parallel placebo controlled	100 mL grape juice or 200 g onions	22	Plasma	Hydrolysis	(Davalos et al., 2006)
Black tea and fried onions	3 weeks	Repeated, cross-over in random order: 4 days wash-out → 3 days intervention, 2 times	1600 mL tea or 129 g onions in 2 to 3 portions/days	15 (7 F)	Plasma and urine	Hydrolysis	(de Vries et al., 1998)
Red wine, fried yellow onions and black tea	3 weeks	Repeated, cross-over in random order: 3 days wash-out → 4 days intervention, 3 times	750 mL wine or 50 g onions or 375 mL tea (14 to 16 mg quercetin in 3 portions/d)	12 (M)	Plasma and urine	Hydrolysis	(de Vries, Hollman, van Amersfoort, Olthof, & Katan, 2001)
Onion paste	1 day	Single dose	350 to 500 g of paste (2.3 mg of quercetin /kg body weight)	4	Plasma	Native	(Kawai et al., 2008)
Fried red onions	1 day	Single dose	270 g onions (275 ± 8.8 μmol of total flavonols)	6 (2 F)	Plasma and urine	Native	(Mullen et al., 2004; Mullen et al., 2006)
Sautéed yellow onions with ketchup and Italian seasonings	1 day	Single dose	76 to 150 g of onion meal (10.9 to 51.6 mg of quercetin glycosides)	4 (3 F) ileostomists	Plasma	Native	(Walle, Otake, Walle, & Wilson, 2000)
Cooked onion slices	1 week	Repeated daily	260 to 360 g (67.6 to 93.6 mg quercetin equivalents) in 3 portions/days	7 (F)	Plasma	Hydrolysis	(Moon et al., 2000)
Shallot flesh or dry skin	1 day	Cross-over, single doses separated by 7 days wash-out	1.4 mg quercetin/kg body weight	9 (5 F)	Plasma	Hydrolysis	(Wiczkowski et al., 2008)
Black currants, lingonberries, and bilberries	8 weeks	Random parallel, controlled, repeated once a day	100 g berries (12.3 ± 1.4 mg quercetin)/d in addition to normal diet	40 (M)	Plasma	Hydrolysis	(Erlund et al., 2003)
Black currant juice	1 week	Partial crossover, single dose	4.4 or 2.7 g juice/kg body weight or 2.7 g juice/kg body weight + rice cake	17 (F)	Plasma	Hydrolysis	(Erlund, Freese, Marnietni, Hakala, & Alfthan, 2006)
Blackcurrants, lingonberries, and bilberries	8 weeks	Random parallel, repeated once a day	100 g berries (12.3 ± 1.4 mg quercetin)/d in addition to normal diet	60 (M)			
Berries, other fruits and vegetables	6 weeks	Random parallel, dietary controlled	24.1 mg quercetin/d	80 (F+M)			
Vegetable diet	15 weeks	Cross-over, dietary controlled: 2 weeks wash-out → 5 weeks intervention → 3 weeks wash-out → 5 weeks intervention	Low-vegetable diet: 60 mg of vitamin C, 8 mg of vitamin E and 200 mg of folate/days. High-vegetable diet: 480 mg of vitamin C, 16 mg of vitamin E, 10 mg of β-carotene and 600 mg of folate/days	37 (F)	Plasma	Native	(Erlund et al., 2002)
Conventionally (CPD) and organically (OPD) produced diets	10 weeks	Cross-over, double-blinded randomized, dietary controlled: 1 week run-in → 3 weeks intervention → 3 weeks wash-out → 3 weeks intervention	CPD: 2632 ± 774 μg quercetin /d; OPD: 4198 ± 1370 μg quercetin /days	16 (10 F)	Urine	Hydrolysis	(Grinder-Pedersen et al., 2003)
Cloudy apple juice	1 day	Single dose	1 L of juice	5 (3 F)	Plasma	Hydrolysis	(Kahle et al., 2011)

(*Continued*)

Table 1–Continued.

Food matrix (raw/processed)	Study design			Nº of subjects (gender)	Analysis		References
	Total time	Frequency (single dose/repeated, cross-over)	Dose		Type of sample	Sample treatment	
				6 (4 F)	Urine		
Whole bilberries, nectar of lingonberries, black currant-strawberry puree and cold-pressed chokeberry-raspberry juice	8 weeks	Randomized, placebo-controlled parallel dietary intervention, repeated daily	160 g of berries (4.9 mg quercetin) in 2 portions/days	72 (46 F)	Plasma and urine	Hydrolysis	(Koli et al., 2010)
Juice mix	1 day	Single dose	6.3 mL of juice (0.189 mg quercetin /kg body weight)	10 (M)	Plasma and urine	Hydrolysis	(Krogholm, Bredsdorff, Knuthsen, Haraldsdottir, & Rasmussen, 2010)
Grape juice preparation	8 weeks	Sequential single doses with 2 weeks wash-outs	200, 400, 600, 1200 mL (~12.7 μM in quercetin)	1 (M)	Plasma and urine	Hydrolysis	(Meng, Maliakal, Lu, Lee, & Yang, 2004)
Blueberry juice mixture with apple juice	4 weeks	Controlled dietary intervention, repeated daily.	1 L of juice mixture (18 mg quercetin)/days	8 (F)	Plasma	Hydrolysis	(Wilms, Hollman, Boots, & Kleinjans, 2005)
Fruit juice (black currant and apple juice)	3 weeks	Cross-over, repeated 1 week interventions separated by 2 weeks	750, 1000, and 1500 mL (4.8, 6.4, and 9.6 mg quercetin/days)	5 (4 F)	Plasma and urine	Hydrolysis	(Young et al., 1999)
Tomato puree	2 weeks	Repeated once/day	25 g purée (2.3 mg quercetin glycosides) plus 5 g of olive oil	12 F	Plasma	Native	(Mauri et al., 1999)
Tomato juice	1 day	Single dose	300 mL	11 (6 F)	Plasma and urine	Native	(Jaganath et al., 2006)
Decaffeinated coffee powder, green tea extract, cocoa powder, grape skin extract, grape and orange juices	14 days	Cross-over, single doses in a randomized order at intervals of 14 days	4 g coffee/200 mL, 0.3 g tea extract/200 mL 10 g cocoa powder/200 mL 18 g grape-skin extract/200 mL 430 mL grape fruit extract and 550 mL orange juice	9 (5 F)	Urine	Hydrolysis	(Ito et al., 2005)
Green tea	1 day	Single dose	340 mL of commercial tea	2 (M)	Plasma	Hydrolysis	(Jin, Hakamata, Takahashi, Kotani, & Kusu, 2004)
Apple peel and onion	3 days	Randomized crossover, 2 days wash-out and single dose	85 g of apple peel or 47.5 g of onion with 100 g of applesauce	16 (8 F)	Plasma	Native	(Lee, Ebeler, Zweigenbaum, & Mitchell, 2012)
Onion and Tofu	1 day	Crossover, single dose	170 to 250 g of sautéed onion or 170 to 250 of tofu with soy sauce or combination of the 2 dishes	5	Plasma	Hydrolysis	(Nakamura et al., 2014)
Fried onion	1 day	Single dose	200 g	4 (2 F)	Plasma	Native	(Day et al., 2001)
Onion	1 day	Randomized crossover, single dose	Control: 25 g of glucose in 400 mL of water 368 g of cooked white onions or cooked yellow onions	8 (3 F)	Plasma	Hydrolysis and native	(de Pascual-Teresa et al., 2004)
Cranberry juice	3 days	Randomized crossover single dose, 2 days wash-out	240 mL	10 (F)	Urine	Native	(Wang et al., 2016)

Table 2–Characterization of studies using quercetin and derivatives as pure compounds.

	Study design				Analysis		
Class	Total time	Frequency (single dose/repeated, cross-over)	Dose	N° of subjects (gender)	Type of sample	Sample treatment	References
Aglycone	4 weeks	Randomized 2-interventions cross-over, double blind, diet controlled, single doses in ascending dosages; wash-out 2 to 3 days between doses and 9 days between interventions	8, 20, 50 mg quercetin	12 (5 F)	Plasma	Hydrolysis	(Erlund et al., 2000)
	3 weeks	Randomized, cross-over, single dose, wash-out 1 week	1095 mg quercetin with low, moderate and high fat meal	9 (5 F)	Plasma and urine	Hydrolysis	(Guo et al., 2013)
	12 weeks	Randomized parallel, double-blind, repeated daily	500/1000 mg quercetin in 2 portions/days	1002 (60% F)	Plasma	Hydrolysis	(Jin et al., 2010)
	1 day	Cross-over, placebo-controlled, single dose	200 mg quercetin	12 (M)	Plasma and urine	Hydrolysis	(Loke et al., 2009)
	3.5 weeks	Randomized double-blind parallel, placebo controlled repeated daily	1000 mg quercetin in 2 portions/days	20 (M)	Plasma	Hydrolysis	(McAnulty et al., 2008)
	1 days	Single doses, parallel	0.5 or 1 mg/kg	2 (M)	Plasma and urine	Hydrolysis	(Meng et al., 2004)
	1 week	Open, repeated	1500 mg quercetin in 3 portions/days	10 (4 F)	Plasma and urine	Hydrolysis	(Moon et al., 2008)
	1 day	Open, single dose	2 mg of quercetin eq./kg body weight	5 (1 F)	Plasma	Hydrolysis	(Murota et al., 2010)
	2 weeks	Partial cross-over, single dose	100 mg quercetin (per os); 2.5 mg quercetin (intravenous)[a]	6 (2 F)	Plasma, urine, feces and expired air	Native	(Walle et al., 2001)
	1 day	Parallel, single dose	50 to 2000 mg/m^3 (intravenous)	51 (25 F)	Plasma and urine	Native	(Ferry et al., 1996)
Glycosides	1 week	Cross-over, single doses in random order, 5 days wash-out	311 μmol quercetin-4′-*O*-glucoside vs. rutin	9	Plasma	Hydrolysis	(Hollman et al., 1999)
	4 weeks	Randomized 2-interventions cross-over, double blind, diet controlled, single doses in ascending dosages; wash-out 2 to 3days between doses and 9 d between doses and periods interventions	16, 40, 100 mg rutin	12 (5 F)	Plasma	Hydrolysis	(Erlund et al., 2000)
	3 month	Cross-over, controlled, various single doses, 1 month wash-out	0/150/300 mg quercetin-4′-*O*-glucoside	6 (3 F)	Plasma	Hydrolysis	(Hubbard, Wolffram, Lovegrove, & Gibbins, 2004)
	1 day	Open, single dose	500 mg rutin	3 (F)	Plasma	Hydrolysis	(Boyle et al., 2000)
	6 weeks	Parallel, placebo controlled, repeated daily	500 mg rutin/days	8 (F)			
	1 day	Open, single dose	2 mg of quercetin glycosides eq./kg body weight	5 (1 F)	Plasma	Hydrolysis	(Murota et al., 2010)
	4 weeks	Dietary and placebo controlled cross-over, 1 week each treatment, no wash-out	440 mg rutin	20 (10 F)	Urine	Hydrolysis and native	(Olthof et al., 2003)
	16 days	Single doses in 2 different days (d 7 and d 13) in random order	325 μmol of quercetin-3-*O*-glucoside or quercetin-4′-*O*-glucoside	9 (4 F)	Plasma	Hydrolysis and native	(Sesink, O'Leary, & Hollman, 2001)

[a]Quercetin source was radiolabeled and sample analysis was based on scintillation counting.

Table 3–Characterization of studies with mixtures or combinations of fruits/vegetables with pure compounds.

	Study design				Analysis		
Mixtures	Total time	Frequency (single dose/repeated, cross-over)	Dose	Nº of subjects (gender)	Type of sample	Sample treatment	References
Onion skin extract enriched cereal bars/capsules with pure quercetin	3 weeks	Cross-over, single-blind, single dose, 1 week run-in, 2 weeks wash-out	130 mg quercetin equivalents	6 (F)	Plasma	Hydrolysis	(Egert et al., 2012)
Quercetin supplemented in white wine/grape juice/vegetable juice	8 weeks	Cross-over, open, random order, single doses, 4 weeks wash-outs	10 mg quercetin./70 kg	4 (M)	Plasma and urine	Hydrolysis	(Goldberg, Yan, & Soleas, 2003)
Stewed onions/quercetin-4′-*O*-glucoside/buckwheat tea powder/quercetin-3-O-rutinoside	10 days	Randomized cross-over, 3 days run-in, single doses with 24 hr wash-out	100 mg or 200 mg quercetin equivalents	12 (3 F)	Plasma and urine	Hydrolysis and native	(Graefe et al., 2001)
Onion supplement/rutin/quercetin tablets	3 days	Randomized cross-over, 12 days run-in, single doses with 3 days wash-out	89/100/100 mg quercetin equivalents	9 (5 F)	Urine	Hydrolysis	(Hollman et al., 1995)
Fried onions/apples/pure rutin	12 days	Cross-over, single doses, 12 days run-in, with 3 days wash-out	64/100/100 mg quercetin equivalents	9	Plasma	Hydrolysis	(Hollman, van Trijp, Mengelers, de Vries, & Katan, 1997
Quercetin dihydrate capsules/apple chips, apple peal extract capsules, apple peel	4 weeks	Randomized, diet controlled, cross-over, single doses, 1 weeks wash-out	71 μmol quercetin equivalents	6 (F)	Plasma	Hydrolysis	(Petersen et al., 2016)

apparent), and the area under the curve (AUC) for each individual chemical species, and often the data are shown as concentration versus time curves. Most studies present the mean value of all of the volunteers together with a value for standard deviation, standard error of the mean (SEM) or percentage coefficient of variation (% CV), and do not explicitly present data on individuals. Where not presented, the % CV was calculated using the standard deviation (SD) or SEM by the formula CV = 100 × SD/mean, and SEM was converted to SD by the formula SD = SEM × $\sqrt{n}$, where n is number of volunteers. To provide an illustration of how the % CV and the interindividual variation are related, theoretical data are used to demonstrate the relationship between typical interindividual variation and a calculated % CV in Figure 4. This should allow the reader to grasp what a % CV means in terms of person-to-person variation in any measured parameter. Real published data from studies on quercetin given to volunteers are shown in full in Table 4 to 6. For analysis of interindividual variation in plasma, we have only included studies where c_{max} and AUC values were presented, or could be calculated based on the data provided in the original paper. Because of the heterogeneity in quercetin sources in the studies with quercetin-containing foods (see Table 1), only variability in studies with onion-derived products were chosen to allow a more appropriate comparison.

For most of the studies with onions, where the quercetin glucosides present are absorbed in the small intestine, and for pure quercetin glucosides, the CV for c_{max} for onions ranged from 38% to 48% (Table 4), and for quercetin glucosides from 34% to 45% (Table 6). For glycosides other than glucosides, the CV values appear higher: c_{max} CV was 58% to 80% (Table 6). This suggests that the % CV could be lower when the site of absorption is the small intestine compared to when it occurs in the colon (including the action of the microbiota). Although these data are far from conclusive, we can hypothesize that compounds which undergo microbial metabolism in the colon exhibit a greater interindividual variation than compounds absorbed in the small intestine. This hypothesis could be tested systematically for quercetin in the future and in addition could apply to other compounds. The work of Graefe et al. (2001) follows the same trend and is consistent with this hypothesis, but all of the values for c_{max} are higher than those from the other papers (see Table 4 and 6). When given as aglycone, quercetin absorption is highly dependent on solubility within the gastrointestinal tract. The proportion of quercetin which is solubilized will be absorbed in the small intestine, but the fraction of quercetin which is out of solution will not be absorbed and will pass to the colon; part will be absorbed at that site after microbe-catalyzed deglycosylation, but part will be catabolized by the gut microbiota into lower-molecular-mass compounds. With administration of quercetin as a pure compound, the interindividual variation (CV) in c_{max} ranged from 29% to 54%, which is similar to the above values for absorption from the small intestine for food. These data, therefore, imply that the extent of interindividual variation is not dependent on food or supplement source, provided that the chemical form is the same in each tested food or supplement.

Pathways of Quercetin Conjugation and Metabolism

Many conjugates and catabolites from quercetin in humans have been identified. Most of the studies considered here focused on the concentration of quercetin and potentially also of isorhamnetin and tamarixetin in samples (plasma, urine) treated by deconjugating enzymes (usually crude β-glucuronidase/sulfatase from *Helix pomatia*) or submitted to acidic hydrolysis

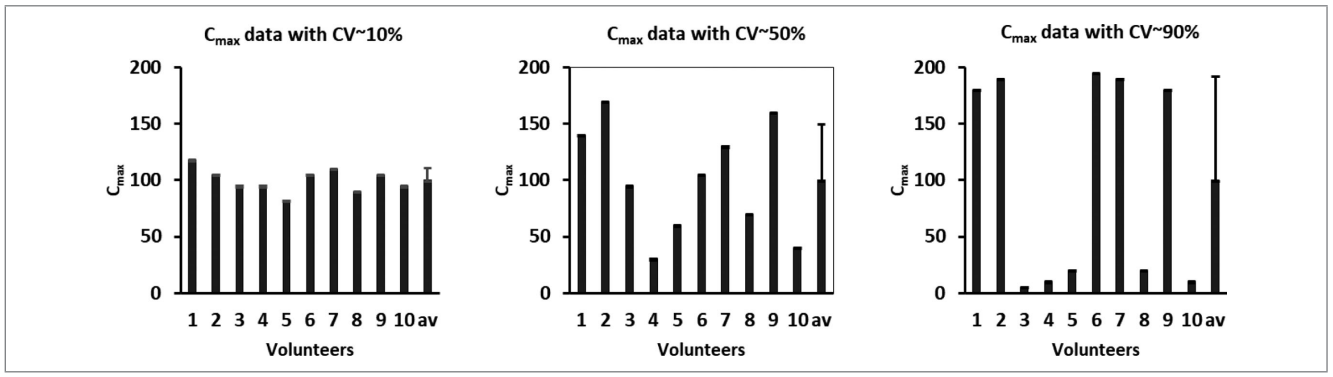

Figure 4–Illustration of the variation in data expected from the reported CV value. Theoretical maximum plasma concentration c_{max} data (mean c_{max} = 100) were calculated for 10 volunteers to allow a CV of 10%, 50%, and 90% to be calculated using the "STDEV" function of the spreadsheet in the Microsoft Excel program. The *x*-axis shows the "volunteer number" and the mean value (av) was set to 100%. Error bar shows the standard deviation in the average values of volunteers 1 to 10. With a CV of 90%, the data appears to stratify between "responders" and "nonresponders."

Table 4–Coefficient of variation in pharmacokinetic parameters when raw and cooked onions were administered and quercetin was measured after hydrolysis (derived from the studies shown in Table 1).

Sample	Parameter	CV (%)[a]	References
Plasma Kinetic data	C_{max}	63	(Graefe et al., 2001)
		48, 39[b]	(de Pascual-Teresa et al., 2004)
		38, 47[c]	(Wiczkowski et al., 2008)
	$AUC_{(0-24)}$	71	(Graefe et al., 2001)
	AUC	31, 48[c]	(Wiczkowski et al., 2008)
Urine		42	(de Vries et al., 1998)
	amount	43	(de Vries et al., 2001)
		47	(Hollman et al., 1995)

[a] % CV was calculated for the parameters with available mean and SD or SEM data by the formula CV = 100 × SD/mean.
[b] Yellow and white onions, respectively.
[c] Flesh and dry skin, respectively.

Table 5–Variations in bioavailability studies on quercetin (details for each study in Table 2 and 3) administered as pure compound.

Sample	Parameter	CV(%)[a]	References
Plasma Kinetic data	C_{max}	29[b]	(Erlund et al., 2000)
		35, 31, 54[c]	(Guo et al., 2013)
		25, 37[d]	(Egert et al., 2012)
		54	(Petersen et al., 2016)
	AUC	27, 14[e]	(Walle et al., 2001)
	$AUC_{(0-24)}$	25[b]	(Erlund et al., 2000)
	$AUC_{(0-32)}$	26[b]	(Erlund et al., 2000)
	$AUC_{0-24\ h}$	26, 31, 42[c]	(Guo et al., 2013)
	AUC	37, 25[d]	(Egert et al., 2012)
	AUC_{0-24}	47	(Petersen et al., 2016)
Urine	amount	21, 18[e]	(Walle et al., 2001)
Feces	amount	77, 44[e]	(Walle et al., 2001)
CO_2	amount	21, 88[e]	(Walle et al., 2001)

[a] % CV was calculated for the parameters with available mean and SD or SEM data.
[b] Calculated for 3 different doses at upper and lower confidence interval (CI) using the formula SD = |Mean-CI|/$z \times \sqrt{n}$ with z = 1.96 and 1.65 for 95% and 90% CI, respectively, and expressed as mean, n = 6 (3 doses, 2 lower and upper interval).
[c] Low, moderate, and high fat meal respectively.
[d] Quercetin enriched cereal bars and quercetin capsules, respectively.
[e] 100 mg oral and 0.3 mg intravenous, respectively, of radiolabelled quercetin and sample analysis by scintillation counting.

Table 6–Variation in pharmacokinetic parameters when quercetin glycosides were administered (derived from the studies shown in Table 2 and 3).

Sample	Parameter	CV (%)[a]	References
Rutin Plasma - kinetic data	C_{max}	80[b]	(Erlund et al., 2000)
		58	(Hollman et al., 1999)
		108	(Graefe et al., 2001)
	$AUC_{(0-32)}$	47[b]	(Erlund et al., 2000)
	$AUC_{(0-\infty)}$	50	(Hollman et al., 1999)
	$AUC_{(0-24)}$	88	(Graefe et al., 2001)
	$AUC_{(0-24)}$	54[b]	(Erlund et al., 2000)
Urine	Amount[c]	24	(Olthof et al., 2003)
	Amount	260	(Hollman et al., 1995)
Glucosides Plasma - kinetic data	C_{max}	45[d]	(Hollman et al., 1999)
		40, 34[d]	(Hubbard et al., 2004)
		41[e]	(Murota et al., 2010)
		77[d]	(Graefe et al., 2001)
	$AUC_{(0-24)}$	108[d]	(Graefe et al., 2001)
	AUC	32[e]	(Murota et al., 2010)
	$AUC_{(0-\infty)}$	34[d]	(Hollman et al., 1999)

[a] Calculated for the parameters with available mean and SD or SEM data.
[b] Calculated for 3 different doses at upper and lower CI using the formula SD = |Mean-CI|/$z \times \sqrt{n}$ with z = 1.96 and 1.65 for 95% and 90% CI, respectively, and expressed as mean, n = 6 (3 doses, 2 lower and upper interval).
[c] 16, 40, and 100 mg, respectively.
[d] Quercetin-4′-*O*-glucoside.
[e] Enzymatically modified quercetin-3-*O*-glucoside.

(Cermak et al., 2003; Day, Gee, DuPont, Johnson, & Williamson, 2003; Paulke, Eckert, Schubert-Zsilavecz, & Wurglics, 2012; Spencer et al., 1999), which does not allow for the precise identification of the conjugated metabolites. In older publications, determination of quercetin using high-performance liquid chromatography (HPLC) with ultraviolet-visible (UV-Vis) (Day et al., 2003; Spencer et al., 1999) or fluorescence (Ader et al., 2000) detection was used with relatively low sensitivity. Quercetin conjugates are now most frequently measured using HPLC/MS^n techniques (Borges & Crozier, 2012; Mullen, Boitier, Stewart, & Crozier, 2004; Stalmach et al., 2009; Valentová, Vrba, Bancířová, Ulrichová, & Křen, 2014), where quercetin, quercetin-3-*O*-glucuronide, quercetin glucuronide sulfate (without determination of the conjugation positions), isorhamnetin-3-*O*-glucuronide, quercetin-3′-*O*-sulfate, and isorhamnetin have been identified in human plasma (Day et al., 2001; Mullen, Edwards, & Crozier, 2006; Murota et al., 2010). Identification of the exact position of conjugation is, in most cases, impossible without authentic standards with known exact structure, as confirmed by nuclear magnetic resonance.

During catabolism by the microbiota in the colon, C-ring fission is the predominant reaction in quercetin degradation. Subsequent products can then be absorbed by the colon epithelial cells, conjugated by mammalian phase II enzymes, and then

ultimately be excreted in the urine, or, alternatively, a proportion may not be absorbed and then appear directly in the feces. Significant increases in urinary concentrations of 4-ethylphenol, benzoic acid, and 4-ethylbenzoic acid were noted in healthy men after oral consumption of 200 mg of pure quercetin (Loke et al., 2009). After supplementation with quercetin-3-*O*-rutinoside, phenylacetic acids, namely, 3-hydroxyphenylacetic acid (36% of the dose ingested), 3-methoxy-4-hydroxyphenylacetic acid (8%), and 3,4-dihydroxyphenylacetic acid (5%) were excreted into the urine of healthy humans. The absence of a conventional microbiota, as in ileostomist subjects, abolished the formation of the majority of the phenolic acid metabolites, indicating the importance of bacterial biotransformation in the formation of these compounds (Olthof, Hollman, Buijsman, van Amelsvoort, & Katan, 2003).

Table 7 summarizes qualitatively all of the studies where the presence of a metabolite is reported or has been definitely identified as absent. The most commonly identified conjugates where a single moiety has been added are quercetin-3′-*O*-sulfate, quercetin-3-*O*-glucuronide, and quercetin-3′-*O*-glucuronide. Quercetin was also methylated and glucuronidated, forming isorhamnetin-3-*O*-glucuronide and isorhamnetin-4′-*O*-glucuronide, but it appears that methylation prevents subsequent sulfation and vice versa. Quercetin can also be doubly substituted with both sulfate and glucuronide groups; and in some papers detection of methylated quercetin which has been diglucuronidated was reported. There is also some evidence for quercetin substituted with both a glucose and a sulfate or glucuronide, but it is not clear if a small amount of quercetin was absorbed in the form of a glucoside and then further conjugated, or if the glucosylation occurred postabsorption (Mullen et al., 2004, 2006). Some microbial metabolites of quercetin were identified when rutin was given in pure form or in tomato juice, and these include phenylacetic and hydroxyhippuric acid derivatives (Jaganath, Mullen, Edwards, & Crozier, 2006; Olthof et al., 2003). Quantitative data on the presence of quercetin conjugates and microbial metabolites are given in Table 8. Some metabolites such as quercetin-3′-*O*-sulfate are found only in plasma and not in urine, whereas many conjugates are found in both urine and plasma.

Assessment of Individual Papers Where Data on Interindividual Variation are Specifically Presented

Specific information on the inter- or intraindividual differences in quercetin bioavailability was available from 10 studies. Of these, 6 show the data in graphical form only (Boyle et al., 2000; Boyle, Dobson, Duthie, Kyle, & Collins, 2000; Davalos, Castilla, Gomez-Cordoves, & Bartolome, 2006; Loke et al., 2009; Moon, Wang, DiCenzo, & Morris, 2008; Petersen et al., 2016), one presents results based on radio-scintillation counting (Walle et al., 2001) and only three provide numerical quantitative data for individual volunteers (Ferry et al., 1996; Jaganath et al., 2006; Moon, Nakata, Oshima, Inakuma, & Terao, 2000). The form of presentation differs substantially for each of these publications, which are discussed below. To be consistent in this part, all original values for C_{max}, AUC and amount in urine were converted to nM, nM.h and nmol, when necessary.

Uptake of quercetin from food was evaluated in six healthy nonobese normocholesterolemic nonsmoking female volunteers in a randomized 2-phase cross-over single-dose supplementation trial using a meal of fried onions (200 g, phase 1) or fried onions (200 g) with fresh cherry tomatoes (100 g, phase 2, Boyle et al., 2000; Table 1). Wash-out periods of 7 days were controlled by a validated food questionnaire and weighed intake record, and plasma concentration of quercetin confirmed compliance. Predominant flavonoids present in plasma were identified as "quercetin-3-glucoside" and "isorhamnetin-3-*O*-glucoside" by HPLC with UV and fluorimetric detection, but they were more probably glucuronides since the authors did not have the appropriate glucuronide standards at the time. Interindividual variation in the extent of "quercetin-3-*O*-glucoside" (that is quercetin-3-*O*-glucuronide) absorption into plasma, and also the time at which the highest concentration was present in the plasma, was observed. Individual data for plasma concentration for two main flavonols in plasma are presented as bar graphs at time points – 24, 0, 4, 8, and 24 hr for the 1st phase only, and the difference between the highest and lowest responder at 4 hr after ingestion can be estimated as approximately one order of magnitude (about 20 compared with 300 nM). In the 2nd phase, total plasma concentration of quercetin measured in hydrolyzed samples was presented as mean ± SEM with CV 24%. This study also evaluated oxidation-stress-related plasma markers, but these were displayed as mean ± SEM only and thus cannot be related to plasma levels of quercetin.

Individual plasma quercetin concentration-time profiles for 10 individuals after 7 days of supplementation with 500 mg quercetin in capsule form three times daily (measured for 8 hr over the last day of the supplementation period) were published separately together with numerical data as means, medians, and range (Moon et al., 2008; Table 2). This study differs from all others in that no baseline level was presented in the paper and no dietary restriction or wash-out was applied for the (pre-) supplementation period, although ingestion of "quercetin products" within 30 d was an exclusion criterion. The study focused on reentry pharmacokinetics, and it is clear that some subjects showed reentry peaks of quercetin conjugates and others did not. The absorption rate constant and bioavailability also showed high interindividual variability. From the individual plasma profiles, two subjects can be assigned as low responders (plasma concentration ≤ 3 nM throughout the measurement period), and at least five as high responders (peak concentration ≥ 25 nM). Peak concentrations of quercetin aglycone and conjugated metabolites varied from 1.6 to 132.1 and 533 to 4000 nM, respectively. No determinants for the variability observed are available. Individual plasma profiles of quercetin concentration were presented also for a pharmacokinetic study with rutin (Boyle et al., 2000; Table 2). In this case, however, the profiles were measured in only three female volunteers following a single dose of 500 mg rutin. Subjects showed different kinetics, with two having maximal plasma level at 7 hr and the third at 4 hr. The extent of absorption varied between 130 and 730 nM and the rate of clearance was also highly variable. The authors then performed a 6-week placebo-controlled supplementation study ($n = 8$ in each group, 500 mg rutin/d). While the plasma levels of quercetin, kaempferol, and isorhamnetin before and after the study were presented as bar graphs using means and SEM, individual bar graphs are available for plasma "total phenols" (using the Folin-Ciocalteu assay) at weeks 1 and 5. In this case, there was no clear high or low responder, with the range between ~11 and 15 μg/mL.

Data were presented individually for 12 healthy men using line graphs for plasma and urinary total quercetin before, and 2 or 5 hr after supplementation with a single dose of 200 mg quercetin in a cross-over design including the control but also (–)-epicatechin and (–)-epigallocatechin gallate (EGCG, 1 week wash-out between treatments, Loke et al., 2009; Table 2). There

Table 7—List of main quercetin metabolites identified in nonhydrolyzed samples (presence indicated by +, Nd - not detected).

Metabolite	Presence		References
	Plasma	Urine	
Quercetin-3′-*O*-sulfate[a]	+	Nd	(Mullen et al., 2006)
	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2004)
	+		(Nakamura et al., 2014)
	+		(de Vries et al., 1998)
	+		(de Pascual-Teresa et al., 2004)
	+		(Lee et al., 2012)
Quercetin-7-*O*-sulfate	+		(de Pascual-Teresa et al., 2004)
Quercetin-3′-*O*-glucuronide	trace	+	(Mullen et al., 2006)
	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2004)
	Nd	+	(Jaganath et al., 2006)
	+		(Lee et al., 2012)
	+		(de Vries et al., 1998)
	+		(de Pascual-Teresa et al., 2004)
Quercetin-4′-*O*-glucuronide	Nd	+	(Jaganath et al., 2006)
	+		(de Vries et al., 1998)
Quercetin-3-*O*-glucuronide	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2006)
	+	+	(Mullen et al., 2004)
	+	+	(Jaganath et al., 2006)
	+		(Lee et al., 2012)
	+		(Nakamura et al., 2014)
	+		(de Vries et al., 1998)
	+		(de Pascual-Teresa et al., 2004)
Quercetin-7-*O*-glucuronide	+	+	(Mullen et al., 2004)
Quercetin glucuronide sulfate	+	+	(Mullen et al., 2006)
	+	+	(Mullen et al., 2004)
	+		(Lee et al., 2012)
Isorhamnetin-3-*O*-glucuronide	+	+	(Mullen et al., 2006)
	+	+	(Mullen et al., 2004)
	+	+	(Jaganath et al., 2006)
	+		(Lee et al., 2012)
	+		(de Vries et al., 1998)
	+		(de Pascual-Teresa et al., 2004)
Isorhamnetin-4′-*O*-glucuronide	+	+	(Mullen et al., 2006)
	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2004)
	+		(de Vries et al., 1998)
	+		(de Pascual-Teresa et al., 2004)
Quercetin diglucuronide	+	+	(Mullen et al., 2006)
	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2004)
	Nd	+	(Jaganath et al., 2006)
	+		(Lee et al., 2012)
	+		(de Vries et al., 1998)
Methyl quercetin diglucuronide	Nd	+	(Mullen et al., 2006)
	Nd	+	(Mullen et al., 2004)
	Nd	+	(Jaganath et al., 2006)
	+		(Lee et al., 2012)
Methyl quercetin glucuronide	+		(Kawai et al., 2008)
	+	+	(Mullen et al., 2004)
	+		(Lee et al., 2012)
Quercetin glucoside sulfate	Nd	+	(Mullen et al., 2006)
	Nd	+	(Mullen et al., 2004)
Quercetin glucoside glucuronide	Nd	+	(Mullen et al., 2006)
	Nd	+	(Mullen et al., 2004)
	Nd	+	(Jaganath et al., 2006)
Quercetin glutathione	+		(Lee et al., 2012)
3-hydroxyphenylacetic acid		+	(Olthof et al., 2003)
	Nd	+	(Jaganath et al., 2006)
3,4-dihydroxyphenylacetic acid		+	(Olthof et al., 2003)
	Nd	+	(Jaganath et al., 2006)
3-OCH_3-4-hydroxyphenylacetic acid		+	(Olthof et al., 2003)
	Nd	+	(Jaganath et al., 2006)
2-hydroxyhippuric acid	Nd	+	(Jaganath et al., 2006)
3-hydroxyhippuric acid	Nd	+	(Jaganath et al., 2006)
4-hydroxyhippuric acid	Nd	+	(Jaganath et al., 2006)

[a] In ref (Lee et al., 2012), quercetin-3-*O*-sulfate was reported, but this is likely to be a typographical error since the authors themselves give the structure of quercetin-3′-*O*-sulfate.

Table 8–Variability in kinetic parameters for quercetin metabolites based on studies with nonhydrolyzed samples with quantitative data presented as mean values.

		Kinetic data			
Conjugate	Sample	Parameter	Value[a]	CV (%)[b]	References
Quercetin 3′-*O*-sulfate[c]	Plasma	C_{max}	12.1 ± 16.5 97.8 ± 81.8	137[d] 84[e]	(Lee et al., 2012)
		$AUC_{0\text{-}24h}$	31.5 ± 45.4 299 ± 227	144[d] 76[e]	
Quercetin-3′-*O*-glucuronide	Urine	Amount	1845 ± 193	26	(Mullen et al., 2006)
Quercetin-3-*O*-glucuronide	Plasma	C_{max}	12 ± 2	17	(Jaganath et al., 2006)
	Urine	Amount	912 ± 149	40	(Mullen et al., 2006)
Quercetin glucuronide	Plasma	C_{max}	31.5 ± 27.1 433 ± 244	86[d] 56[e]	(Lee et al., 2012)
		AUC	75.9 ± 75.1 1827 ± 1336	99[d] 73[e]	
Quercetin-glucuronide sulfate	Plasma	C_{max}	2.3 ±8.4 75.4 ± 113.4	369[d] 150[e]	(Lee et al., 2012)
		AUC	20.3 ± 76.4 795 ± 1172	375[d] 147[e]	
	Urine	Amount	1229, 1384[f]	29, 38[f]	(Mullen et al., 2006)
Isorhamnetin-3-*O*-glucuronide	Plasma	C_{max}	4.3 ± 1.5	35	(Jaganath et al., 2006)
	Urine	Amount	1789 ± 239	33	(Mullen et al., 2006)
Isorhamnetin-4′-*O*-glucuronide	Urine	Amount	700 ± 114	40	(Mullen et al., 2006)
Quercetin diglucuronide	Plasma	C_{max}	13.7 ± 22.3 248 ± 137	163[d] 55[e]	(Lee et al., 2012)
		AUC	35.9 ± 59.7 869 ± 431	166[d] 50[e]	
	Urine	Amount	2223 ± 417	46	(Mullen et al., 2006)
Methyl quercetin diglucuronide	Plasma	C_{max}	5.2 ± 7.9 94.2 ± 36.9	150[d] 39[e]	(Lee et al., 2012)
		AUC	61.3 ± 123.5 1033 ± 409	201[d] 40[e]	
	Urine	Amount	426, 1003[f]	38, 57[f]	(Mullen et al., 2006)
Methyl quercetin glucuronide	Plasma	C_{max}	14.8 ± 17.2 178 ± 61	116[d] 34[e]	(Lee et al., 2012)
		AUC	53.8 ± 82.7 1008 ± 404	153[d] 40[e]	
Quercetin glucoside sulfate	Urine	Amount	392, 821[f]	37, 47[f]	(Mullen et al., 2006)
Quercetin glucoside glucuronide	Urine	Amount	163 ± 23	35	(Mullen et al., 2006)
3-hydroxyphenylacetic acid	Urine	Amount	259 ± 51	88	(Olthof et al., 2003)
3,4-dihydroxyphenylacetic acid	Urine	Amount	52 ± 6	52	(Olthof et al., 2003)
3-methoxy-4-hydroxyphenylacetic acid	Urine	Amount	103 ± 15	65	(Olthof et al., 2003)

[a] All values for C_{max}, AUC and amount in urine are shown as nM, nM.h and nmol, respectively; values were converted from the original papers if necessary.
[b] %CV was calculated for the parameters with available mean and SD or SEM data.
[c] In Lee et al. (2012), quercetin-3-*O*-sulfate was reported, but this is likely to be a typographical error since the authors themselves give the structure of quercetin-3′-*O*-sulfate.
[d] Apple peel powder.
[e] Onion powder.
[f] The same metabolite was identified and quantified at 2 retention times, values presented correspond to the data for the 2 peaks.

were apparently high and low responders (four subjects with 4- to 5-fold increase and at least two subjects with a slight increase). More importantly, this study also evaluated 11 aromatic phenolic compounds that increased significantly in the urine of the participants, probably catabolites from flavonoid microbial degradation. Unfortunately, these data are not presented individually, and, therefore, we cannot conclude if low response in plasma or urine quercetin concentration is related to the (increased) level of microbial metabolites. However, significant increases occurred in urinary excretion of 4-ethylphenol (increased in 100% of participants), benzoic acid (83%), and 4-ethylbenzoic acid (83%), which all significantly correlated with the changes in plasma and urinary total quercetin. Moreover, 67% of the participants showed increased urinary excretion of 2-methoxyphenylacetic acid and 3-phenylpropionic acid, and 58% for 3-(4-hydroxyphenyl)-propionic acid (Loke et al., 2009). A similar form of data presentation using line graphs was chosen also for a parallel single-treatment supplementation study with grape juice ($n = 14$) and fried onions ($n = 2$), but for quercetin plasma level at 0 and 2 hr in placebo ($n = 6$) and grape juice treatment groups only (Davalos et al., 2006; Table 1). The limitation of this study is a high baseline level of quercetin (there was only a 24-hr "wash-out" before the intervention during which the volunteers were "advised" to refrain from quercetin containing food, with no compliance control) and also a very low number of subjects in the onion group. A decrease in plasma quercetin level from ~130 to 80 and 50 nM was observed in two volunteers from the placebo group. In the grape juice group, seven subjects displayed no increase in plasma quercetin and there was only one relatively high responder (2-fold increase). Mean plasma concentration was 46 nM with SD 20 nM (CV 43%). This might be related to very low quercetin intake (4.9 mg) from the grape juice or measurement too early after administration.

Bioavailability of quercetin from four different sources (apple peel, vacuum-impregnated apple chips, apple peel extract capsules, and quercetin dihydrate capsules, all providing 71 μmol of quercetin equivalents) was investigated in six healthy subjects (Petersen et al., 2016; Table 3). This single dose, diet-controlled, cross-over study had 1-week wash-out periods before the study and between each treatment. The compliance seems to be satisfactory with no measurable quercetin and total flavonols at baseline

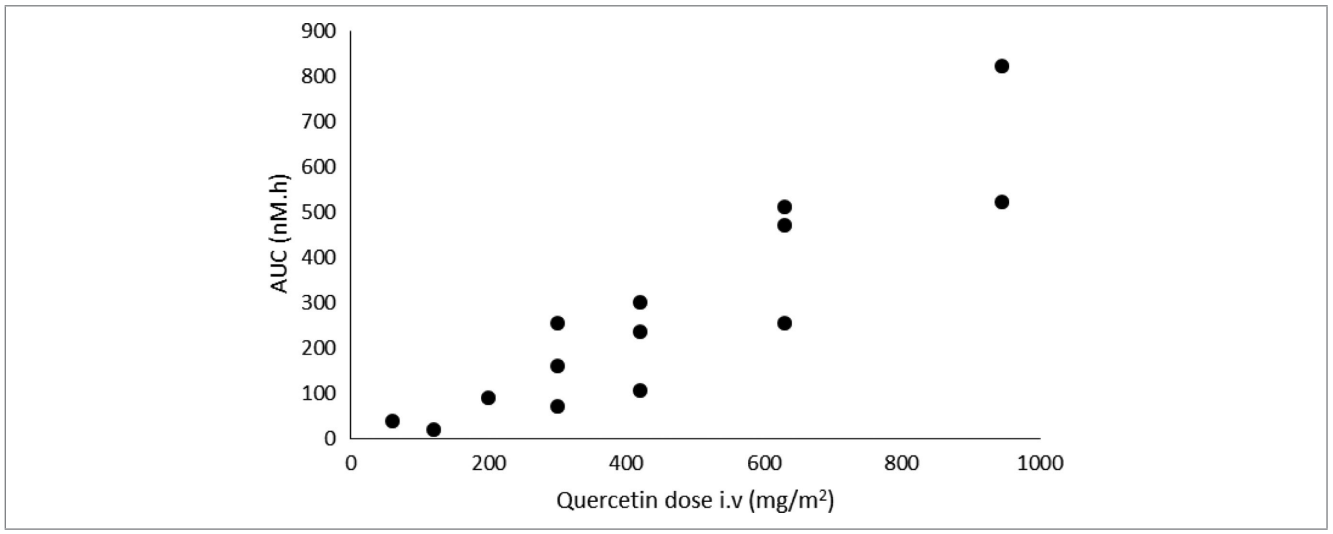

Figure 5–Dependence of area under the curve (AUC) values on quercetin dose (Ferry et al., 1996). AUC values obtained by pharmacokinetic modeling for all 14 patients (each patient represented by a filled circle) for the tested doses of quercetin administered by intravenous (i.v.) injection (AUC data normalized to nM × h).

(estimated from plasma concentration curves). Plasma pharmacokinetic parameters and quercetin plasma concentration curves were presented as mean ± SEM, but individual $AUC_{0\text{-}24\ h}$ values were also shown in graphical form (bar graphs) separately for each treatment. Individual response varied substantially and allowed the authors to divide the participants into subgroups of high and low responders, with the difference in AUC being up to 10-fold higher in the highest responder compared with the lowest (estimated from the bar graphs (Petersen et al., 2016).

Absorption and disposition of ^{14}C-radiolabeled quercetin was studied in six healthy subjects after oral and intravenous (i.v.) administrations (Walle et al., 2001; Table 2). Data are presented individually, but also as mean ± SEM. The main limitation of this study is that quercetin was ^{14}C-labeled only on the C-4 position of the C ring. Although this was a cross-over study, only 4 subjects followed both oral and intravenous treatment, and recovery in the exhaled air after both treatments was available for only 1 volunteer. On the other hand, radioactivity was measured not only in urine and plasma, but also in feces and expired air, with individual volunteer data presented in a tabulated form. The CV calculated in this study was ~27 and 14% for AUC (37 to 68 and 0.30 to 0.37 μmol.h/L for oral and intravenous dose, respectively) and 21% and 18% for radioactivity recovery from urine (3.3% to 5.7% and 18.4% to 26.8% for oral and intravenous dose, respectively). A large variability was found for the recovery of radioactivity from exhaled air. In some individuals, $^{14}CO_2$ started to appear 4 hr after administration and in others not until 8 hr and, therefore, $^{14}CO_2$ in the expired air represented 23.0% to 81.1% of the radioactivity administered. Taking into account the limitations of this study, 2 volunteers can, however, probably be classified as relatively high responders (AUC 65.5, 68.0 and 0.37, 0.39 μmol.h/L for oral and intravenous doses, respectively; urine recovery 5.4%, 5.7%, and 20.1, 19.7%), but recovery as $^{14}CO_2$ is known for intravenous dose only and differs markedly (81.1% and 25.5% of the radioactivity administered; Walle et al., 2001).

Quercetin concentration in human plasma from seven volunteers was determined before and after a short-term ingestion of onions (Moon et al., 2000; Table 1). The subjects were given diets containing onion slices (67.6 to 93.6 mg of quercetin equivalents/d) with meals for 1 week. After 10 hr of fasting, quercetin was measured in plasma after β-glucuronidase-sulfatase treatment, and the concentration increased on average 16-fold after the 1-week trial. However, individual data again indicated a substantial variation between volunteers, some with a very low response (8-fold, calculated from data) compared to others with a higher response (27-fold, calculated from data). In a Phase I clinical trial, quercetin was administered by short intravenous infusion at escalating doses at 3-week intervals in cancer patients (Ferry et al., 1996; Table 2). Quercetin pharmacokinetics were measured during the first 3 hr at frequent intervals, and individual plasma profiles were plotted for seven tested doses in seven different patients. By analyzing the curves, it is clear that the patients responded differently to quercetin administration. For example, one patient given a dose of 630 mg quercetin/m^2 showed, after 120 min, a circulating blood level of quercetin lower than a patient on 200 mg/m^2. This variation is also reflected in the parameters calculated by pharmacokinetics modeling for 14 patients (shown in Figure 5). For seven patients treated with 945 mg quercetin/m^2, the mean amount of quercetin excreted in urine ranged from 0.03% to 7.6% of the dose administered, also indicating a considerable interpatient variability. In this study, quercetin levels were determined after intravenous injection, which eliminates variables derived from microbiota and intestinal absorption, suggesting that variations in quercetin-metabolizing enzymes and transporters contribute highly to interindividual variability.

In order to study the contribution of the small and large intestine to the absorption and metabolism of rutin in humans, a study was conducted with a single dose of tomato juice containing rutin (176 μmol) by healthy volunteers and ileostomists (Jaganath et al., 2006; Table 1). Quercetin-3-*O*-glucuronide and isorhamnetin-3-*O*-glucuronide were absent at baseline, and were measured at 4, 5, 6, 7, and 8 hr postingestion. The authors noted a high extent of variation between the volunteers, and also for excretion of urinary metabolites. Over a 24-hr period, one of the volunteers excreted a total of 4981 nmol of metabolites corresponding to 2.8% of the ingested dose of rutin. In contrast, excretion by the other subjects ranged from 40 to 608 nmol, equivalent to 0.02% to 0.35% of intake. The lower level of excretion of rutin metabolites

by volunteers was limited to isorhamnetin-3-*O*-glucuronide and the 3-, 3′-, and 4′-glucuronides of quercetin. The authors concluded that this large interindividual variation, either in plasma or urine, may be related to the dependency of rutin metabolism on the microbiota. The low urinary recovery of the ingested rutin as glucuronides, glucosides, and methylated metabolites of quercetin, and identification of low molecular weight phenolic acids metabolized by microbiota, suggest that the latter may account for the most significant proportion of the metabolism of rutin/quercetin. No individual data were presented for the low-molecular-weight phenolic acids, but CV for total levels of excretion varie from 24% for 4-hydroxyhippuric acid to 77% for 3-methoxy-4-hydroxyphenylacetic acid (estimated). Importantly, this study highlights that an individual who would be considered a low responder, as judged by evaluating glucuronides, glucosides, and methylated metabolites of quercetin, may actually be revealed as a faster metabolizer and therefore higher responder when assessed by the concentration of low-molecular-weight phenolic acids. This emphasizes that a precise understanding of interindividual variability of quercetin bioavailability requires measurement of all metabolic routes, including the gut microbiota.

Factors Affecting Interindividual Variation in Quercetin Bioavailability

The present paper clearly indicates that a substantial interindividual variability in quercetin bioavailability was observed in all studies. Given the complexity of the pathways of metabolism, which is obvious from Figure 1 and 2, interindividual variation in quercetin metabolism can arise from numerous factors. These can include, but are not limited to, genetic polymorphisms, dietary adaptation, composition of gut microbiota, drug exposure, and other subject characteristics such as body mass index (BMI) and health status. There are several genetic polymorphisms in the enzymes and transporters, shown in Figure 1, which could account for some variability. Polymorphisms have been reported for LPH (Flatz & Rotthauwe, 1977), UGTs (Sugatani, 2013), COMT (Ding, Fu, Chen, & Wang, 2010), SULTs (Glatt et al., 2000; Rossi et al., 2004), ABC transporters (Kerb, Hoffmeyer, & Brinkmann, 2001), and organic anion transporters (OAT, Fujita et al., 2005). However, to date, none of the studies have examined the contribution that these polymorphisms might make to quercetin metabolism *in vivo*. In addition, many of these enzymes and transporters are modulated by diet, drugs, and environment, adding an additional layer of complexity.

Conclusions and Future Recommendations

An important and probably the most essential question, which has not yet been addressed, is the presence of any link between bioavailability and bioefficacy. Such a study would address the hypothesis: Does a high absorber of quercetin also show a greater biological response to quercetin? This is complicated by the gut microbiota, and one could equally ask the question: Does the presence of high quantities of microbial metabolites correlate with a more pronounced biological response? Recently, the role of interindividual variability on the impact of flavonols on cardiometabolic biomarkers was investigated, but owing to the lack of data effects could not be correlated with bioavailability (Menezes et al., 2017).

Further studies designed specifically to address interindividual variation are needed. At least moderately larger ($n \geq 20$) studies presenting individual data for the pharmacokinetics of quercetin (and glycosides occurring in foods), including parent compound and best-known low-molecular-weight metabolites, together with details about the study subjects such as age, gender, genotype, composition of gut microbiota, diet, life style, and health status are necessary to address this knowledge gap in the future. Ideally, this information would be coupled with bioactivity and biomarker measurements. The most important aspect for future studies to consider, but in some ways the most difficult to address, is to determine whether a "low responder" exhibits a smaller response in a health biomarker compared to a "high responder."

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Author Contributions

All authors helped with the data collection process involving the initially selected papers. AFA, KV, GW, and CNS wrote the manuscript draft. The final manuscript was edited and revised with contributions from all authors.

References

Ader, P., Wessmann, A., & Wolffram, S. (2000). Bioavailability and metabolism of the flavonol quercetin in the pig. *Free Radical Biology and Medicine*, *28*(7), 1056–1067. doi: https://doi.org/10.1016/S0891-5849(00)00195-7

Araujo, K. C. F., Costa, E. M. D. B., Pazini, F., Valadares, M. C., & de Oliveira, V. (2013). Bioconversion of quercetin and rutin and the cytotoxicity activities of the transformed products. *Food and Chemical Toxicology*, *51*, 93–96. https://doi.org/10.1016/j.fct.2012.09.015

Arts, I. C. W., Sesink, A. L. A., Faassen-Peters, M., & Hollman, P. C. H. (2004). The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. *British Journal of Nutrition*, *91*(6), 841–847. https://doi.org/10.1079/Bjn20041123

Azuma, K., Ippoushi, K., Ito, H., Higashio, H., & Terao, J. (2002). Combination of lipids and emulsifiers enhances the absorption of orally administered quercetin in rats. *Journal of Agricultural and Food Chemistry*, *50*(6), 1706–1712.

Beekmann, K., Actis-Goretta, L., van Bladeren, P. J., Dionisi, F., Destaillats, F., & Rietjens, I. M. C. M. (2012). A state-of-the-art overview of the effect of metabolic conjugation on the biological activity of flavonoids. *Food & Function*, *3*(10), 1008–1018. https://doi.org/10.1039/c2fo30065f

Boersma, M. G., van der Woude, H., Bogaards, J., Boeren, S., Vervoort, J., Cnubben, N. H. P., . . . Rietjens, I. M. C. M. (2002). Regioselectivity of phase 11 metabolism of luteolin and quercetin by UDP-glucuronosyl transferases. *Chemical Research in Toxicology*, *15*(5), 662–670. https://doi.org/10.1021/tx0101705

Boots, A. W., Haenen, G. R. M. M., & Bast, A. (2008). Health effects of quercetin: From antioxidant to nutraceutical. *European Journal of*

Pharmacology, *585*(2-3), 325–337. https://doi.org/10.1016/j.ejphar.2008.03.008

Borges, G., & Crozier, A. (2012). HPLC-PDA-MS fingerprinting to assess the authenticity of pomegranate beverages. *Food Chemistry*, *135*(3), 1863–1867. https://doi.org/10.1016/j.foodchem.2012.05.108

Boyle, S. P., Dobson, V. L., Duthie, S. J., Hinselwood, D. C., Kyle, J. A. M., & Collins, A. R. (2000). Bioavailability and efficiency of rutin as an antioxidant: A human supplementation study. *European Journal of Clinical Nutrition*, *54*(10), 774–782. https://doi.org/10.1038/sj.ejcn.1601090

Boyle, S. P., Dobson, V. L., Duthie, S. J., Kyle, J. A. M., & Collins, A. R. (2000). Absorption and DNA protective effects of flavonoid glycosides from an onion meal. *European Journal of Nutrition*, *39*(5), 213–223. https://doi.org/10.1007/s003940070014

Cermak, R., Breves, G., Lupke, M., & Wolffram, S. (2006). In vitro degradation of the flavonol quercetin and of quercetin glycosides in the porcine hindgut. *Archives of Animal Nutrition*, *60*(2), 180–189. https://doi.org/10.1080/17450390500467695

Cermak, R., Landgraf, S., & Wolffram, S. (2003). The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. *Journal of Nutrition*, *133*(9), 2802–2807.

Cermak, R., & Wolffram, S. (2006). The potential of flavonoids to influence drug metabolism and pharmacokinetics by local gastrointestinal mechanisms. *Current Drug Metabolism*, *7*(7), 729–744. https://doi.org/10.2174/138920006778520570

Clifford, M. N., van der Hooft, J. J., & Crozier, A. (2013). Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. *American Journal of Clinical Nutrition*, *98*(6 Suppl), 1619S–1630S. doi: Retrieved from ajcn.113.058958[pii];10.3945/ajcn.113.058958[doi]

Correa, C. R., Chen, C. Y. O., Aldini, G., Rasmussen, H., Ronchi, C. F., Berchieri-Ronchi, C., . . . Yeum, K. J. (2014). Bioavailability of plant pigment phytochemicals in Angelica keiskei in older adults: A pilot absorption kinetic study. *Nutrition Research and Practice*, *8*(5), 550–557. doi: Retrieved from ajcn.113.058958

Crespy, V., Morand, C., Besson, C., Manach, C., Demigne, C., & Remesy, C. (2002). Quercetin, but not its glycosides, is absorbed from the rat stomach. *Journal of Agricultural and Food Chemistry*, *50*(3), 618–621. https://doi.org/10.1021/jf010919h

Crozier, A., Del Rio, D., & Clifford, M. N. (2010). Bioavailability of dietary flavonoids and phenolic compounds. *Molecular Aspects of Medicine*, *31*(6), 446–467. https://doi.org/10.1016/j.mam.2010.09.007

Dajas, F. (2012). Life or death: Neuroprotective and anticancer effects of quercetin. *Journal of Ethnopharmacology*, *143*(2), 383–396. https://doi.org/10.1016/j.jep.2012.07.005

Davalos, A., Castilla, P., Gomez-Cordoves, C., & Bartolome, B. (2006). Quercetin is bioavailable from a single ingestion of grape juice. *International Journal of Food Sciences and Nutrition*, *57*(5-6), 391–398. https://doi.org/10.1080/09637480600858662

Day, A. J., Gee, J. M., DuPont, M. S., Johnson, I. T., & Williamson, G. (2003). Absorption of quercetin-3-glucoside and quercetin-4 '-glucoside in the rat small intestine: The role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter. *Biochemical Pharmacology*, *65*(7), 1199–1206. https://doi.org/10.1016/S0006-2952(03)00039-X

Day, A. J., Mellon, F., Barron, D., Sarrazin, G., Morgan, M. R. A., & Williamson, G. (2001). Human metabolism of dietary flavonoids: Identification of plasma metabolites of quercetin. *Free Radical Research*, *35*(6), 941–952. doi: https://doi.org/10.1080/10715760100301441

Day, A. J., Canada, F. J., Diaz, J. C., Kroon, P. A., McLauchlan, W. R., Faulds, C. B., . . . Williamson, G. (2000). Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Letters*, *468*, 166–170. https://doi.org/10.1016/S0014-5793(00)01211-4

de Pascual-Teresa, S., Johnston, K. L., DuPont, M. S., O'Leary, K. A., Needs, P. W., Morgan, L. M., . . . Williamson, G. (2004). Quercetin metabolites downregulate cyclooxygenase-2 transcription in human lymphocytes ex vivo but not in vivo. *Journal of Nutrition*, *134*(3), 552–557.

de Vries, J. H., Hollman, P. C., Meyboom, S., Buysman, M. N., Zock, P. L., van Staveren, W. A., & Katan, M. B. (1998). Plasma concentrations and urinary excretion of the antioxidant flavonols quercetin and kaempferol as biomarkers for dietary intake. *American Journal of Clinical Nutrition*, *68*(1), 60–65.

de Vries, J. H., Hollman, P. C., van Amersfoort, I., Olthof, M. R., & Katan, M. B. (2001). Red wine is a poor source of bioavailable flavonols in men. *Journal of Nutrition*, *131*(3), 745–748.

Del Rio, D., Rodriguez-Mateos, A., Spencer, J. P., Tognolini, M., Borges, G., & Crozier, A. (2013). Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling*, *18*(14), 1818–1892. https://doi.org/10.1089/ars.2012.4581

Ding, H., Fu, Y., Chen, W., & Wang, Z. (2010). COMT Val158Met polymorphism and breast cancer risk: Evidence from 26 case-control studies. *Breast Cancer Research and Treatment*, https://doi.org/10.1007/s10549-010-0759-5

Dragoni, S., Gee, J., Bennett, R., Valoti, M., & Sgaragli, G. (2006). Red wine alcohol promotes quercetin absorption and directs its metabolism towards isorhamnetin and tamarixetin in rat intestine in vitro. *British Journal of Pharmacology*, *147*(7), 765–771. https://doi.org/10.1038/sj.bjp.0706662

Egert, S., Wolffram, S., Schulze, B., Langguth, P., Hubbermann, E. M., Schwarz, K., . . . Muller, M. J. (2012). Enriched cereal bars are more effective in increasing plasma quercetin compared with quercetin from powder-filled hard capsules. *British Journal of Nutrition*, *107*(4), 539–546. https://doi.org/10.1017/S0007114511003242

Erlund, I., Freese, R., Marnietni, J., Hakala, P., & Alfthan, G. (2006). Bioavailability of quercetin from berries and the diet. *Nutrition and Cancer-an International Journal*, *54*(1), 13–17. doi: https://doi.org/10.1207/s15327914nc5401_3

Erlund, I., Kosonen, T., Alfthan, G., Maenpaa, J., Perttunen, K., Kenraali, J., . . . Aro, A. (2000). Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. *European Journal Clinical Pharmacology*, *56*(8), 545–553.

Erlund, I., Marniemi, J., Hakala, P., Alfthan, G., Meririnne, E., & Aro, A. (2003). Consumption of black currants, lingonberries and bilberries increases serum quercetin concentrations. *European Journal of Clinical Nutrition*, *57*(1), 37–42. https://doi.org/10.1038/sj.ejcn.1601513

Erlund, I., Silaste, M. L., Alfthan, G., Rantala, M., Kesaniemi, Y. A., & Aro, A. (2002). Plasma concentrations of the flavonoids hesperetin, naringenin and quercetin in human subjects following their habitual diets, and diets high or low in fruit and vegetables. *European Journal of Clinical Nutrition*, *56*(9), 891–898. https://doi.org/10.1038/sj.ejcn.1601409

FDA. (2010). GRAS Notice for high purity quercetin. Retrieved from https://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn341-1.pdf Downloaded on the 25th February 2014.

Ferry, D. R., Smith, A., Malkhandi, J., Fyfe, D. W., deTakats, P. G., Anderson, D., . . . Kerr, D. J. (1996). Phase I clinical trial of the flavonoid quercetin: Pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clinical Cancer Research*, *2*(4), 659–668.

Flatz, G., & Rotthauwe, H. W. (1977). The human lactase polymorphism: Physiology and genetics of lactose absorption and malabsorption. *Progress in Medical Genetics*, *2*, 205–249.

Fujita, T., Brown, C., Carlson, E. J., Taylor, T., de la Cruz, M., Johns, S. J., . . . Giacomini, K. M. (2005). Functional analysis of polymorphisms in the organic anion transporter, SLC22A6 (OAT1). *Pharmacogenetics and Genomics*, *15*(4), 201–209.

Galindo, P., Rodriguez-Gomez, I., Gonzalez-Manzano, S., Duenas, M., Jimenez, R., Menendez, C., . . . Duarte, J. (2012). Glucuronidated quercetin lowers blood pressure in spontaneously hypertensive rats via deconjugation. *Plos One*, *7*(3). doi: ARTN e32673 Retrieved from 10.1371/journal.pone.0032673

Gibellini, L., Pinti, M., Nasi, M., Montagna, J. P., De Biasi, S., Roat, E., . . . Cossarizza, A. (2011). Quercetin and cancer chemoprevention. *Evidence-Based Complementary and Alternative Medicine*, 1–15. https://doi.org/10.1093/ecam/neq053

Glatt, H., Engelke, C. E., Pabel, U., Teubner, W., Jones, A. L., Coughtrie, M. W., . . . Meinl, W. (2000). Sulfotransferases: Genetics and role in toxicology. *Toxicology Letters*, *112–113*, 341–348.

Goldberg, D. A., Yan, J., & Soleas, G. J. (2003). Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clinical Biochemistry*, *36*(1), 79–87. https://doi.org/10.1016/S0009-9120(02)00397-1

Gonzalez-Sarrias, A., Garcia-Villalba, R., Romo-Vaquero, M., Alasalvar, C., Orem, A., Zafrilla, P., . . . Espin, J. C. (2017). Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomized clinical trial. *Molecular Nutrition & Food Research*, *61*(5). doi: ARTN 1600830 Retrieved from 10.1002/mnfr.201600830

Govind, P. T., Suiko, M., Sakakibara, Y., & Ming, C. L. (2001). Sulfation of flavonoids and other phenolic dietary compounds by the human cytosolic

sulfotransferases. *Biochemical and Biophysical Research Communications*, *285*(5), 1175–1179. https://doi.org/10.1006/bbrc.2001.5316

Graefe, E. U., Derendorf, H., & Veit, M. (1999). Pharmacokinetics and bioavailability of the flavonol quercetin in humans. *International Journal of Clinical Pharmacology and Therapeutics*, *37*(5), 219–233.

Graefe, E. U., Wittig, J., Mueller, S., Riethling, A. K., Uehleke, B., Drewelow, B., . . . Veit, M. (2001). Pharmacokinetics and bioavailability of quercetin glycosides in humans. *Journal of Clinical Pharmacology*, *41*(5), 492–499.

Grinder-Pedersen, L., Rasmussen, S. E., Bugel, S., Jorgensen, L. V., Dragsted, L. O., Gundersen, V., & Sandstrom, B. (2003). Effect of diets based on foods from conventional versus organic production on intake and excretion of flavonoids and markers of antioxidative defense in humans. *Journal of Agricultural and Food Chemistry*, *51*(19), 5671–5676. https://doi.org/10.1021/jf030217n

Guo, Y., Mah, E., Davis, C. G., Jalili, T., Ferruzzi, M. G., Chun, O. K., & Bruno, R. S. (2013). Dietary fat increases quercetin bioavailability in overweight adults. *Molecular Nutrition & Food Research*, *57*(5), 896–905. https://doi.org/10.1002/mnfr.201200619

Harwood, M., Danielewska-Nikiel, B., Borzelleca, J. F., Flamm, G. W., Williams, G. M., & Lines, T. C. (2007). A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. *Food Chemical Toxicology*, *45*(11), 2179–2205. https://doi.org/10.1016/j.fct.2007.05.015

Hollman, P. C., Bijsman, M. N., van Gameren, Y., Cnossen, E. P., de Vries, J. H., & Katan, M. B. (1999). The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides in man. *Free Radical Research*, *31*(6), 569–573.

Hollman, P. C., & Katan, M. B. (1999). Health effects and bioavailability of dietary flavonols. *Free Radical Research* (31 Suppl), S75–S80.

Hollman, P. C., van Trijp, J. M., Buysman, M. N., van der Gaag, M. S., Mengelers, M. J., de Vries, J. H., & Katan, M. B. (1997). Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. *FEBS Letters*, *418*(1-2), 152–156.

Hollman, P. C., van Trijp, J. M., Mengelers, M. J., de Vries, J. H., & Katan, M. B. (1997). Bioavailability of the dietary antioxidant flavonol quercetin in man. *Cancer Letters*, *114*(1-2), 139–140.

Hollman, P. C. H., Devries, J. H. M., Vanleeuwen, S. D., Mengelers, M. J. B., & Katan, M. B. (1995). Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. *American Journal of Clinical Nutrition*, *62*(6), 1276–1282.

Hollman, P. C. H., vanderGaag, M., Mengelers, M. J. B., vanTrijp, J. M. P., deVries, J. H., & Katan, M. B. (1996). Absorption and disposition kinetics of the dietary antioxidant quercetin in man. *Free Radical Biology and Medicine*, *21*(5), 703–707. doi: https://doi.org/10.1016/0891-5849(96)00129-3

Hong, Y., & Mitchell, A. E. (2004). Metabolic profiling of flavonol metabolites in human urine by liquid chromatography and tandem mass spectrometry. *Journal of Agricultural and Food Chemistry*, *52*(22), 6794–6801. https://doi.org/10.1021/jf040274w

Hubbard, G. P., Wolffram, S., Lovegrove, J. A., & Gibbins, J. M. (2004). Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. *Journal of Thrombosis and Haemostasis*, *2*(12), 2138–2145. https://doi.org/10.1111/j.1538-7836.2004.01067.x

Ito, H., Gonthier, M. P., Manach, C., Morand, C., Mennen, L., Remesy, C., & Scalbert, A. (2005). Polyphenol levels in human urine after intake of six different polyphenol-rich beverages. *British Journal of Nutrition*, *94*(4), 500–509.

Jaganath, I. B., Mullen, W., Edwards, C. A., & Crozier, A. (2006). The relative contribution of the small and large intestine to the absorption and metabolism of rutin in man. *Free Radical Research*, *40*(10), 1035–1046. https://doi.org/10.1080/10715760600771400

Jin, D., Hakamata, H., Takahashi, K., Kotani, A., & Kusu, F. (2004). Determination of quercetin in human plasma after ingestion of commercial canned green tea by semi-micro HPLC with electrochemical detection. *Biomedical Chromatography*, *18*(9), 662–666. https://doi.org/10.1002/bmc.370

Jin, F., Nieman, D. C., Shanely, R. A., Knab, A. M., Austin, M. D., & Sha, W. (2010). The variable plasma quercetin response to 12-week quercetin supplementation in humans. *European Journal of Clinical Nutrition*, *64*(7), 692–697. https://doi.org/10.1038/ejcn.2010.91

Kaddurah-Daouk, R., & Weinshilboum, R. M., & Pharmacometabolomics Research Network. (2014). Pharmacometabolomics: Implications for clinical pharmacology and systems pharmacology. *Clinical Pharmacology and Therapeutics*, *95*(2), 154–167. https://doi.org/10.1038/clpt.2013.217

Kahle, K., Kempf, M., Schreier, P., Scheppach, W., Schrenk, D., Kautenburger, T., . . . Richling, E. (2011). Intestinal transit and systemic metabolism of apple polyphenols. *European Journal of Nutrition*, *50*(7), 507–522. https://doi.org/10.1007/s00394-010-0157-0

Kawabata, K., Mukai, R., & Ishisaka, A. (2015). Quercetin and related polyphenols: New insights and implications for their bioactivity and bioavailability. *Food & Function*, *6*(5), 1399–1417. https://doi.org/10.1039/C4FO01178C

Kawai, Y. (2014). β-Glucuronidase activity and mitochondrial dysfunction: The sites where flavonoid glucuronides act as anti-inflammatory agents. *Journal of Clinical Biochemistry and Nutrition*, *54*(3), 145–150. https://doi.org/10.3164/jcbn.14-9</bib>

Kawai, Y., Nishikawa, T., Shiba, Y., Saito, S., Murota, K., Shibata, N., . . . Terao, J. (2008). Macrophage as a target of quercetin glucuronides in human atherosclerotic arteries - Implication in the anti-atherosclerotic mechanism of dietary flavonoids. *Journal of Biological Chemistry*, *283*(14), 9424–9434. https://doi.org/10.1074/jbc.M706571200

Kerb, R., Hoffmeyer, S., & Brinkmann, U. (2001). ABC drug transporters: Hereditary polymorphisms and pharmacological impact in MDR1, MRP1 and MRP2. *Pharmacogenomics*, *2*(1), 51–64. https://doi.org/10.1517/14622416.2.1.51

Kerimi, A., & Williamson, G. (2017). Differential impact of flavonoids on redox modulation, bioenergetics, and cell signaling in normal and tumor cells: A comprehensive review. *Antioxidants & Redox Signaling*. doi: https://doi.org/10.1089/ars.2017.7086

Koli, R., Erlund, I., Jula, A., Marniemi, J., Mattila, P., & Alfthan, G. (2010). Bioavailability of various polyphenols from a diet containing moderate amounts of berries. *Journal of Agricultural and Food Chemistry*, *58*(7), 3927–3932. https://doi.org/10.1021/jf9024823

Krogholm, K. S., Bredsdorff, L., Knuthsen, P., Haraldsdottir, J., & Rasmussen, S. E. (2010). Relative bioavailability of the flavonoids quercetin, hesperetin and naringenin given simultaneously through diet. *European Journal of Clinical Nutrition*, *64*(4), 432–435. https://doi.org/10.1038/ejcn.2010.6

Lee, J., Ebeler, S. E., Zweigenbaum, J. A., & Mitchell, A. E. (2012). UHPLC-(ESI)QTOF MS/MS profiling of quercetin metabolites in human plasma postconsumption of applesauce enriched with apple peel and onion. *Journal of Agricultural and Food Chemistry*, *60*(34), 8510–8520. https://doi.org/10.1021/jf302637t

Lesser, S., Cermak, R., & Wolffram, S. (2004). Bioavailability of quercetin in pigs is influenced by the dietary fat content. *Journal of Nutrition*, *134*(6), 1508–1511.

Lodi, F., Jimenez, R., Moreno, L., Kroon, P. A., Needs, P. W., Hughes, D. A., . . . Perez-Vizcaino, F. (2009). Glucuronidated and sulfated metabolites of the flavonoid quercetin prevent endothelial dysfunction but lack direct vasorelaxant effects in rat aorta. *Atherosclerosis*, *204*(1), 34–39. https://doi.org/10.1016/j.atherosclerosis.2008.08.007

Loke, W. M., Jenner, A. M., Proudfoot, J. M., McKinley, A. J., Hodgson, J. M., Halliwel, B., & Croft, K. D. (2009). A metabolite profiling approach to identify biomarkers of flavonoid intake in humans. *Journal of Nutrition*, *139*(12), 2309–2314. https://doi.org/10.3945/jn.109.113613

Lu, L. L., Qian, D. W., Yang, J., Jiang, S., Guo, J. M., Shang, E. X., & Duan, J. A. (2013). Identification of isoquercitrin metabolites produced by human intestinal bacteria using UPLC-Q-TOF/MS. *Biomedical Chromatography*, *27*(4), 509–514. doi: https://doi.org/10.1002/Bmc.2820

Matsukawa, N., Matsumoto, M., Shinoki, A., Hagio, M., Inoue, R., & Hara, H. (2009). Nondigestible saccharides suppress the bacterial degradation of quercetin aglycone in the large intestine and enhance the bioavailability of quercetin glucoside in rats. *Journal of Agricultural and Food Chemistry*, *57*(20), 9462–9468. https://doi.org/10.1021/jf9024079

Mauri, P. L., Iemoli, L., Gardana, C., Riso, P., Simonetti, P., Porrini, M., & Pietta, P. G. (1999). Liquid chromatography electrospray ionization mass spectrometric characterization of flavonol glycosides in tomato extracts and human plasma. *Rapid Communications in Mass Spectrometry*, *13*(10), 924–931. doi: https://doi.org/10.1002/(Sici)1097-0231(19990530)13:10<924::Aid-Rcm588>3.3.Co;2-7

McAnulty, S. R., McAnulty, L. S., Nieman, D. C., Quindry, J. C., Hosick, P. A., Hudson, M. H., . . . Dibarnardi, A. (2008). Chronic quercetin ingestion and exercise-induced oxidative damage and inflammation. *Applied Physiology Nutrition and Metabolism-Physiologie Appliquee Nutrition Et Metabolisme*, *33*(2), 254–262. https://doi.org/10.1139/H07-177

Menendez, C., Duenas, M., Galindo, P., Gonzalez-Manzano, S., Jimenez, R., Moreno, L., . . . Perez-Vizcaino, F. (2011). Vascular deconjugation of

quercetin glucuronide: The flavonoid paradox revealed? *Molecular Nutrition & Food Research*, *55*(12), 1780–1790. https://doi.org/10.1002/mnfr.201100378

Menezes, R., Rodriguez-Mateos, A., Kaltsatou, A., Gonzalez-Sarrias, A., Greyling, A., Giannaki, C., . . . Pinto, P. (2017). Impact of flavonols on cardiometabolic biomarkers: A meta-analysis of randomized controlled human trials to explore the role of inter-individual variability. *Nutrients*, *9*(2). https://doi.org/10.3390/nu9020117

Meng, X. F., Maliakal, P., Lu, H., Lee, M. J., & Yang, C. S. (2004). Urinary and plasma levels of resveratrol and quercetin in humans, mice, and rats after ingestion of pure compounds and grape juice. *Journal of Agricultural and Food Chemistry*, *52*(4), 935–942. https://doi.org/10.1021/jf030582e

Moon, J. H., Nakata, R., Oshima, S., Inakuma, T., & Terao, J. (2000). Accumulation of quercetin conjugates in blood plasma after the short-term ingestion of onion by women. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology*, *279*(2), R461–R467.

Moon, Y. J., Wang, L., DiCenzo, R., & Morris, M. E. (2008). Quercetin pharmacokinetics in humans. *Biopharmaceutics & Drug Disposition*, *29*(4), 205–217. https://doi.org/10.1002/bdd.605

Mullen, W., Boitier, A., Stewart, A. J., & Crozier, A. (2004). Flavonoid metabolites in human plasma and urine after the consumption of red onions: Analysis by liquid chromatography with photodiode array and full scan tandem mass spectrometric detection. *Journal of Chromatography A*, *1058*(1-2), 163–168. https://doi.org/10.1016/j.chroma.2004.08117

Mullen, W., Edwards, C. A., & Crozier, A. (2006). Absorption, excretion and metabolite profiling of methyl-, glucuronyl-, glucosyl- and sulpho-conjugates of quercetin in human plasma and urine after ingestion of onions. *British Journal of Nutrition*, *96*(1), 107–116. https://doi.org/10.1079/Bjn20061809

Murota, K., Matsuda, N., Kashino, Y., Fujikura, Y., Nakamura, T., Kato, Y., . . . Terao, J. (2010). a-Oligoglucosylation of a sugar moiety enhances the bioavailability of quercetin glucosides in humans. *Archives of Biochemistry and Biophysics*, *501*(1), 91–97. https://doi.org/10.1016/j.abb.2010.06.036

Nakamura, T., Murota, K., Kumamoto, S., Misumi, K., Bando, N., Ikushiro, S., . . . Terao, J. (2014). Plasma metabolites of dietary flavonoids after combination meal consumption with onion and tofu in humans. *Molecular Nutrition & Food Research*, *58*(2), 310–317. https://doi.org/10.1002/mnfr.201300234

Okamoto, T. (2005). Safety of quercetin for clinical application (Review). *International Journal Molecular Medicine*, *16*(2), 275–278.

Olthof, M. R., Hollman, P. C. H., Buijsman, M. N. C. P., van Amelsvoort, J. M. M., & Katan, M. B. (2003). Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. *Journal of Nutrition*, *133*(6), 1806–1814.

Paulke, A., Eckert, G. P., Schubert-Zsilavecz, M., & Wurglics, M. (2012). Isoquercitrin provides better bioavailability than quercetin: Comparison of quercetin metabolites in body tissue and brain sections after six days administration of isoquercitrin and quercetin. *Pharmazie*, *67*(12), 991–996. https://doi.org/10.1691/ph.2012.2050

Perez-Jimenez, J., Fezeu, L., Touvier, M., Arnault, N., Manach, C., Hercberg, S., . . . Scalbert, A. (2011). Dietary intake of 337 polyphenols in French adults. *American Journal of Clinical Nutrition*, *93*(6), 1220–1228. https://doi.org/10.3945/ajcn.110.007096

Perez-Jimenez, J., Neveu, V., Vos, F., & Scalbert, A. (2010). Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *European Journal of Clinical Nutrition*, *64*(Suppl 3), S112–S120. https://doi.org/10.1038/ejcn.2010.221

Pérez-Jiménez, J., Hubert, J., Hooper, L., Cassidy, A., Manach, C., Williamson, G., & Scalbert, A. (2010). Urinary metabolites as biomarkers of polyphenol intake in humans: A systematic review. *American Journal of Clinical Nutrition*, *92*(4), 801–809. https://doi.org/10.3945/ajcn.2010.29924

Perez, A., Gonzalez-Manzano, S., Jimenez, R., Perez-Abud, R., Haro, J. M., Osuna, A., . . . Perez-Vizcaino, F. (2014). The flavonoid quercetin induces acute vasodilator effects in healthy volunteers: Correlation with beta-glucuronidase activity. *Pharmacological Research*, *89*, 11–18. https://doi.org/10.1016/j.phrs.2014.07.005

Petersen, B., Egert, S., Bosy-Westphal, A., Muller, M. J., Wolffram, S., Hubbermann, E. M., . . . Schwarz, K. (2016). Bioavailability of quercetin in humans and the influence of food matrix comparing quercetin capsules and different apple sources. *Food Research International*, *88*, 159–165. https://doi.org/10.1016/j.foodres.2016.02.013

Pimpao, R. C., Ventura, M. R., Ferreira, R. B., Williamson, G., & Santos, C. N. (2015). Phenolic sulfates as new and highly abundant metabolites in human plasma after ingestion of a mixed berry fruit puree. *British Journal of Nutrition*, *113*, 454–463. doi: Retrieved from S0007114514003511 [pii];10.1017/S0007114514003511 [doi]

Prot, J. M., Maciel, L., Bricks, T., Merlier, F., Cotton, J., Paullier, P., . . . Leclerc, E. (2014). First pass intestinal and liver metabolism of paracetamol in a microfluidic platform coupled with a mathematical modeling as a means of evaluating ADME processes in humans. *Biotechnology and Bioengineering*, *111*(10), 2027–2040. https://doi.org/10.1002/bit.25232

Ramesova, S., Sokolova, R., Degano, I., Bulickova, J., Zabka, J., & Gal, M. (2012). On the stability of the bioactive flavonoids quercetin and luteolin under oxygen-free conditions. *Analytical and Bioanalytical Chemistry*, *402*(2), 975–982. https://doi.org/10.1007/s00216-011-5504-3

Reinboth, M., Wolffram, S., Abraham, G., Ungemach, F. R., & Cermak, R. (2010). Oral bioavailability of quercetin from different quercetin glycosides in dogs. *British Journal of Nutrition*, *104*(2), 198–203. https://doi.org/10.1017/S000711451000053x

Rescigno, A., Thakur, A. K., & Marzo, A. (1994). On definition and use of the term bioavailability. *Arzneimittel-Forschung/Drug Research*, *44-2*(10), 1167–1169.

Rossi, A. M., Maggini, V., Fredianelli, E., Di Bello, D., Pietrabissa, A., Mosca, F., . . . Pacifici, G. M. (2004). Phenotype-genotype relationships of SULT1A1 in human liver and variations in the IC50 of the SULT1A1 inhibitor quercetin. *International Journal of Clinical Pharmacology and Therapeutics*, *42*(10), 561–567.

Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., & Russo, G. L. (2012). The flavonoid quercetin in disease prevention and therapy: Facts and fancies. *Biochemical Pharmacology*, *83*(1), 6–15. https://doi.org/10.1016/j.bcp.2011.08.010

Schlemmer, U. (1995). Bioavailability of nutrients conceptual aspects of definition and problems of determination. *British Journal of Nutrition*, *73*(1), 150–151.

Schneider, H., Schwiertz, A., Collins, M. D., & Blaut, M. (1999). Anaerobic transformation of quercetin-3-glucoside by bacteria from the human intestinal tract. *Archives of Microbiology*, *171*(2), 81–91.

Schulz, H. U., Schurer, M., Bassler, D., & Weiser, D. (2005). Investigation of pharmacokinetic data of hypericin, pseudohypericin, hyperforin and the flavonoids quercetin and isorhamnetin revealed from single and multiple oral dose studies with a hypericum extract containing tablet in healthy male volunteers. *Arzneimittel-Forschung-Drug Research*, *55*(10), 561–568. https://doi.org/10.1055/s-0031-1296905

Serra, A., Macia, A., Romero, M. P., Reguant, J., Ortega, N., & Motilva, M. J. (2012). Metabolic pathways of the colonic metabolism of flavonoids (flavonols, flavones and flavanones) and phenolic acids. *Food Chemistry*, *130*(2), 383–393. https://doi.org/10.1016/j.foodchem.2011.07.055

Sesink, A. L. A., O'Leary, K. A., & Hollman, P. C. H. (2001). Quercetin gluouronides but not glucosides are present in human plasma after consumption of quercetin-3-glucoside or quercetin-4 '-glucoside. *Journal of Nutrition*, *131*(7), 1938–1941.

Shimoi, K., Saka, N., Nozawa, R., Sato, M., Amano, I., Nakayama, T., & Kinae, N. (2001). Deglucuronidation of a flavonoid, luteolin monoglucuronide, during inflammation. *Drug Metabolism and Disposition*, *29*(12), 1521–1524.

Smith, A. J., Kavuru, P., Wojtas, L., Zaworotko, M. J., & Shytle, R. D. (2011). Cocrystals of quercetin with improved solubility and oral bioavailability. *Molecular Pharmaceutics*, *8*(5), 1867–1876. https://doi.org/10.1021/mp200209j

Sokolova, R., Degano, I., Ramesova, S., Bulickova, J., Hromadova, M., Gal, M., . . . Valasek, M. (2011). The oxidation mechanism of the antioxidant quercetin in nonaqueous media. *Electrochimica Acta*, *56*(21), 7421–7427. https://doi.org/10.1016/j.electacta.2011.04.121

Sokolova, R., Ramesova, S., Degano, I., Hromadova, M., Gal, M., & Zabka, J. (2012). The oxidation of natural flavonoid quercetin. *Chemical Communications*, *48*(28), 3433–3435. https://doi.org/10.1039/c2cc18018a

Spencer, J. P. E., Chowrimootoo, G., Choudhury, R., Debnam, E. S., Srai, S. K., & Rice-Evans, C. (1999). The small intestine can both absorb and glucuronidate luminal flavonoids. *FEBS Letters*, *458*(2), 224–230. doi: https://doi.org/10.1016/S0014-5793(99)01160-6

Stalmach, A., Mullen, W., Barron, D., Uchida, K., Yokota, T., Cavin, C., . . . Crozier, A. (2009). Metabolite profiling of hydroxycinnamate derivatives in plasma and urine after the ingestion of coffee by humans: Identification of biomarkers of coffee consumption. *Drug Metabolism and Disposition*, *37*(8), 1749–1758. https://doi.org/10.1124/dmd.109.028019

Sugatani, J. (2013). Function, genetic polymorphism, and transcriptional regulation of human UDP-glucuronosyltransferase (UGT) 1A1. *Drug Metabolism and Pharmacokinetics*, *28*(2), 83–92.

Tribolo, S., Lodib, F., Connor, C., Suri, S., Wilson, V. G., Taylor, M. A., . . . Hughes, D. A. (2008). Comparative effects of quercetin and its predominant human metabolites on adhesion molecule expression in activated human vascular endothelial cells. *Atherosclerosis*, *197*(1), 50–56. https://doi.org/10.1016/j.atherosclerosis.2007.07.040

Vacek, J., Papouskova, B., Kosina, P., Vrba, J., Kren, V., & Ulrichova, J. (2012). Biotransformation of flavonols and taxifolin in hepatocyte in vitro systems as determined by liquid chromatography with various stationary phases and electrospray ionization-quadrupole time-of-flight mass spectrometry. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences*, *899*, 109–115. https://doi.org/10.1016/j.jchromb.2012.05.009

Valentová, K., Vrba, J., Bancířová, M., Ulrichová, J., & Křen, V. (2014). Isoquercitrin: Pharmacology, toxicology, and metabolism. *Food and Chemical Toxicology*, *68*, 267–282. https://doi.org/10.1016/j.fct.2014.03.018

Walle, T. (2004). Absorption and metabolism of flavonoids. *Free Radical Biology and Medicine*, *36*(7), 829–837. https://doi.org/10.1016/j.freeradbiomed.2004.01.002

Walle, T., Otake, Y., Walle, U. K., & Wilson, F. A. (2000). Quercetin glucosides are completely hydrolyzed in ileostomy patients before absorption. *Journal of Nutrition*, *130*(11), 2658–2661.

Walle, T., Walle, U. K., & Halushka, P. V. (2001). Carbon dioxide is the major metabolite of quercetin in humans. *Journal of Nutrition*, *131*(10), 2648–2652.

Wang, Y. F., Singh, A. P., Nelson, H. N., Kaiser, A. J., Reker, N. C., Hooks, T. L., . . . Vorsa, N. (2016). Urinary clearance of cranberry flavonol glycosides in humans. *Journal of Agricultural and Food Chemistry*, *64*(42), 7931–7939. https://doi.org/10.1021/acs.jafc.6b03611

Wiczkowski, W., Romaszko, J., Bucinski, A., Szawara-Nowak, D., Honke, J., Zielinski, H., & Piskula, M. K. (2008). Quercetin from shallots (Allium cepa L. var. aggregatum) is more bioavailable than its glucosides. *Journal of Nutrition*, *138*(5), 885–888.

Williamson, G., Barron, D., Shimoi, K., & Terao, J. (2005). In vitro biological properties of flavonoid conjugates found in vivo. *Free Radical Research*, *39*(5), 457–469. https://doi.org/10.1080/10715760500053610

Wilms, L. C., Hollman, P. C. H., Boots, A. W., & Kleinjans, J. C. S. (2005). Protection by quercetin and quercetin-rich fruit juice against induction of oxidative DNA damage and formation of BPDE-DNA adducts in human lymphocytes. *Mutation Research-Genetic Toxicology and Environmental Mutagenesis*, *582*(1-2), 155–162. https://doi.org/10.1016/j.mrgentox.2005.01.006

Wojcicki, J., Gawronska-Szklarz, B., Bieganowski, W., Patalan, M., Smulski, H. K., Samochowiec, L., & Zakrzewski, J. (1995). Comparative pharmacokinetics and bioavailability of flavonoid glycosides of Ginkgo biloba after a single oral administration of three formulations to healthy volunteers. *Materia Medica Polona (Polish Journal of Medicine and Pharmacy)*, *27*(4), 141–146.

Young, J. F., Nielsen, S. E., Haraldsdottir, J., Daneshvar, B., Lauridsen, S. T., Knuthsen, P., . . . Dragsted, L. O. (1999). Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. *American Journal of Clinical Nutrition*, *69*(1), 87–94.

Yousri, N. A., Kastenmuller, G., Gieger, C., Shin, S. Y., Erte, I., Menni, C., . . . Suhre, K. (2014). Long term conservation of human metabolic phenotypes and link to heritability. *Metabolomics*, *10*(5), 1005–1017. https://doi.org/10.1007/s11306-014-0629-y