Bioavailability of Quercetin in Humans with a Focus on Inter-Individual 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 are subject to catabolism by the microbiota followed by absorption of the products by the colon. The resulting compounds are bioavailable, circulate in the blood as conjugates with glucuronide, methyl or sulfate groups attached, and 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 inter-individual 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 inter-individual 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 inter-individual differences in biological responses.

Introduction

Quercetin is a polyphenolic compound of the flavonoid class (sub-class flavonol) and is regularly consumed in the diet. Rich sources are kale, onion, various berries, apples, black tea and red grapes (Perez-Jimenez and others 2010, Perez-Jimenez and others 2011), and certain commercially available food supplements (Serra and others 2012). Quercetin safety has been critically reviewed (Okamoto 2005, Harwood and others 2007) and high-purity quercetin was given *Generally Recognized As Safe* (GRAS) status in 2010 (FDA 2010). Over the last few decades, a large number of 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 (Okamoto 2005, Harwood and others 2007, Boots and others 2008, Gibellini and others 2011, Dajas 2012, Russo and others 2012, Kawabata and others 2015, Kerimi and Williamson 2017).

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 and others 2010, Del Rio and others 2013). Only a minor proportion of quercetin is absorbed in the stomach (Crespy and others 2002), and the primary site of absorption is the small intestine (Graefe and others 1999, Ader and others 2000, Erlund and others 2000). In planta, quercetin is found attached to sugars, since the aglycone is highly reactive and relatively insoluble in aqueous media (Azuma and others 2002, Smith and others 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, which remove glucose groups from flavonols (Day and others 2000). Paradoxically, quercetin glycosides are generally more bioavailable than the aglycone since the latter is more insoluble in the lumen of the gut (Hollman and others 1995, Hollman and others 1996, Hollman and others 1997a). 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 (Cermak and others 2003, Arts and others 2004, Reinboth and others 2010, Russo and others 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 (Lesser and others 2004, Guo and others 2013), alcohol (Dragoni and others 2006) or with non-digestible oligosaccharides (Matsukawa and others 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 (Fig. 1). These biotransformation reactions are also observed in rat or human hepatocytes *in vitro* (Vacek and others 2012). Once absorbed, quercetin enters the bloodstream and appears as various different chemical species, including methylated forms. In plasma, 78-79% was estimated as conjugates of quercetin, 10-13% as tamarixetin (4′-*O*-methyl-quercetin) and 8.5-11% as isorhamnetin (3′-*O*-methyl-quercetin) conjugates (Cermak and others 2003, Lesser and others 2004, Reinboth and others 2010). A significant proportion of conjugated flavonoids are excreted back into the intestinal lumen by enterocytes *via* multidrug resistance-associated protein 2 (MRP2 (ABCC2)) or breast cancer resistance protein (BCRP (ABCG2)) (Cermak and Wolffram 2006). Quercetin

glucuronides serve as a more stable form of quercetin for transport in the bloodstream, but may be deconjugated for example in vascular smooth muscle cells (Menendez and others 2011, Galindo and others 2012) and at sites of inflammation (Shimoi and others 2001, Menendez and others 2011, Kawai 2014, Perez and others 2014). The conjugates themselves 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 (Williamson and others 2005, Tribolo and others 2008, Lodi and others 2009, Beekmann and others 2012, Araujo and others 2013). 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 passes into the circulation, or is subject to catabolic reactions to form lower molecular weight phenolic species, as outlined in Fig. 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 and others 2006). Quercetin was also metabolized by porcine hindgut contents *in vitro* (Cermak and others 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 and others 2012). Similar degradation products were observed when quercetin was exposed to exhaustive electrochemical hydrolysis (Sokolova and others 2011, Ramesova and others 2012, Sokolova and others 2012). Degradation of quercetin by rat gut microbiota therefore involves C-ring fission, formation of 3-(3,4-dihydroxyphenyl)propionic acid, and subsequent transformation to

126 3,4-dihydroxyphenylacetic acid. Further transformation leads to protocatechuic acid
127 and then to 4-hydroxybenzoic acid. 3,4-Dihydroxyphenylacetic acid can also be
128 dehydroxylated to *m*- or *p*-hydroxyphenylacetic and phenylacetic acids (Fig. 2) (Serra
129 and others 2012). These compounds are further degraded into various simpler products
130 and finally to carbon dioxide (Walle and others 2001, Walle 2004).
131
132 The main pathways of metabolism of quercetin depend on conjugating enzymes, most
133 of which have known genetic polymorphisms, but are also inducible by drugs, food,
134 environment. Quercetin catabolism is also affected by microbiota composition, which
135 is influenced by multiple factors. It is not surprising, therefore, that there is substantial
136 inter-individual variation in absorption and metabolism of quercetin between
137 individuals. This has been observed for other groups of polyphenols. For example, the
138 metabolism of ellagitannins in humans shows several metabolizing phenotypes, or
139 "metabotypes" (Gonzalez-Sarrias and others 2017). These phenotypes are determined
140 by the concentration and activity of intestinal carriers and post-absorptive phase I and
141 phase II metabolizing enzymes, and by the composition and activities of the gut
142 microbiota, many of which will be influenced by the genotype of the subject (Yousri
143 and others 2014). Pharmacogenomic studies have demonstrated that for some drugs,
144 individuals can be categorized into poor, intermediate or extensive absorbers or
145 metabolizers, and dosing has to be adapted clinically (Kaddurah-Daouk and others
146 2014). Plant food phytochemicals are absorbed and metabolized through the same
147 polymorphic carriers and enzymatic systems as drugs, and so their pharmacokinetics
148 are also likely to depend on the same determinants.
149

In this review, we have examined inter-individual 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 and Katan 1999, Pérez-Jiménez and others 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 and others 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 and others 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 inter-individual 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 inter-individual 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 on March 2016 and July 2017 and retrieved 20 and 25 additional abstracts,

respectively. Kaempferol was originally included as it is also a flavonol, but since no relevant papers on inter-individual 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 (Fig. 3).

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, 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 (6 studies, Table 3) or food extracts (3 studies (data not shown))

(Wojcicki and others 1995, Schulz and others 2005, Correa and others 2014). 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 (Fig. 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 5 studies reported measuring both conjugates and aglycone after hydrolysis in urine and/or plasma. The number of subjects, however, was usually relatively small (<10).

Inter-Individual 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 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 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 standard error of the mean (SEM) by the formula $CV=100\times SD/mean$, and SEM was converted to SD by the formula $SD = SEM\times\sqrt{n}$, where n is number of volunteers. To provide an illustration of how the % CV and the

inter-individual variation are related, theoretical data are used to demonstrate the relationship between typical inter-individual variation and a calculated % CV in Fig. 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 Tables 4-6. For analysis of inter-individual 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 58-80% (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 inter-individual 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 and co-workers (Graefe and others 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 gut microbiota into lower molecular mass compounds. With administration of quercetin as a pure compound, the inter-individual 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 inter-individual 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 de-conjugating enzymes (usually crude β-glucuronidase/sulfatase from *Helix pomatia*) or submitted to acidic hydrolysis (Spencer and others 1999, Cermak and others 2003, Day and others 2003, Paulke and others 2012), which does not allow for the precise identification of the conjugated metabolites. In older publications, determination of quercetin using HPLC with UV-Vis (Spencer and others 1999, Day and others 2003) or fluorescence (Ader and others 2000) was used with relatively low sensitivity. Quercetin conjugates are now most frequently measured using HPLC/MS^n techniques (Mullen and others 2004, Stalmach and others 2009, Borges and Crozier 2012, Valentová and others 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 and others 2001, Mullen and others 2006, Murota and others 2010). Identification of the exact position of conjugation is, in most cases, impossible without authentic standards with known exact structure, confirmed by nuclear magnetic resonance.

During catabolism in the colon by the microbiota, 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 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 and others 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 formation of these compounds (Olthof and others 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

300 glucuronidated, forming isorhamnetin-3-*O*-glucuronide and isorhamnetin-4′-*O*-
301 glucuronide, but it appears that methylation prevents subsequent sulfation and *vice*
302 *versa*. Quercetin can also be doubly substituted with both sulfate and glucuronide
303 groups, and in some papers detection of methylated quercetin which has been
304 diglucuronidated was reported. There is also some evidence for quercetin substituted
305 with both a glucose and a sulfate or glucuronide, but it is not clear if a small amount of
306 quercetin was absorbed in the form of a glucoside and then further conjugated, or if
307 the glucosylation occurred post-absorption (Mullen and others 2004, Mullen and
308 others 2006). Some microbial metabolites of quercetin were identified when rutin was
309 given in pure form or in tomato juice, and these include phenylacetic and
310 hydroxyhippuric acid derivatives (Olthof and others 2003, Jaganath and others 2006).
311 Quantitative data on the presence of quercetin conjugates and microbial metabolites
312 are given in Table 8. Some metabolites such as quercetin-3′-*O*-sulfate are found only
313 in plasma and not in urine, whereas many conjugates are found in both urine and
314 plasma.
315
316 **Assessment of Individual Papers Where Data on Inter-Individual Variation are**
317 **Specifically Presented**
318
319 Specific information on the inter- or intra-individual differences in quercetin
320 bioavailability was available from 10 studies. Of these, 6 show the data in graphical
321 form only (Boyle and others 2000a, Boyle and others 2000b, Davalos and others 2006,
322 Moon and others 2008, Loke and others 2009, Petersen and others 2016), 1 presents
323 results based on radio-scintillation counting (Walle and others 2001) and only 3
324 provide numerical quantitative data for individual volunteers (Ferry and others 1996,

Moon and others 2000, Jaganath and others 2006). The form of presentation differs substantially for each of these publications, which are discussed below.

Uptake of quercetin from food was evaluated in 6 healthy non-obese normocholesterolemic non-smoking 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 and others 2000b) (Table 1). Wash-out periods of 7 d 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 are more probably glucuronides since the authors did not have the appropriate glucuronide standards at the time. Inter-individual 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 2 main flavonols in plasma are presented as bar graphs at time points -24, 0, 4, 8 and 24 h for the first phase only and difference between the highest and lowest responder at 4 h after ingestion can be estimated as approximately one order of magnitude (about 20 compared with 300 nM). In the second 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 d supplementation with 500 mg of quercetin in capsule form 3 times daily (measured for 8 h over the last day of the supplementation period) were published separately together with numerical data as means, medians and range (Moon and others 2008) (Table 2). This study differs from all others in that no baseline level is presented in the paper and no dietary restriction or wash-out were applied for the (pre-) supplementation period, although ingestion of 'quercetin products' within 30 d was an exclusion criteria. The study focused on re-entry pharmacokinetics, and it is clear that some subjects showed re-entry peaks of quercetin conjugates and other did not. The absorption rate constant and bioavailability also showed high inter-individual variability. From the individual plasma profiles, 2 subjects can be assigned as low responders (plasma concentration $\leq$ 3 nM throughout the measurement period), and at least 5 as high responders (peak concentration $\geq$ 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 and others 2000a)(Table 2). In this case, however, the profiles were measured in only 3 female volunteers following a single dose of 500 mg rutin. Subjects showed different kinetics, with 2 having maximal plasma level at 7 h and the third at 4 h. 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 wk placebo controlled supplementation study (n = 8 in each group, 500 mg rutin/d). While the plasma level 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 h after supplementation with a single dose of 200 mg of quercetin in a cross-over design including the control but also (−)-epicatechin and (−)-epigallocatechin gallate (EGCG, 1 wk wash-out between treatments, (Loke and others 2009) (Table 2). There were apparently high and low responders (4 subjects with 4-5 fold increase and at least 2 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 and others 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 h in placebo (n = 6) and grape juice treatment groups only (Davalos and others 2006) (Table 1). The limitation of this study is a high baseline level of quercetin (there was only 24 h "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 2 volunteers from the placebo group. In the grape juice group, 7 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 4 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 6 healthy subjects (Petersen and others 2016) (Table 3). This single dose, diet-controlled, cross-over study had 1 wk 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 (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 and others 2016).

Absorption and disposition of ^{14}C-radiolabelled quercetin was studied in 6 healthy subjects after oral and intravenous (i.v.) administration (Walle and others 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 is 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 – 68 and 0.30 – 0.37 μmol.h/L for oral and intravenous dose, respectively) and 21 and 18% for radioactivity recovery from urine (3.3 – 5.7% and 18.4 – 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 h after administration and in others not until 8 h, and therefore, $^{14}CO_2$ in the expired air represented 23.0-81.1% 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 dose, 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 and others 2001).

Quercetin concentration in human plasma from 7 volunteers was determined before and after a short-term ingestion of onions (Moon and others 2000) (Table 1). The subjects were given diets containing onion slices (67.6-93.6 mg of quercetin equivalents /d) with meals for 1 wk. After 10 h of fasting, quercetin was measured in plasma after β-glucuronidase-sulfatase treatment, and the concentration increased on average 16-fold after the 1-wk trial. However, individual data again indicated a

448 substantial variation between volunteers, some with a very low response (8-fold,
449 calculated from data) compared to others with a higher response (27-fold, calculated
450 from data). In a Phase I clinical trial, quercetin was administered by short intravenous
451 infusion at escalating doses at 3-wk intervals in cancer patients (Ferry and others
452 1996) (Table 2). Quercetin pharmacokinetics were defined during the first 3 h at
453 frequent intervals, and individual plasma profiles were plotted for 7 tested doses in 7
454 different patients. By analyzing the curves, it is clear that the patients responded
455 differently to quercetin administration. For example, 1 patient given a dose of 630 mg
456 quercetin/m^2 showed, after 120 min, a circulating blood level of quercetin lower than a
457 patient on 200 mg/m^2. This variation is also reflected in the parameters calculated by
458 pharmacokinetic modelling for 14 patients (shown in Fig. 5). For 7 patients treated
459 with 945 mg quercetin/m^2, the mean amount of quercetin excreted in urine ranged
460 from 0.03 to 7.6% of the dose administered, also indicating a considerable inter-patient
461 variability. In this study quercetin levels were determined after intravenous injection,
462 which eliminates variables derived from microbiota and intestinal absorption,
463 suggesting that variation in quercetin metabolizing enzymes and transporters
464 contribute highly to inter-individual variability.
465
466 In order to study the contribution of the small and large intestine to the absorption and
467 metabolism of rutin in humans, a study was conducted with a single dose of tomato
468 juice containing rutin (176 µmol) by healthy volunteers and ileostomists (Jaganath and
469 others 2006) Table1). Quercetin-3-*O*-glucuronide and isorhamnetin-3-*O*-glucuronide
470 were absent at baseline, and were measured at 4, 5, 6, 7 and 8 h post-ingestion. The
471 authors note a high extent of variation between the volunteers, and also for excretion
472 of urinary metabolites. Over a 24 h period, 1 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 0.02–0.35% 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 conclude that this large inter-individual 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 varies 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 highlights that a precise understanding of inter-individual variability of quercetin bioavailability requires measurement of all metabolic routes, including the gut microbiota.

Factors Affecting Inter-Individual Variation in Quercetin Bioavailability

The present paper clearly indicates that a substantial inter-individual variability in quercetin bioavailability is observed in all studies. Given the complexity of the pathways of metabolism which is obvious from Fig. 1 and 2, inter-individual 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 BMI and health status. There are several genetic polymorphisms in the enzymes and transporters shown in Fig. 1, which could account for some variability. Polymorphisms have been reported for LPH (Flatz and Rotthauwe 1977), UGTs (Sugatani 2013), COMT (Ding and others 2010), SULTs (Glatt and others 2000, Rossi and others 2004), ABC transporters (Kerb and others 2001) and OAT transporters (Fujita and others 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 inter-individual variability on the impact of flavonols on cardiometabolic biomarkers was investigated but owing to lack of data, effects could not be correlated with bioavailability (Menezes and others 2017).

Further studies designed specifically to address inter-individual variation are needed. At least moderately larger ($n \geq 20$) studies presenting individual data for pharmacokinetics of quercetin (and glycosides occurring in foods) including parent compound and most known low molecular weight metabolites, together with the details about the study subjects such as their 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 if 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 in data collection process from 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 and Wolffram S. 2000. Bioavailability and metabolism of the flavonol quercetin in the pig. Free Radical Bio Med 28:1056-67. Doi 10.1016/S0891-5849(00)00195-7

Araujo KCF, Costa EMDB, Pazini F, Valadares MC and de Oliveira V. 2013. Bioconversion of quercetin and rutin and the cytotoxicity activities of the transformed products. Food Chem Toxicol 51:93-96. 10.1016/j.fct.2012.09.015

Arts ICW, Sesink ALA, Faassen-Peters M and Hollman PCH. 2004. The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. Brit J Nutr 91:841-47. Doi 10.1079/Bjn20041123

Azuma K, Ippoushi K, Ito H, Higashio H and Terao J. 2002. Combination of lipids and emulsifiers enhances the absorption of orally administered quercetin in rats. J Agric Food Chem 50:1706-12.

Beekmann K, Actis-Goretta L, van Bladeren PJ, Dionisi F, Destaillats F and Rietjens IMCM. 2012. A state-of-the-art overview of the effect of metabolic conjugation on the

biological activity of flavonoids. Food & Function 3:1008-18. 10.1039/c2fo30065f

Boersma MG, van der Woude H, Bogaards J, Boeren S, Vervoort J, Cnubben NHP, van Iersel MLPS, van Bladeren PJ and Rietjens IMCM. 2002. Regioselectivity of phase 11 metabolism of luteolin and quercetin by UDP-glucuronosyl transferases. Chem Res Toxicol 15:662-70. 10.1021/tx0101705

Boots AW, Haenen GRMM and Bast A. 2008. Health effects of quercetin: From antioxidant to nutraceutical. Eur J Pharmacol 585:325-37. 10.1016/j.ejphar.2008.03.008

Borges G and Crozier A. 2012. HPLC-PDA-MS fingerprinting to assess the authenticity of pomegranate beverages. Food Chem 135:1863-67. 10.1016/j.foodchem.2012.05.108

Boyle SP, Dobson VL, Duthie SJ, Hinselwood DC, Kyle JAM and Collins AR. 2000a. Bioavailability and efficiency of rutin as an antioxidant: a human supplementation study. Eur J Clin Nutr 54:774-82. DOI 10.1038/sj.ejcn.1601090

Boyle SP, Dobson VL, Duthie SJ, Kyle JAM and Collins AR. 2000b. Absorption and DNA protective effects of flavonoid glycosides from an onion meal. Eur J Nutr 39:213-23. DOI 10.1007/s003940070014

Cermak R, Breves G, Lupke M and Wolffram S. 2006. In vitro degradation of the flavonol quercetin and of quercetin glycosides in the porcine hindgut. Arch Anim Nutr 60:180-89. 10.1080/17450390500467695

Cermak R, Landgraf S and Wolffram S. 2003. The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. J Nutr 133:2802-07.

592 Cermak R and Wolffram S. 2006. The potential of flavonoids to influence drug
593 metabolism and pharmacokinetics by local gastrointestinal mechanisms. Curr Drug
594 Metab 7:729-44. 10.2174/138920006778520570

595 Clifford MN, van der Hooft JJ and Crozier A. 2013. Human studies on the absorption,
596 distribution, metabolism, and excretion of tea polyphenols. Am J Clin Nutr 98:1619S-
597 30S. ajcn.113.058958 [pii];10.3945/ajcn.113.058958 [doi]

598 Correa CR, Chen CYO, Aldini G, Rasmussen H, Ronchi CF, Berchieri-Ronchi C, Cho
599 SM, Blumberg JB and Yeum KJ. 2014. Bioavailability of plant pigment
600 phytochemicals in Angelica keiskei in older adults: A pilot absorption kinetic study.
601 Nutr Res Pract 8:550-57. ajcn.113.058958

602 Crespy V, Morand C, Besson C, Manach C, Demigne C and Remesy C. 2002.
603 Quercetin, but not its glycosides, is absorbed from the rat stomach. J Agric Food
604 Chem 50:618-21. 10.1021/jf010919h

605 Crozier A, Del Rio D and Clifford MN. 2010. Bioavailability of dietary flavonoids and
606 phenolic compounds. Mol Aspects Med 31:446-67. 10.1016/j.mam.2010.09.007

607 Dajas F. 2012. Life or death: neuroprotective and anticancer effects of quercetin. J
608 Ethnopharmacol 143:383-96. 10.1016/j.jep.2012.07.005

609 Davalos A, Castilla P, Gomez-Cordoves C and Bartolome B. 2006. Quercetin is
610 bioavailable from a single ingestion of grape juice. Int J Food Sci Nutr 57:391-98.
611 10.1080/09637480600858662

612 Day AJ, Canada FJ, Diaz JC, Kroon PA, McLauchlan WR, Faulds CB, Plumb GW,
613 Morgan MRA and Williamson G. 2000. Dietary flavonoid and isoflavone glycosides
614 are hydrolysed by the lactase site of lactase phlorizin hydrolase. Febs Lett 468:166-70.

615 10.1016/S0014-5793(00)01211-4

616 Day AJ, Gee JM, DuPont MS, Johnson IT and Williamson G. 2003. Absorption of
617 quercetin-3-glucoside and quercetin-4 '-glucoside in the rat small intestine: the role of
618 lactase phlorizin hydrolase and the sodium-dependent glucose transporter. Biochem
619 Pharmacol 65:1199-206. 10.1016/S0006-2952(03)00039-X

620 Day AJ, Mellon F, Barron D, Sarrazin G, Morgan MRA and Williamson G. 2001.
621 Human metabolism of dietary flavonoids: Identification of plasma metabolites of
622 quercetin. Free Radical Res 35:941-52. Doi 10.1080/10715760100301441

623 de Pascual-Teresa S, Johnston KL, DuPont MS, O'Leary KA, Needs PW, Morgan LM,
624 Clifford MN, Bao Y and Williamson G. 2004. Quercetin metabolites downregulate
625 cyclooxygenase-2 transcription in human lymphocytes ex vivo but not in vivo. J Nutr
626 134:552-7.

627 de Vries JH, Hollman PC, Meyboom S, Buysman MN, Zock PL, van Staveren WA
628 and Katan MB. 1998. Plasma concentrations and urinary excretion of the antioxidant
629 flavonols quercetin and kaempferol as biomarkers for dietary intake. Am J Clin Nutr
630 68:60-5.

631 de Vries JH, Hollman PC, van Amersfoort I, Olthof MR and Katan MB. 2001. Red
632 wine is a poor source of bioavailable flavonols in men. J Nutr 131:745-8.

633 Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G and Crozier A.
634 2013. Dietary (poly)phenolics in human health: structures, bioavailability, and
635 evidence of protective effects against chronic diseases. Antioxid Redox Signal
636 18:1818-92. 10.1089/ars.2012.4581

637 Ding H, Fu Y, Chen W and Wang Z. 2010. COMT Val158Met polymorphism and

breast cancer risk: evidence from 26 case-control studies. Breast Cancer Res Treat. 10.1007/s10549-010-0759-5 [doi]

Dragoni S, Gee J, Bennett R, Valoti M and Sgaragli G. 2006. Red wine alcohol promotes quercetin absorption and directs its metabolism towards isorhamnetin and tamarixetin in rat intestine in vitro. Brit J Pharmacol 147:765-71. 10.1038/sj.bjp.0706662

Egert S, Wolffram S, Schulze B, Langguth P, Hubbermann EM, Schwarz K, Adolphi B, Bosy-Westphal A, Rimbach G and Muller MJ. 2012. Enriched cereal bars are more effective in increasing plasma quercetin compared with quercetin from powder-filled hard capsules. Brit J Nutr 107:539-46. 10.1017/S0007114511003242

Erlund I, Freese R, Marnietni J, Hakala P and Alfthan G. 2006. Bioavailability of quercetin from berries and the diet. Nutr Cancer 54:13-17. DOI 10.1207/s15327914nc5401_3

Erlund I, Kosonen T, Alfthan G, Maenpaa J, Perttunen K, Kenraali J, Parantainen J and Aro A. 2000. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol 56:545-53.

Erlund I, Marniemi J, Hakala P, Alfthan G, Meririnne E and Aro A. 2003. Consumption of black currants, lingonberries and bilberries increases serum quercetin concentrations. Eur J Clin Nutr 57:37-42. 10.1038/sj.ejcn.1601513

Erlund I, Silaste ML, Alfthan G, Rantala M, Kesaniemi YA and 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. Eur J Clin Nutr 56:891-98. 10.1038/sj.ejcn.1601409

661 FDA. 2010. GRAS Notice for high purity quercetin.
662 http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn341-1.pdf. Downloaded on
663 the 25th February 2014. In.

664 Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, Baker J and
665 Kerr DJ. 1996. Phase I clinical trial of the flavonoid quercetin: Pharmacokinetics and
666 evidence for in vivo tyrosine kinase inhibition. Clin Cancer Res 2:659-68.

667 Flatz G and Rotthauwe HW. 1977. The human lactase polymorphism: physiology and
668 genetics of lactose absorption and malabsorption. Prog Med Genet 2:205-49.

669 Fujita T, Brown C, Carlson EJ, Taylor T, de la Cruz M, Johns SJ, Stryke D,
670 Kawamoto M, Fujita K, Castro R, Chen CW, Lin ET, Brett CM, Burchard EG, Ferrin
671 TE, Huang CC, Leabman MK and Giacomini KM. 2005. Functional analysis of
672 polymorphisms in the organic anion transporter, SLC22A6 (OAT1). Pharmacogenet
673 Genomics 15:201-9.

674 Galindo P, Rodriguez-Gomez I, Gonzalez-Manzano S, Duenas M, Jimenez R,
675 Menendez C, Vargas F, Tamargo J, Santos-Buelga C, Perez-Vizcaino F and Duarte J.
676 2012. Glucuronidated quercetin lowers blood pressure in spontaneously hypertensive
677 rats via deconjugation. PloS One 7. ARTN e32673

678 10.1371/journal.pone.0032673

679 Gibellini L, Pinti M, Nasi M, Montagna JP, De Biasi S, Roat E, Bertoncelli L, Cooper
680 EL and Cossarizza A. 2011. Quercetin and cancer chemoprevention. Evid-Based
681 Compl Alt 1-15. 10.1093/ecam/neq053

682 Glatt H, Engelke CE, Pabel U, Teubner W, Jones AL, Coughtrie MW, Andrae U,
683 Falany CN and Meinl W. 2000. Sulfotransferases: genetics and role in toxicology.

684 Toxicol Lett 112-113:341-48.

685 Goldberg DA, Yan J and Soleas GJ. 2003. Absorption of three wine-related
686 polyphenols in three different matrices by healthy subjects. Clin Biochem 36:79-87.
687 10.1016/S0009-9120(02)00397-1

688 Gonzalez-Sarrias A, Garcia-Villalba R, Romo-Vaquero M, Alasalvar C, Orem A,
689 Zafrilla P, Tomas-Barberan FA, Selma MV and Espin JC. 2017. Clustering according
690 to urolithin metabotype explains the interindividual variability in the improvement of
691 cardiovascular risk biomarkers in overweight-obese individuals consuming
692 pomegranate: A randomized clinical trial. Mol Nutr Food Res 61. ARTN 1600830

693 10.1002/mnfr.201600830

694 Govind PT, Suiko M, Sakakibara Y and Ming CL. 2001. Sulfation of flavonoids and
695 other phenolic dietary compounds by the human cytosolic sulfotransferases. Biochem
696 Bioph Res Co 285:1175-79. 10.1006/bbrc.2001.5316

697 Graefe EU, Derendorf H and Veit M. 1999. Pharmacokinetics and bioavailability of
698 the flavonol quercetin in humans. Int J Clin Pharm Th 37:219-33.

699 Graefe EU, Wittig J, Mueller S, Riethling AK, Uehleke B, Drewelow B, Pforte H,
700 Jacobasch G, Derendorf H and Veit M. 2001. Pharmacokinetics and bioavailability of
701 quercetin glycosides in humans. J Clin Pharmacol 41:492-99.

702 Grinder-Pedersen L, Rasmussen SE, Bugel S, Jorgensen LV, Dragsted LO, Gundersen
703 V and Sandstrom B. 2003. Effect of diets based on foods from conventional versus
704 organic production on intake and excretion of flavonoids and markers of antioxidative
705 defense in humans. J Agr Food Chem 51:5671-76. 10.1021/jf030217n

706 Guo Y, Mah E, Davis CG, Jalili T, Ferruzzi MG, Chun OK and Bruno RS. 2013.
707 Dietary fat increases quercetin bioavailability in overweight adults. Mol Nutr Food
708 Res 57:896-905. 10.1002/mnfr.201200619

709 Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM and
710 Lines TC. 2007. A critical review of the data related to the safety of quercetin and lack
711 of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties.
712 Food Chem Toxicol 45:2179-205. 10.1016/j.fct.2007.05.015

713 Hollman PC, Bijsman MN, van Gameren Y, Cnossen EP, de Vries JH and Katan MB.
714 1999. The sugar moiety is a major determinant of the absorption of dietary flavonoid
715 glycosides in man. Free Radic Res 31:569-73.

716 Hollman PC and Katan MB. 1999. Health effects and bioavailability of dietary
717 flavonols. Free Radic Res 31 Suppl:S75-80.

718 Hollman PC, van Trijp JM, Buysman MN, van der Gaag MS, Mengelers MJ, de Vries
719 JH and Katan MB. 1997a. Relative bioavailability of the antioxidant flavonoid
720 quercetin from various foods in man. Febs Lett 418:152-6.

721 Hollman PC, van Trijp JM, Mengelers MJ, de Vries JH and Katan MB. 1997b.
722 Bioavailability of the dietary antioxidant flavonol quercetin in man. Cancer Lett
723 114:139-40.

724 Hollman PCH, Devries JHM, Vanleeuwen SD, Mengelers MJB and Katan MB. 1995.
725 Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy
726 volunteers. Am J Clin Nutr 62:1276-82.

727 Hollman PCH, vanderGaag M, Mengelers MJB, vanTrijp JMP, deVries JH and Katan
728 MB. 1996. Absorption and disposition kinetics of the dietary antioxidant quercetin in

729 man. Free Radical Bio Med 21:703-07. Doi 10.1016/0891-5849(96)00129-3

730 Hong Y and Mitchell AE. 2004. Metabolic profiling of flavonol metabolites in human
731 urine by liquid chromatography and tandem mass spectrometry. J Agr Food Chem
732 52:6794-801. 10.1021/jf040274w

733 Hubbard GP, Wolffram S, Lovegrove JA and Gibbins JM. 2004. Ingestion of
734 quercetin inhibits platelet aggregation and essential components of the collagen-
735 stimulated platelet activation pathway in humans. J Thromb Haemost 2:2138-45. DOI
736 10.1111/j.1538-7836.2004.01067.x

737 Ito H, Gonthier MP, Manach C, Morand C, Mennen L, Remesy C and Scalbert A.
738 2005. Polyphenol levels in human urine after intake of six different polyphenol-rich
739 beverages. Brit J Nutr 94:500-9.

740 Jaganath IB, Mullen W, Edwards CA and Crozier A. 2006. The relative contribution
741 of the small and large intestine to the absorption and metabolism of rutin in man. Free
742 Radical Res 40:1035-46. 10.1080/10715760600771400

743 Jin D, Hakamata H, Takahashi K, Kotani A and Kusu F. 2004. Determination of
744 quercetin in human plasma after ingestion of commercial canned green tea by semi-
745 micro HPLC with electrochemical detection. Biomed Chromatogr 18:662-6.
746 10.1002/bmc.370

747 Jin F, Nieman DC, Shanely RA, Knab AM, Austin MD and Sha W. 2010. The
748 variable plasma quercetin response to 12-week quercetin supplementation in humans.
749 Eur J Clin Nutr 64:692-97. 10.1038/ejcn.2010.91

750 Kaddurah-Daouk R, Weinshilboum RM and Pharmacometabolomics Research N.
751 2014. Pharmacometabolomics: implications for clinical pharmacology and systems

752 pharmacology. Clin Pharmacol Ther 95:154-67. 10.1038/clpt.2013.217

753 Kahle K, Kempf M, Schreier P, Scheppach W, Schrenk D, Kautenburger T, Hecker D,
754 Huemmer W, Ackermann M and Richling E. 2011. Intestinal transit and systemic
755 metabolism of apple polyphenols. Eur J Nutr 50:507-22. 10.1007/s00394-010-0157-0

756 Kawabata K, Mukai R and Ishisaka A. 2015. Quercetin and related polyphenols: new
757 insights and implications for their bioactivity and bioavailability. Food & Function
758 6:1399-417. 10.1039/C4FO01178C

759 Kawai Y. 2014. β-Glucuronidase activity and mitochondrial dysfunction: the sites
760 where flavonoid glucuronides act as anti-inflammatory agents. J Clin Biochem Nutr
761 54:145-50. 10.3164/jcbn.14-9

762 Kawai Y, Nishikawa T, Shiba Y, Saito S, Murota K, Shibata N, Kobayashi M,
763 Kanayama M, Uchida K and Terao J. 2008. Macrophage as a target of quercetin
764 glucuronides in human atherosclerotic arteries - Implication in the anti-atherosclerotic
765 mechanism of dietary flavonoids. J Biol Chem 283:9424-34.
766 10.1074/jbc.M706571200

767 Kerb R, Hoffmeyer S and Brinkmann U. 2001. ABC drug transporters: hereditary
768 polymorphisms and pharmacological impact in MDR1, MRP1 and MRP2.
769 Pharmacogenomics 2:51-64. 10.1517/14622416.2.1.51

770 Kerimi A and Williamson G. 2017. Differential Impact of Flavonoids on Redox
771 Modulation, Bioenergetics, and Cell Signaling in Normal and Tumor Cells: A
772 Comprehensive Review. Antioxid Redox Sign. https://doi.org/10.1089/ars.2017.7086

773

774 Koli R, Erlund I, Jula A, Marniemi J, Mattila P and Alfthan G. 2010. Bioavailability
775 of various polyphenols from a diet containing moderate amounts of berries. J Agr
776 Food Chem 58:3927-32. 10.1021/jf9024823

777 Krogholm KS, Bredsdorff L, Knuthsen P, Haraldsdottir J and Rasmussen SE. 2010.
778 Relative bioavailability of the flavonoids quercetin, hesperetin and naringenin given
779 simultaneously through diet. Eur J Clin Nutr 64:432-35. 10.1038/ejcn.2010.6

780 Lee J, Ebeler SE, Zweigenbaum JA and Mitchell AE. 2012. UHPLC-(ESI)QTOF
781 MS/MS profiling of quercetin metabolites in human plasma postconsumption of
782 applesauce enriched with apple peel and onion. J Agr Food Chem 60:8510-20.
783 10.1021/jf302637t

784 Lesser S, Cermak R and Wolffram S. 2004. Bioavailability of quercetin in pigs is
785 influenced by the dietary fat content. J Nutr 134:1508-11.

786 Lodi F, Jimenez R, Moreno L, Kroon PA, Needs PW, Hughes DA, Santos-Buelga C,
787 Gonzalez-Paramas A, Cogolludo A, Lopez-Sepulveda R, Duarte J and Perez-Vizcaino
788 F. 2009. Glucuronidated and sulfated metabolites of the flavonoid quercetin prevent
789 endothelial dysfunction but lack direct vasorelaxant effects in rat aorta.
790 Atherosclerosis 204:34-39. 10.1016/j.atherosclerosis.2008.08.007

791 Loke WM, Jenner AM, Proudfoot JM, McKinley AJ, Hodgson JM, Halliwel B and
792 Croft KD. 2009. A metabolite profiling approach to identify biomarkers of flavonoid
793 intake in humans. J Nutr 139:2309-14. 10.3945/jn.109.113613

794 Lu LL, Qian DW, Yang J, Jiang S, Guo JM, Shang EX and Duan JA. 2013.
795 Identification of isoquercitrin metabolites produced by human intestinal bacteria using
796 UPLC-Q-TOF/MS. Biomed Chromatogr 27:509-14. Doi 10.1002/Bmc.2820

797 Matsukawa N, Matsumoto M, Shinoki A, Hagio M, Inoue R and Hara H. 2009.
798 Nondigestible saccharides suppress the bacterial degradation of quercetin aglycone in
799 the large intestine and enhance the bioavailability of quercetin glucoside in rats. J Agr
800 Food Chem 57:9462-68. 10.1021/jf9024079

801 Mauri PL, Iemoli L, Gardana C, Riso P, Simonetti P, Porrini M and Pietta PG. 1999.
802 Liquid chromatography electrospray ionization mass spectrometric characterization of
803 flavonol glycosides in tomato extracts and human plasma. Rapid Commun Mass Sp
804 13:924-31. Doi 10.1002/(Sici)1097-0231(19990530)13:10<924::Aid-
805 Rcm588>3.3.Co;2-7

806 McAnulty SR, McAnulty LS, Nieman DC, Quindry JC, Hosick PA, Hudson MH, Still
807 L, Henson DA, Milne GL, Morrow JD, Dumke CL, Utter AC, Triplett NT and
808 Dibarnardi A. 2008. Chronic quercetin ingestion and exercise-induced oxidative
809 damage and inflammation. Appl Physiol Nutr Me 33:254-62. 10.1139/H07-177

810 Menendez C, Duenas M, Galindo P, Gonzalez-Manzano S, Jimenez R, Moreno L,
811 Zarzuelo MJ, Rodriguez-Gomez I, Duarte J, Santos-Buelga C and Perez-Vizcaino F.
812 2011. Vascular deconjugation of quercetin glucuronide: the flavonoid paradox
813 revealed? Mol Nutr Food Res 55:1780-90. 10.1002/mnfr.201100378

814 Menezes R, Rodriguez-Mateos A, Kaltsatou A, Gonzalez-Sarrias A, Greyling A,
815 Giannaki C, Andres-Lacueva C, Milenkovic D, Gibney ER, Dumont J, Schar M,
816 Garcia-Aloy M, Palma-Duran SA, Ruskovska T, Maksimova V, Combet E and Pinto
817 P. 2017. Impact of flavonols on cardiometabolic biomarkers: A meta-analysis of
818 randomized controlled human trials to explore the role of inter-individual variability.
819 Nutrients 9. 10.3390/nu9020117

820 Meng XF, Maliakal P, Lu H, Lee MJ and Yang CS. 2004. Urinary and plasma levels
821 of resveratrol and quercetin in humans, mice, and rats after ingestion of pure
822 compounds and grape juice. J Agr Food Chem 52:935-42. 10.1021/jf030582e

823 Moon JH, Nakata R, Oshima S, Inakuma T and Terao J. 2000. Accumulation of
824 quercetin conjugates in blood plasma after the short-term ingestion of onion by
825 women. Am J Physiol-Reg I 279:R461-R67.

826 Moon YJ, Wang L, DiCenzo R and Morris ME. 2008. Quercetin pharmacokinetics in
827 humans. Biopharm Drug Dispos 29:205-17. 10.1002/bdd.605

828 Mullen W, Boitier A, Stewart AJ and Crozier A. 2004. Flavonoid metabolites in
829 human plasma and urine after the consumption of red onions: analysis by liquid
830 chromatography with photodiode array and full scan tandem mass spectrometric
831 detection. J Chromatogr A 1058:163-68. 10.1016/j.chroma.2004.08117

832 Mullen W, Edwards CA and Crozier A. 2006. Absorption, excretion and metabolite
833 profiling of methyl-, glucuronyl-, glucosyl- and sulpho-conjugates of quercetin in
834 human plasma and urine after ingestion of onions. Brit J Nutr 96:107-16.
835 10.1079/Bjn20061809

836 Murota K, Matsuda N, Kashino Y, Fujikura Y, Nakamura T, Kato Y, Shimizu R,
837 Okuyama S, Tanaka H, Koda T, Sekido K and Terao J. 2010. a-Oligoglucosylation of
838 a sugar moiety enhances the bioavailability of quercetin glucosides in humans. Arch
839 Biochem Biophys 501:91-7. 10.1016/j.abb.2010.06.036

840 Nakamura T, Murota K, Kumamoto S, Misumi K, Bando N, Ikushiro S, Takahashi N,
841 Sekido K, Kato Y and Terao J. 2014. Plasma metabolites of dietary flavonoids after
842 combination meal consumption with onion and tofu in humans. Mol Nutr Food Res

58:310-17. 10.1002/mnfr.201300234

Okamoto T. 2005. Safety of quercetin for clinical application (Review). Int J Mol Med 16:275-8.

Olthof MR, Hollman PCH, Buijsman MNCP, van Amelsvoort JMM and Katan MB. 2003. Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. J Nutr 133:1806-14.

Paulke A, Eckert GP, Schubert-Zsilavecz M and 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 67:991-96. 10.1691/ph.2012.2050

Perez-Jimenez J, Fezeu L, Touvier M, Arnault N, Manach C, Hercberg S, Galan P and Scalbert A. 2011. Dietary intake of 337 polyphenols in French adults. Am J Clin Nutr 93:1220-8. 10.3945/ajcn.110.007096

Pérez-Jiménez J, Hubert J, Hooper L, Cassidy A, Manach C, Williamson G and Scalbert A. 2010. Urinary metabolites as biomarkers of polyphenol intake in humans: a systematic review. Am J Clin Nutr 92:801-09. 10.3945/ajcn.2010.29924

Perez-Jimenez J, Neveu V, Vos F and Scalbert A. 2010. Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database. Eur J Clin Nutr 64 Suppl 3:S112-20. 10.1038/ejcn.2010.221

Perez A, Gonzalez-Manzano S, Jimenez R, Perez-Abud R, Haro JM, Osuna A, Santos-Buelga C, Duarte J and Perez-Vizcaino F. 2014. The flavonoid quercetin induces acute vasodilator effects in healthy volunteers: correlation with beta-glucuronidase activity. Pharmacol Res 89:11-8. 10.1016/j.phrs.2014.07.005

866 Petersen B, Egert S, Bosy-Westphal A, Muller MJ, Wolffram S, Hubbermann EM,
867 Rimbach G and Schwarz K. 2016. Bioavailability of quercetin in humans and the
868 influence of food matrix comparing quercetin capsules and different apple sources.
869 Food Res Int 88:159-65. 10.1016/j.foodres.2016.02.013

870 Pimpao RC, Ventura MR, Ferreira RB, Williamson G and Santos CN. 2015. Phenolic
871 sulfates as new and highly abundant metabolites in human plasma after ingestion of a
872 mixed berry fruit puree. Br J Nutr 113:454-63. S0007114514003511
873 [pii];10.1017/S0007114514003511 [doi]

874 Prot JM, Maciel L, Bricks T, Merlier F, Cotton J, Paullier P, Bois FY and Leclerc E.
875 2014. First Pass Intestinal and Liver Metabolism of Paracetamol in a Microfluidic
876 Platform Coupled With a Mathematical Modeling as a Means of Evaluating ADME
877 Processes in Humans. Biotechnol Bioeng 111:2027-40. 10.1002/bit.25232

878 Ramesova S, Sokolova R, Degano I, Bulickova J, Zabka J and Gal M. 2012. On the
879 stability of the bioactive flavonoids quercetin and luteolin under oxygen-free
880 conditions. Anal Bioanal Chem 402:975-82. 10.1007/s00216-011-5504-3

881 Reinboth M, Wolffram S, Abraham G, Ungemach FR and Cermak R. 2010. Oral
882 bioavailability of quercetin from different quercetin glycosides in dogs. Brit J Nutr
883 104:198-203. 10.1017/S000711451000053x

884 Rescigno A, Thakur AK and Marzo A. 1994. On Definition and Use of the Term
885 Bioavailability. Arzneimittel-Forschung/Drug Research 44-2:1167-69.

886 Rossi AM, Maggini V, Fredianelli E, Di Bello D, Pietrabissa A, Mosca F, Barale R
887 and Pacifici GM. 2004. Phenotype-genotype relationships of SULT1A1 in human liver
888 and variations in the IC50 of the SULT1A1 inhibitor quercetin. Int J Clin Pharmacol

889 Ther 42:561-67.

890 Russo M, Spagnuolo C, Tedesco I, Bilotto S and Russo GL. 2012. The flavonoid
891 quercetin in disease prevention and therapy: facts and fancies. Biochem Pharmacol
892 83:6-15. 10.1016/j.bcp.2011.08.010

893 Schlemmer U. 1995. Bioavailability of Nutrients Conceptual Aspects of Definition
894 and Problems of Determination. Brit J Nutr 73:150-51.

895 Schneider H, Schwiertz A, Collins MD and Blaut M. 1999. Anaerobic transformation
896 of quercetin-3-glucoside by bacteria from the human intestinal tract. Arch Microbiol
897 171:81-91.

898 Schulz HU, Schurer M, Bassler D and Weiser D. 2005. Investigation of
899 pharmacokinetic data of hypericin, pseudohypericin, hyperforin and the flavonoids
900 quercetin and isorhamnetin revealed from single and multiple oral dose studies with a
901 hypericum extract containing tablet in healthy male volunteers. Arzneimittel-Forsch
902 55:561-68. 10.1055/s-0031-1296905

903 Serra A, Macia A, Romero MP, Reguant J, Ortega N and Motilva MJ. 2012. Metabolic
904 pathways of the colonic metabolism of flavonoids (flavonols, flavones and flavanones)
905 and phenolic acids. Food Chem 130:383-93. 10.1016/j.foodchem.2011.07.055

906 Sesink ALA, O'Leary KA and Hollman PCH. 2001. Quercetin gluouronides but not
907 glucosides are present in human plasma after consumption of quercetin-3-glucoside or
908 quercetin-4 '-glucoside. J Nutr 131:1938-41.

909 Shimoi K, Saka N, Nozawa R, Sato M, Amano I, Nakayama T and Kinae N. 2001.
910 Deglucuronidation of a flavonoid, luteolin monoglucuronide, during inflammation.
911 Drug Metab Dispos 29:1521-4.

912 Smith AJ, Kavuru P, Wojtas L, Zaworotko MJ and Shytle RD. 2011. Cocrystals of
913 quercetin with improved solubility and oral bioavailability. Mol Pharm 8:1867-76.
914 10.1021/mp200209j

915 Sokolova R, Degano I, Ramesova S, Bulickova J, Hromadova M, Gal M, Fiedler J and
916 Valasek M. 2011. The oxidation mechanism of the antioxidant quercetin in
917 nonaqueous media. Electrochim Acta 56:7421-27. 10.1016/j.electacta.2011.04.121

918 Sokolova R, Ramesova S, Degano I, Hromadova M, Gal M and Zabka J. 2012. The
919 oxidation of natural flavonoid quercetin. Chem Commun 48:3433-35.
920 10.1039/c2cc18018a

921 Spencer JPE, Chowrimootoo G, Choudhury R, Debnam ES, Srai SK and Rice-Evans
922 C. 1999. The small intestine can both absorb and glucuronidate luminal flavonoids.
923 Febs Lett 458:224-30. Doi 10.1016/S0014-5793(99)01160-6

924 Stalmach A, Mullen W, Barron D, Uchida K, Yokota T, Cavin C, Steiling H,
925 Williamson G and Crozier A. 2009. Metabolite Profiling of Hydroxycinnamate
926 Derivatives in Plasma and Urine after the Ingestion of Coffee by Humans:
927 Identification of Biomarkers of Coffee Consumption. Drug Metab Dispos 37:1749-58.
928 10.1124/dmd.109.028019

929 Sugatani J. 2013. Function, genetic polymorphism, and transcriptional regulation of
930 human UDP-glucuronosyltransferase (UGT) 1A1. Drug Metab Pharmacokinet 28:83-
931 92.

932 Tribolo S, Lodib F, Connor C, Suri S, Wilson VG, Taylor MA, Needs PW, Kroon PA
933 and Hughes DA. 2008. Comparative effects of quercetin and its predominant human
934 metabolites on adhesion molecule expression in activated human vascular endothelial

935 cells. Atherosclerosis 197:50-56. 10.1016/j.atherosclerosis.2007.07.040

936 Vacek J, Papouskova B, Kosina P, Vrba J, Kren V and Ulrichova J. 2012.
937 Biotransformation of flavonols and taxifolin in hepatocyte in vitro systems as
938 determined by liquid chromatography with various stationary phases and electrospray
939 ionization-quadrupole time-of-flight mass spectrometry. J Chromatogr B 899:109-15.
940 10.1016/j.jchromb.2012.05.009

941 Valentová K, Vrba J, Bancířová M, Ulrichová J and Křen V. 2014. Isoquercitrin:
942 Pharmacology, toxicology, and metabolism. Food Chem Toxicol 68:267-82.
943 10.1016/j.fct.2014.03.018

944 Walle T. 2004. Absorption and metabolism of flavonoids. Free Rad Biol Med 36:829-
945 37. 10.1016/j.freeradbiomed.2004.01.002

946 Walle T, Otake Y, Walle UK and Wilson FA. 2000. Quercetin glucosides are
947 completely hydrolyzed in ileostomy patients before absorption. J Nutr 130:2658-61.

948 Walle T, Walle UK and Halushka PV. 2001. Carbon dioxide is the major metabolite of
949 quercetin in humans. J Nutr 131:2648-52.

950 Wang YF, Singh AP, Nelson HN, Kaiser AJ, Reker NC, Hooks TL, Wilson T and
951 Vorsa N. 2016. Urinary clearance of cranberry flavonol glycosides in humans. J Agr
952 Food Chem 64:7931-39. 10.1021/acs.jafc.6b03611

953 Wiczkowski W, Romaszko J, Bucinski A, Szawara-Nowak D, Honke J, Zielinski H
954 and Piskula MK. 2008. Quercetin from shallots (Allium cepa L. var. aggregatum) is
955 more bioavailable than its glucosides. J Nutr 138:885-88.

956 Williamson G, Barron D, Shimoi K and Terao J. 2005. In vitro biological properties of

957 flavonoid conjugates found in vivo. Free Radical Res 39:457-69.
958 10.1080/10715760500053610

959 Wilms LC, Hollman PCH, Boots AW and Kleinjans JCS. 2005. Protection by
960 quercetin and quercetin-rich fruit juice against induction of oxidative DNA damage
961 and formation of BPDE-DNA adducts in human lymphocytes. Mutat Res-Gen Tox En
962 582:155-62. 10.1016/j.mrgentox.2005.01.006

963 Wojcicki J, Gawronska-Szklarz B, Bieganowski W, Patalan M, Smulski HK,
964 Samochowiec L and Zakrzewski J. 1995. Comparative pharmacokinetics and
965 bioavailability of flavonoid glycosides of Ginkgo biloba after a single oral
966 administration of three formulations to healthy volunteers. Materia medica Polona
967 Polish J Med Pharmacy 27:141-6.

968 Young JF, Nielsen SE, Haraldsdottir J, Daneshvar B, Lauridsen ST, Knuthsen P,
969 Crozier A, Sandstrom B and Dragsted LO. 1999. Effect of fruit juice intake on urinary
970 quercetin excretion and biomarkers of antioxidative status. Am J Clin Nutr 69:87-94.

971 Yousri NA, Kastenmuller G, Gieger C, Shin SY, Erte I, Menni C, Peters A, Meisinger
972 C, Mohney RP, Illig T, Adamski J, Soranzo N, Spector TD and Suhre K. 2014. Long
973 term conservation of human metabolic phenotypes and link to heritability.
974 Metabolomics 10:1005-17. 10.1007/s11306-014-0629-y

975 **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 wk	Single dose, cross-over: 1 wk wash-out → Phase 1 → 2 wk wash-out → Phase 2	Phase 1: 200 g onions Phase 2: 200 g onions + 100 g tomatoes	6 (F)	Plasma	Hydrolysis and native	(Boyle and others 2000b)
Red grape juice and fried onions	1 d	Single dose, parallel placebo controlled	100 mL grape juice or 200 g onions	22	Plasma	Hydrolysis	(Davalos and others 2006)
Black tea and fried onions	3 wk	Repeated, cross-over in random order: 4 d wash-out → 3 d intervention, 2 times	1600 mL tea or 129 g onions in 2-3 portions/d	15 (7 F)	Plasma and urine	Hydrolysis	(de Vries and others 1998)
Red wine, fried yellow onions and black tea	3 wk	Repeated, cross-over in random order: 3 d wash-out → 4 d intervention, 3 times	750 mL wine or 50 g onions or 375 mL tea (14-16 mg quercetin in 3 portions/d)	12 (M)	Plasma and urine	Hydrolysis	(de Vries and others 2001)
Onion paste	1 d	Single dose	350–500 g of paste (2.3 mg of quercetin /kg body weight)	4	Plasma	Native	(Kawai and others 2008)
Fried red onions	1 d	Single dose	270 g onions (275 ± 8.8	6 (2 F)	Plasma	Native	(Mullen and others

			µmol of total flavonols)		and urine		2004, Mullen and others 2006)
Sautéed yellow onions with ketchup and Italian seasonings	1 d	Single dose	76 – 150 g of onion meal (10.9 to 51.6 mg of quercetin glycosides)	4 (3 F) ileostomists	Plasma	Native	(Walle and others 2000)
Cooked onion slices	1 wk	Repeated daily	260 – 360 g (67.6–93.6 mg quercetin equivalents) in 3 portions/d	7 (F)	Plasma	Hydrolysis	(Moon and others 2000)
Shallot flesh or dry skin	1 d	Cross-over, single doses separated by 7 d wash-out	1.4 mg quercetin/kg body weight	9 (5 F)	Plasma	Hydrolysis	(Wiczkowski and others 2008)
Black currants, lingonberries, and bilberries	8 wk	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 and others 2003)
Black currant juice	1 wk	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 and others 2006)
Blackcurrants, lingonberries, and bilberries	8 wk	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 wk	Random parallel, dietary controlled	24.1 mg quercetin/d	80 (F+M)			

Vegetable diet	15 wk	Cross-over, dietary controlled: 2 wk wash-out → 5 wk intervention → 3 wk wash-out → 5 wk intervention	Low-vegetable diet: 60 mg of vitamin C, 8 mg of vitamin E and 200 mg of folate/d. High-vegetable diet: 480 mg of vitamin C, 16 mg of vitamin E, 10 mg of β-carotene and 600 mg of folate/d	37 (F)	Plasma	Native	(Erlund and others 2002)
Conventionally (CPD) and organically (OPD) produced diets	10 wk	Cross-over, double-blinded randomized, dietary controlled: 1 wk run-in → 3 wk intervention → 3 wk wash-out → 3 wk intervention	CPD: 2632 ± 774 µg quercetin /d; OPD: 4198 ± 1370 µg quercetin /d	16 (10 F)	Urine	Hydrolysis	(Grinder-Pedersen and others 2003)
Cloudy apple juice	1 d	Single dose	1 L of juice	5 (3 F) 6 (4 F)	Plasma Urine	Hydrolysis	(Kahle and others 2011)
Whole bilberries, nectar of lingonberries, black currant-strawberry puree and cold-pressed chokeberry-raspberry	8 wk	Randomized, placebo-controlled parallel dietary intervention, repeated daily	160 g of berries (4.9 mg quercetin) in 2 portions/d	72 (46 F)	Plasma and urine	Hydrolysis	(Koli and others 2010)

juice							
Juice mix	1 d	Single dose	6.3 mL of juice (0.189 mg quercetin /kg body weight)	10 (M)	Plasma and urine	Hydrolysis	(Krogholm and others 2010)
Grape juice preparation	8 wk	Sequential single doses with 2 wk wash-outs	200, 400, 600, 1200 mL (~ 12.7 µM in quercetin)	1 (M)	Plasma and urine	Hydrolysis	(Meng and others 2004)
Blueberry juice mixture with apple juice	4 wk	Controlled dietary intervention, repeated daily .	1L of juice mixture (18 mg quercetin)/d	8 (F)	Plasma	Hydrolysis	(Wilms and others 2005)
Fruit juice (black currant and apple juice)	3 wk	Cross-over, repeated 1 wk interventions separated by 2 wk	750, 1000, and 1500 mL (4.8, 6.4, and 9.6 mg quercetin/d)	5 (4 F)	Plasma and urine	Hydrolysis	(Young and others 1999)
Tomato puree	2 wk	Repeated once/d	25 g purée (2.3 mg quercetin glycosides) plus 5 g of olive oil	12 F	Plasma	Native	(Mauri and others 1999)
Tomato juice	1 d	Single dose	300 mL	11 (6 F)	Plasma and urine	Native	(Jaganath and others 2006)
Decaffeinated coffee powder, green tea extract, cocoa powder, grape skin extract, grape	14 d	Cross-over, single doses in a randomized order at intervals of 14 d	4 g coffee/200 mL, 0.3 g tea extract/200 mL 10 g cocoa powder/200 mL 18 g grape-skin	9 (5 F)	Urine	Hydrolysis	(Ito and others 2005)

and orange juices			extract/200 mL 430 mL grape fruit extract and 550 mL orange juice				
Green tea	1 d	Single dose	340 mL of commercial tea	2 (M)	Plasma	Hydrolysis	(Jin and others 2004)
Apple peel and onion	3 d	Randomized crossover, 2 d 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 and others 2012)
Onion and Tofu	1 d	Crossover, single dose	170-250 g of sautéed onion or 170-250 of tofu with soy sauce or combination of the 2 dishes	5	Plasma	Hydrolysis	(Nakamura and others 2014)
Fried onion	1 d	Single dose	200 g	4 (2 F)	Plasma	Native	(Day and others 2001)
Onion	1 d	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 and others 2004)
Cranberry juice	3 d	Randomized crossover single dose, 2 d wash-out	240 mL	10 (F)	Urine	Native	(Wang and others 2016)

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979 **Table 2** Characterization of studies using quercetin and derivatives as pure compounds

Class	Study design			Nº of subjects (gender)	Analysis		References
	Total time	Frequency (single dose/repeated, cross-over)	Dose		Type of sample	Sample treatment	
Aglycone	4 wk	Randomized 2-interventions cross-over, double blind, diet controlled, single doses in ascending dosages; wash-out 2 – 3 d between doses and 9 d between interventions	8, 20, 50 mg quercetin	12 (5 F)	Plasma	Hydrolysis	(Erlund and others 2000)
	3 wk	Randomized, cross-over, single dose, wash-out 1 wk	1095 mg quercetin with low, moderate and high fat meal	9 (5 F)	Plasma and urine	Hydrolysis	(Guo and others 2013)
	12 wk	Randomized parallel, double-blind, repeated daily	500/1000 mg quercetin in 2 portions/d	1002 (60% F)	Plasma	Hydrolysis	(Jin and others 2010)
	1 d	Cross-over, placebo-controlled, single dose	200 mg quercetin	12 (M)	Plasma and urine	Hydrolysis	(Loke and others 2009)
	3.5 wk	Randomized double-blind parallel, placebo controlled repeated daily	1000 mg quercetin in 2 portions/d	20 (M)	Plasma	Hydrolysis	(McAnulty and others 2008)
	1 d	Single doses, parallel	0.5 or 1 mg/kg	2 (M)	Plasma and	Hydrolysis	(Meng and others 2004)

					urine		
	1 wk	Open, repeated	1500 mg quercetin in 3 portions/d	10 (4 F)	Plasma and urine	Hydrolysis	(Moon and others 2008)
	1 d	Open, single dose	2 mg of quercetin eq./kg body weight	5 (1 F)	Plasma	Hydrolysis	(Murota and others 2010)
	2 wk	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 and others 2001)
	1 d	Parallel, single dose	50 – 2000 mg/m^3 (intravenous)	51 (25 F)	Plasma and urine	Native	(Ferry and others 1996)
Glycosides	1 wk	Cross-over, single doses in random order, 5 d wash-out	311 µmol quercetin-4'-*O*-glucoside *vs.* rutin	9	Plasma	Hydrolysis	(Hollman and others 1999)
	4 wk	Randomized 2-interventions cross-over, double blind, diet controlled, single doses in ascending dosages; wash-out 2 – 3d between doses and 9 d between doses and periods interventions	16, 40, 100 mg rutin	12 (5 F)	Plasma	Hydrolysis	(Erlund and others 2000)
	3 mo	Cross-over, controlled, various single	0/150/300 mg	6 (3 F)	Plasma	Hydrolysis	(Hubbard and others

	doses, 1 mo wash-out	quercetin-4'-*O*-glucoside				2004)
1 d	Open, single dose	500 mg rutin	3 (F)	Plasma	Hydrolysis	(Boyle and others 2000a)
6 wk	Parallel, placebo controlled, repeated daily	500 mg rutin / d	8 (F)			
1 d	Open, single dose	2 mg of quercetin glycosides eq./kg body weight	5 (1 F)	Plasma	Hydrolysis	(Murota and others 2010)
4 wk	Dietary and placebo controlled cross-over, 1 wk each treatment, no wash-out	440 mg rutin	20 (10 F)	Urine	Hydrolysis and native	(Olthof and others 2003)
16 d	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 and others 2001)

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

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982 **Table 3** Characterization of studies with mixtures or combinations of fruits/vegetables with pure compounds

Mixtures	Study design			Nº of subjects (gender)	Analysis		References
	Total time	Frequency (single dose/repeated, cross-over)	Dose		Type of sample	Sample treatment	
Onion skin extract enriched cereal bars / capsules with pure quercetin	3 wk	Cross-over, single-blind, single dose, 1 wk run-in, 2 wk wash-out	130 mg quercetin equivalents	6 (F)	Plasma	Hydrolysis	(Egert and others 2012)
Quercetin supplemented in white wine / grape juice / vegetable juice	8 wk	Cross-over, open, random order, single doses, 4 wk wash-outs	10 mg quercetin/70 kg	4 (M)	Plasma and urine	Hydrolysis	(Goldberg and others 2003)
Stewed onions/ quercetin-4'-*O*-glucoside / buckwheat tea powder/ quercetin-3-O-rutinoside	10 d	Randomized cross-over, 3 d run-in, single doses with 24 h wash-out	100 mg or 200 mg quercetin equivalents	12 (3 F)	Plasma and urine	Hydrolysis and native	(Graefe and others 2001)
Onion supplement / rutin / quercetin tablets	3 d	Randomized cross-over, 12 d run-in, single doses with 3 d wash-out	89/100/100 mg quercetin equivalents	9 (5 F)	Urine	Hydrolysis	(Hollman and others 1995)
Fried onions / apples / pure rutin	12 d	Cross-over, single doses, 12 d run-in, with 3 d wash-	64/100/100 mg quercetin	9	Plasma	Hydrolysis	(Hollman and others 1997b)

		out	equivalents				
Quercetin dihydrate capsules / apple chips, apple peal extract capsules, apple peel	4 wk	Randomized, diet controlled, cross-over, single doses, 1 wk wash-out	71 µmol quercetin equivalents	6 (F)	Plasma	Hydrolysis	(Petersen and others 2016)

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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 and others 2001)
			48, 39[b]	(de Pascual-Teresa and others 2004)
			38, 47[c]	(Wiczkowski and others 2008)
		$AUC_{(0-24)}$	71	(Graefe and others 2001)
		AUC	31, 48[c]	(Wiczkowski and others 2008)
Urine		amount	42	(de Vries and others 1998)
			43	(de Vries and others 2001)
			47	(Hollman and others 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 Tables 2 and 3) administered as pure compound.

Sample		Parameter	CV(%)[a]	References
Plasma	Kinetic data	C_{max}	29[b]	(Erlund and others 2000)
			35, 31, 54[c]	(Guo and others 2013)
			25, 37[d]	(Egert and others 2012)
			54	(Petersen and others 2016)
		AUC	27, 14[e]	(Walle and others 2001)
		$AUC_{(0-24)}$	25[b]	(Erlund and others 2000)
		$AUC_{(0-32)}$	26[b]	(Erlund and others 2000)
		$AUC_{0-24\ h}$	26, 31, 42[c]	(Guo and others 2013)
		AUC	37, 25[d]	(Egert and others 2012)
		AUC_{0-24}	47	(Petersen and others 2016)
Urine			21, 18[e]	(Walle and others 2001)
Feces			77, 44[e]	(Walle and others 2001)
CO_2			21, 88[e]	(Walle and others 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 per os 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 Tables 2 and 3).

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

1010 **Table 7** List of main quercetin metabolites identified in non-hydrolyzed samples (presence
1011 indicated by +, Nd-not detected)

Metabolite	Presence		References
	Plasma	Urine	
Quercetin-3'-*O*-sulfate[a]	+	Nd	(Mullen and others 2006)
	+		(Kawai and others 2008)
	+	+	(Mullen and others 2004)
	+		(Nakamura and others 2014)
	+		(de Vries and others 1998)
	+		(de Pascual-Teresa and others 2004)
	+		(Lee and others 2012)
Quercetin-7-*O*-sulfate	+		(de Pascual-Teresa and others 2004)
Quercetin-3'-*O*-glucuronide	trace	+	(Mullen and others 2006)
	+		(Kawai and others 2008)
	+	+	(Mullen and others 2004)
	Nd	+	(Jaganath and others 2006)
	+		(Lee and others 2012)
	+		(de Vries and others 1998)
	+		(de Pascual-Teresa and others 2004)
Quercetin-4'-*O*-glucuronide	Nd	+	(Jaganath and others 2006)
	+		(de Vries and others 1998)
Quercetin-3-*O*-glucuronide	+		(Kawai and others 2008)
	+	+	(Mullen and others 2006)
	+	+	(Mullen and others 2004)
	+	+	(Jaganath and others 2006)
	+		(Lee and others 2012)
	+		(Nakamura and others 2014)
	+		(de Vries and others 1998)
	+		(de Pascual-Teresa and others 2004)
Quercetin-7-*O*-glucuronide	+	+	(Mullen and others 2004)
Quercetin glucuronide sulfate	+	+	(Mullen and others 2006)
	+	+	(Mullen and others 2004)

	+		(Lee and others 2012)
Isorhamnetin-3-*O*-glucuronide	+	+	(Mullen and others 2006)
	+	+	(Mullen and others 2004)
	+	+	(Jaganath and others 2006)
	+		(Lee and others 2012)
	+		(de Vries and others 1998)
	+		(de Pascual-Teresa and others 2004)
Isorhamnetin-4'-*O*-glucuronide	+	+	(Mullen and others 2006)
	+		(Kawai and others 2008)
	+	+	(Mullen and others 2004)
	+		(de Vries and others 1998)
	+		(de Pascual-Teresa and others 2004)
Quercetin diglucuronide	+	+	(Mullen and others 2006)
	+		(Kawai and others 2008)
	+	+	(Mullen and others 2004)
	Nd	+	(Jaganath and others 2006)
	+		(Lee and others 2012)
	+		(de Vries and others 1998)
Methyl quercetin diglucuronide	Nd	+	(Mullen and others 2006)
	Nd	+	(Mullen and others 2004)
	Nd	+	(Jaganath and others 2006)
	+		(Lee and others 2012)
Methyl quercetin glucuronide	+		(Kawai and others 2008)
	+	+	(Mullen and others 2004)
	+		(Lee and others 2012)
Quercetin glucoside sulfate	Nd	+	(Mullen and others 2006)
	Nd	+	(Mullen and others 2004)
Quercetin glucoside glucuronide	Nd	+	(Mullen and others 2006)
	Nd	+	(Mullen and others 2004)
	Nd	+	(Jaganath and others 2006)
Quercetin glutathione	+		(Lee and others 2012)
3-hydroxyphenylacetic acid		+	(Olthof and others 2003)
	Nd	+	(Jaganath and others 2006)

3,4-dihydroxyphenylacetic acid		+	(Olthof and others 2003)
	Nd	+	(Jaganath and others 2006)
3-OCH_3-4-hydroxyphenylacetic acid		+	(Olthof and others 2003)
	Nd	+	(Jaganath and others 2006)
2-hydroxyhippuric acid	Nd	+	(Jaganath and others 2006)
3-hydroxyhippuric acid	Nd	+	(Jaganath and others 2006)
4-hydroxyhippuric acid	Nd	+	(Jaganath and others 2006)

[a] In ref (Lee and others 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.

1015 **Table 8**-Variability in kinetic parameters for quercetin metabolites based on studies with non-hydrolyzed samples with quantitative data
1016 presented as mean values.

Conjugate	Sample	Kinetic data			References
		Parameter	Value[a]	CV (%)[b]	
Quercetin 3'-*O*-sulfate[c]	Plasma	C_{max}	12.1 ± 16.5	137[d]	(Lee and others 2012)
			97.8 ± 81.8	84[e]	
		AUC_{0-24h}	31.5 ± 45.4	144[d]	
			299 ± 227	76[e]	
Quercetin-3'-*O*-glucuronide	Urine	Amount	1845 ± 193	26	(Mullen and others 2006)
Quercetin-3-*O*-glucuronide	Plasma	C_{max}	12 ± 2	17	(Jaganath and others 2006)
	Urine	Amount	912 ± 149	40	(Mullen and others 2006)
Quercetin glucuronide	Plasma	C_{max}	31.5 ± 27.1	86[d]	(Lee and others 2012)
			433 ± 244	56[e]	
		AUC	75.9 ± 75.1	99[d]	
			1827 ± 1336	73[e]	
Quercetin-glucuronide sulfate	Plasma	C_{max}	2.3 ±8.4	369[d]	(Lee and others 2012)
			75.4 ± 113.4	150[e]	
		AUC	20.3 ± 76.4	375[d]	
			795 ± 1172	147[e]	
	Urine	Amount	1229, 1384[f]	29, 38[f]	(Mullen and others 2006)

Isorhamnetin-3-*O*-glucuronide	Plasma	C_{max}	4.3 ± 1.5	35	(Jaganath and others 2006)
	Urine	Amount	1789 ± 239	33	(Mullen and others 2006)
Isorhamnetin-4'-*O*-glucuronide	Urine	Amount	700 ± 114	40	(Mullen and others 2006)
Quercetin diglucuronide	Plasma	C_{max}	13.7 ± 22.3	163[d]	(Lee and others 2012)
			248 ± 137	55[e]	
		AUC	35.9 ± 59.7	166[d]	
			869 ± 431	50[e]	
	Urine	Amount	2223 ± 417	46	(Mullen and others 2006)
Methyl quercetin diglucuronide	Plasma	C_{max}	5.2 ± 7.9	150[d]	(Lee and others 2012)
			94.2 ± 36.9	39[e]	
		AUC	61.3 ± 123.5	201[d]	
			1033 ± 409	40[e]	
	Urine	Amount	426, 1003[f]	38, 57[f]	(Mullen and others 2006)
Methyl quercetin glucuronide	Plasma	C_{max}	14.8 ± 17.2	116[d]	(Lee and others 2012)
			178 ± 61	34[e]	
		AUC	53.8 ± 82.7	153[d]	
			1008 ± 404	40[e]	
Quercetin glucoside sulfate	Urine	Amount	392, 821[f]	37, 47[f]	(Mullen and others 2006)
Quercetin glucoside glucuronide	Urine	Amount	163 ± 23	35	(Mullen and others 2006)
3-hydroxyphenylacetic acid	Urine	Amount	259 ± 51	88	(Olthof and others 2003)

3,4-dihydroxyphenylacetic acid	Urine	Amount	52 ± 6	52	(Olthof and others 2003)
3-methoxy-4-hydroxyphenylacetic acid	Urine	Amount	103 ± 15	65	(Olthof and others 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 and others 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.

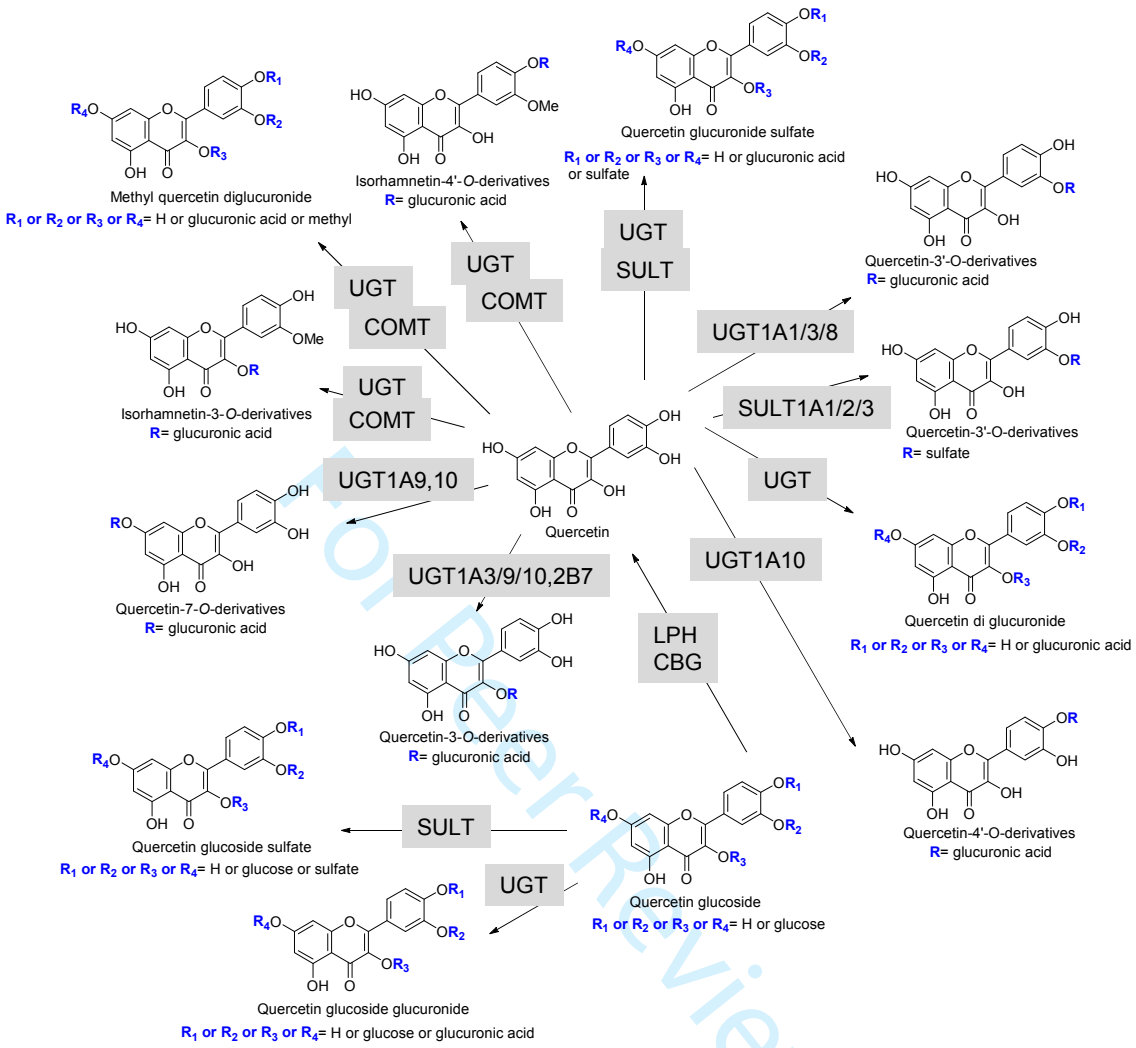

Fig. 1 Metabolism of quercetin to form conjugates.

Where information on the involvement of a specific enzyme is published (Boersma and others 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 and others 2000, Day

1036 and others 2001, Govind and others 2001, Hong and Mitchell 2004, Del Rio and
1037 others 2013).
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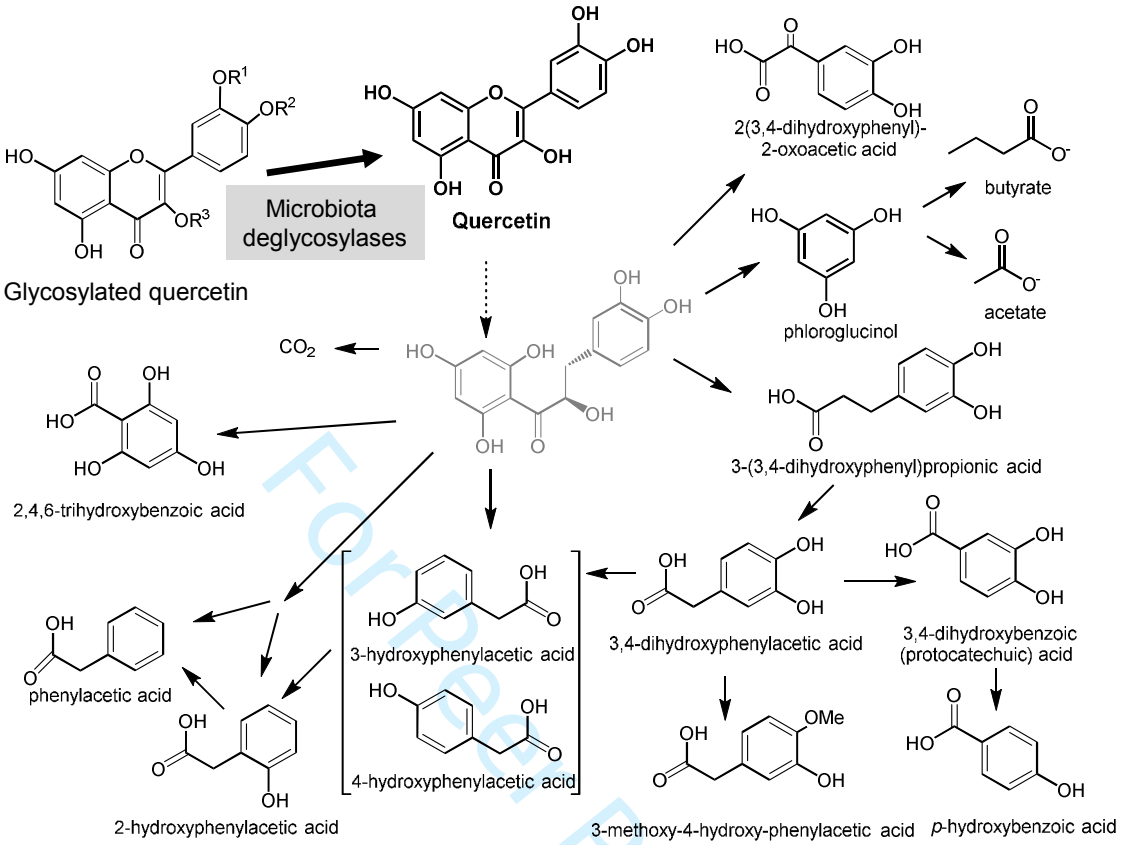

Fig. 2 Schematic representation of quercetin metabolism by gut microbiota Information is taken from (Schneider and others 1999, Walle 2004, Harwood and others 2007, Ramesova and others 2012, Serra and others 2012, Vacek and others 2012, Lu and others 2013, Valentová and others 2014); the speculative 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 and others 2013, Pimpao and others 2015).

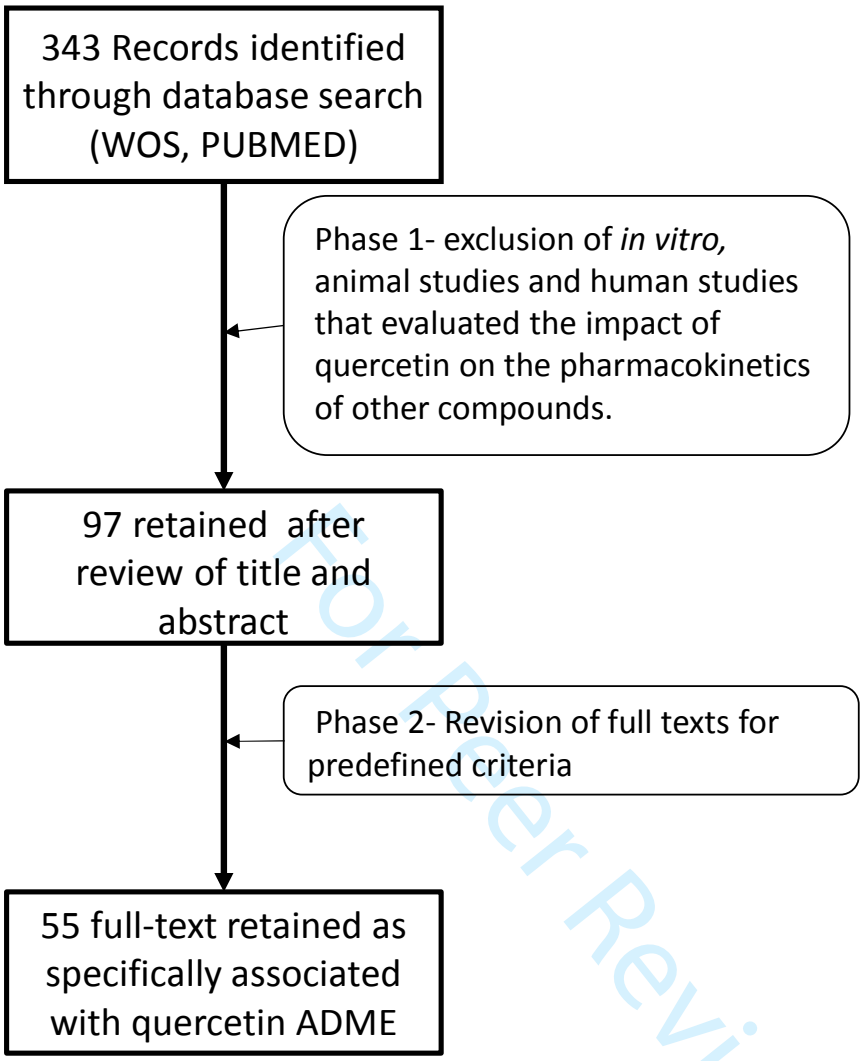

Fig. 3 Scheme showing the literature search and revision process.

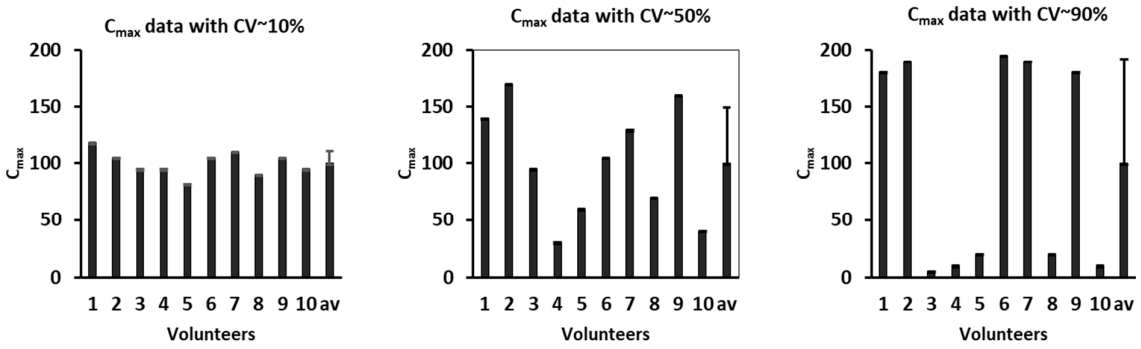

Fig. 4 Illustration of the variation in data expected from the reported CV value. Theoretical maximum plasma concentration c_{max} data (c_{max} = 100) were calculated for 10 volunteers to allow a CV of 10, 50 and 90% to be calculated using the "STDEV" function of the spreadsheet in the Microsoft Excel 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 1-10. With a CV of 90%, the data appears to stratify between "responders" and "non-responders".

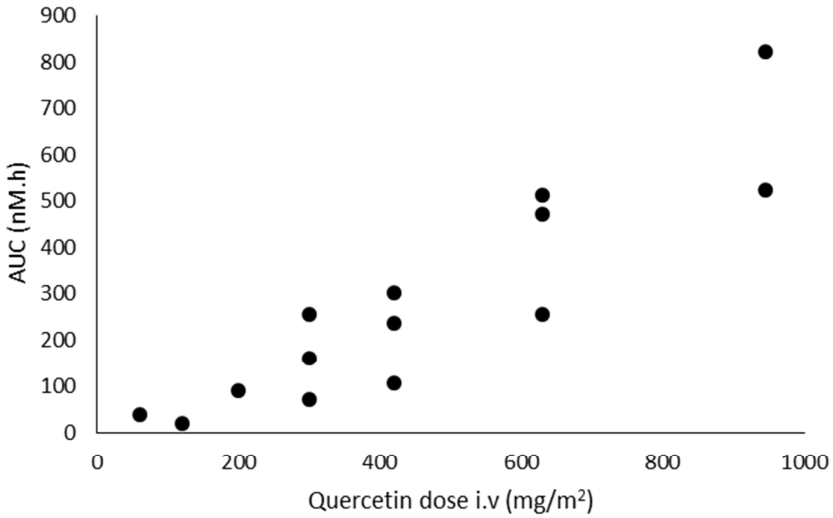

Fig. 5. Dependence of area under the curve (AUC) values on quercetin dose (Ferry and others 1996). AUC values obtained by pharmacokinetic modelling for all 14 patients (each patient represented by a filled circle) for the tested doses of quercetin administered by intravenous (i.v.) injection (AUC data normalised to nM×h).