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Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man

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Abstract Quercetin is a strong antioxidant and a major dietary flavonoid. Epidemiological studies suggest that consumption of quercetin protects against cardiovascular disease, but its absorption in man is controversial. We fed nine subjects a single large dose of onions, which contain glucose conjugates of quercetin, apples, which contain both glucose and non-glucose quercetin glycosides, or pure quercetin-3-rutinoside, the major quercetin glycoside in tea. Plasma levels were then measured over 36 h. Bioavailability of quercetin from apples and of pure quercetin rutinoside was both 30% relative to onions. Peak levels were achieved less than 0.7 h after ingestion of onions, 2.5 h after apples and 9 h after the rutinoside. Half-lives of elimination were 28 h for onions and 23 h for apples. We conclude that conjugation with glucose enhances absorption from the small gut. Because of the long half-lives of elimination, repeated consumption of quercetin-containing foods will cause accumulation of quercetin in blood.

Key words: Flavonoid glycoside; Dietary quercetin; Bioavailability; Pharmacokinetics; Human

1. Introduction

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin [1]. Quercetin is the major representative of the flavonoid subclass of flavonols [2]. Quercetin is a strong antioxidant because it can chelate metals, scavenge oxygen free radicals [3,4] and prevent the oxidation of low density lipoprotein (LDL) in vitro [5]. Oxidized LDL is hypothesized to be an intermediate in the formation of atherosclerotic plaques [6]. Quercetin might therefore contribute to the prevention of atherosclerosis [7]. Indeed, the intake of flavonols was inversely associated with subsequent cardiovascular disease in several though not all prospective epidemiological studies [8].

An evaluation of the role of dietary quercetin as a protective antioxidant in man is hampered by uncertainties about its absorption. Pharmacokinetic data are scarce and contradictory [9,10]. Until now, determination of the bioavailability of quercetin from real foods was not possible, because analytical methods for the determination of quercetin in plasma lacked sensitivity. We have recently developed a specific and sensitive detection technique for quercetin in plasma which allows studies on its bioavailability from foods [11].

Flavonols are present in foods as flavonoid-sugar compounds, which are called glycosides in general, or more specifically glucosides, rutinosides, or xylosides depending on their sugar moiety. The sugar-flavonol bond is a β-glycosidic bond which is resistant to hydrolysis by pancreatic enzymes. It was thought that such glycosides cannot be absorbed [1]. However, when we measured faecal quercetin in ileostomy subjects we found that human absorption of quercetin-β-glucosides from onions was 52%, whereas absorption of quercetin without its sugar moiety, the so-called aglycone, and of quercetin-β-rutinoside were both only about 20% [12]. These data suggest that the sugar moiety of quercetin glycosides affects their absorption. In the present study we determined the bioavailability and other pharmacokinetic parameters of various quercetin glycosides contained in foods. Subjects ingested onions, apples and pure quercetin rutinoside (rutin), the major quercetin compound found in tea [13]. Onions contain mainly glucose glycosides of quercetin [14,15]. Apples contain a variety of quercetin glycosides, including galactosides, arabinosides, rhamnosides, xylosides, and glucosides (Fig. 1) [16–18]. Preliminary pharmacokinetic data on onions have been published [19].

2. Materials and methods

2.1. Subjects

We recruited five women and four men, with a mean age of 24.8 (range 20–47) years. All were healthy based on a medical questionnaire and routine hematological and biochemical measurements in blood and urine. Subjects did not use any medication. The protocol was approved by the Wageningen University Ethical Committee, and was fully explained to the participants, who gave their written informed consent.

2.2. Study design, foods, and supplements

Subjects followed a quercetin-free diet [12] during three experimental periods each of 5 days. These periods were separated by 9 days without treatment and without a prescribed diet. On day 4 of each experimental period we provided one out of three different quercetin-containing supplements in random order, namely fried onions, apples, and rutinoside. Supplements were given at breakfast; blood was collected periodically over the next 36 h and urine continuously for 24 h. The onions provided 225 ± 43 (S.D.) μmol (68 ± 13 mg quercetin equivalents) and the apple supplement, consisting of applesauce plus apple peel, provided 325 ± 7 μmol of quercetin. For the third treatment 331 μmol quercetin-3-*O*-β-rutinoside (Rutosidum DAB, #339994; OPG Farma, Utrecht, The Netherlands) was administered in a capsule. The breakfasts which were given together with these supplements have been described previously [12]. Subjects also took a capsule containing 80 mg *para*-aminobenzoic acid (#361334; OPG Farma) as a recovery marker for urine [20] at breakfast, lunch and dinner. Subjects were instructed not to eat anything and to drink only water or coffee without milk from after the experimental breakfasts until lunch.

Average energy intake on day 3 of each period according to 24-h

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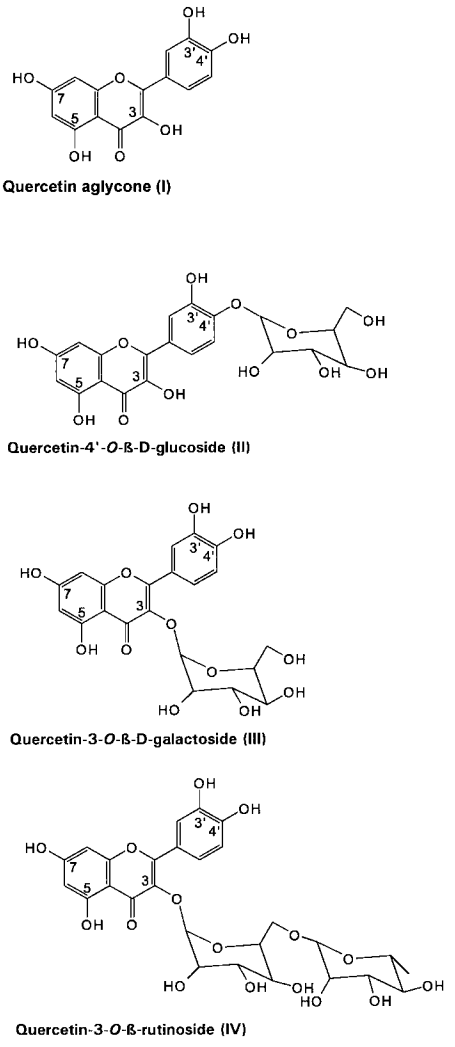

Fig. 1. Structure of quercetin aglycone (I), quercetin glucoside (II) as present in onions, quercetin galactoside (III) as present in apples, and quercetin rutinoside or rutin (IV).

dietary recalls [21] was 10.4 ± 1.5 MJ, of which protein provided 13.2 ± 1.8% of energy, fat 33.9 ± 5.4%, and carbohydrates 52.5 ± 5.7%, with no differences between treatment periods.

2.3. Collection of samples

Venous blood samples were taken into vacuum tubes containing EDTA; zero time was 10 min after the start of the breakfast. Platelet-rich plasma was prepared within 15 min by centrifugation at 20°C for 10 min at 200×*g*; it was stored at −80°C until analysis.

Subjects collected urine in plastic bottles containing 0.13 g thymol (#8167; Merck) for 24 h after each supplemented breakfast and stored them in dry ice immediately after voiding. Upon arrival at the laboratory, urine samples were thawed in a water bath at 40°C, homogenized and pooled per subject and per treatment day. Aliquots were taken within 30 min, frozen, and stored at −40°C until analyzed.

2.4. Analytical methods

Quercetin, quercetin glycosides, glucuronides, and sulfates were extracted from plasma or urine and hydrolyzed to the aglycone form in 2 M HCl in aqueous methanol [19]. For plasma we extended the hydrolysis period to 5 h. For urine 15.0 ml methanol containing 2 g *tert*-butyl hydroxyquinone/l and 5 ml 10 M HCl were added to 5 g urine followed by mixing. The mixture was refluxed at 90°C for 8 hours with regular swirling, allowed to cool, subsequently brought to a final volume of 50 ml with methanol, and sonicated for 5 min.

For HPLC analysis we transferred 1.5 ml of the plasma or urine extract into an HPLC vial and added 15 µl 100 g/l ascorbic acid. We injected 20 µl onto a reversed-phase C18 column connected to a post-column reaction coil, where quercetin was transformed into a fluorescent quercetin-aluminum complex [11,19]. Peak identity was confirmed by comparing the retention time of the plasma quercetin peak with that of a standard quercetin. Potential co-elution of fluorescent non-flavonol compounds was checked by repeating the HPLC procedure, this time by omitting the aluminum. Such compounds were never observed.

The limit of detection was 0.007 µM (2 ng/ml) for plasma and 0.01 µM (3 ng/ml) for urine. Recovery of 0.33 nmol (100 ng) quercetin aglycone added to 1 ml plasma was 88 ± 3% (6 additions). Addition of 0.83 nmol (250 ng) quercetin aglycone per gram of urine yielded a recovery of 99 ± 7% (3 additions).

The relative standard deviation of duplicates was 4% for plasma and 6% for urine. We included a control sample of plasma and urine in each series of analyses; all values were within 0.23 ± 0.046 µM (mean ± 2 S.D., 15 single determinations) for plasma and within 3.02 ± 0.55 µM (mean ± 2 S.D., 15 duplicate determinations) for urine.

para-Aminobenzoic acid in urine was determined as described [22].

2.5. Data analysis

We used the two-compartment open model $C(t) = -Ce^{-kt} + Ae^{-\alpha t} + Be^{-\beta t}$ to describe the absorption and disposition, i.e. distribution, metabolism and elimination, of quercetin [23] using PCNONLIN version 4.0 (SCI Software, ClinTrials Inc., Lexington, KY, USA).

Values were normalized by conversion to $\log_{10}$ values for statistical testing. Analysis of variance (SPSS Inc., Chicago, IL, USA) was performed with subject, type of quercetin source, and type of quercetin source in preceding period as independent variables. The significance of differences was determined by paired *t*-test. No significant relation

Table 1
Kinetic parameters of quercetin absorption and disposition in nine subjects after one-time ingestion of fried onions, apples, or pure quercetin rutinoside

Parameter	Supplement		
	Onions	Apples	Rutinoside
Absorption			
time to reach peak level (h)	0.70 ± 1.08[a]	2.51 ± 0.72[b]	9.3 ± 1.8[c]
peak level (µM)	0.74 ± 0.15[a]	0.30 ± 0.06[b]	0.30 ± 0.30[b]
peak level (ng/ml)	224 ± 44[a]	92 ± 19[b]	90 ± 93[b]
Distribution half-life (h)	4.4 ± 4.3	2.4 ± 3.7	–
Elimination half-life (h)	28 ± 92	23 ± 32	–
$AUC_{0\rightarrow\infty}$ (h·ng/ml)	2974 ± 2315	1334 ± 465	–
$AUC_{0\rightarrow 36h}$ (h·ng/ml)	2330 ± 849[a]	1061 ± 375[b]	983 ± 978[b]

Each subject received each supplement in random order at 14-day intervals.
Data are means ± S.D. for nine subjects.
[a,b,c]Results with a different superscript letter differ significantly ($P < 0.001$).
–, not calculated because of too few data points.
$AUC_{0\rightarrow\infty}$, total area under the plasma concentration-time curve; $AUC_{0\rightarrow 36h}$, area under the plasma concentration-time curve over the first 36 h.

with individual subject or with supplement given in the preceding period was found.

We calculated the relative bioavailability by comparing the areas under the plasma concentration-time curve (AUC) up to 36 h (Table 1) after correction for dosage.

3. Results

3.1. Plasma concentration of quercetin

Intake of onions and apples led to a rapid rise, and of the rutinoside (rutin) to a very slow rise of quercetin levels in plasma. The area under the plasma concentration-time curve (AUC), the quercetin peak plasma level, and the time to reach the peak plasma level differed markedly between supplements (Table 1).

The mean peak level was 0.74 μM (224 ng/ml) after onions, 0.30 μM (92 ng/ml) after apples, and 0.30 μM (90 ng/ml) after quercetin-3-rutinoside. Peak levels were reached 0.7 h after ingestion of the onions, 2.5 h after the apples, and 9 h after the quercetin-3-rutinoside (Fig. 2, Table 1). In four out of nine subjects the quercetin concentration had reached its maximum observed concentration already at 0.5 h after the onions supplement, the first data point after consumption of the supplement. Therefore, the time needed to reach the peak level may have been overestimated, and the height of the peak underestimated.

Distribution, metabolism and elimination of quercetin in plasma after the onions and apples supplements was best described by a two-compartment model (Fig. 2). Data analysis for quercetin-3-rutinoside escaped the model because the delayed absorption resulted in too few data points. The average half-lives of the distribution and elimination phases were not statistically different between onions and apples (Table 1). We could still detect quercetin 36 h after ingestion of the supplements; at that time the mean plasma concentration was 0.060 ± 0.027 μM after onions, 0.030 ± 0.030 μM after apples, and 0.027 ± 0.023 μM after quercetin-3-rutinoside (Fig. 2). The bioavailability of quercetin from both apples and the rutinoside was 30% of that of quercetin from onions.

3.2. Urinary excretion of quercetin

Excretion of quercetin and its conjugates in urine after ingestion of the onions was 1.39% of the administered dose, whereas it was only 0.44% after the apples, and 0.35% after the rutinoside (Table 2). One subject (#3) excreted much more quercetin in urine after consumption of quercetin-3-rutinoside than did the other subjects (Fig. 3). Quercetin excretion of this subject after the rutinoside was only 30% less than that after the onions, whereas all the other subjects excreted at least 80% less after the rutinoside than after the onions.

Three of the subjects collected urine every few hours. They reached 90% of their cumulative 24 h urinary excretion of quercetin within 8–13 h with all supplements. This suggests that urinary excretion of quercetin is almost complete after 24 h.

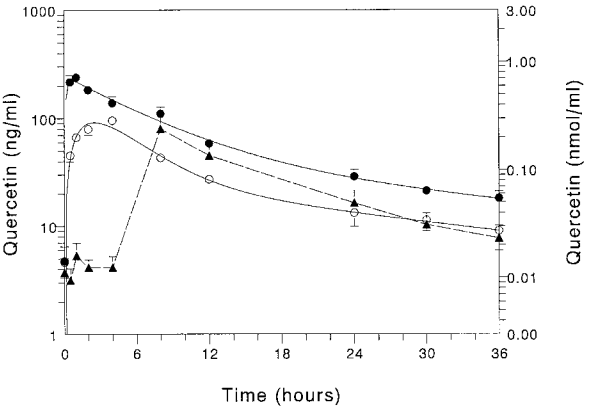

Fig. 2. Time course of the quercetin concentration in plasma of nine subjects after ingestion of fried onions, apples, or quercetin rutinoside. Each subject received each supplement in random order at 14-day intervals. Data are means ± S.E.M. for nine subjects. ●, onions; ○, apples; ▲, rutinoside.

For all three supplements, the area under the plasma concentration-time curve correlated highly with 24-h urinary excretion of quercetin per subject (Fig. 3).

3.3. Compliance with the quercetin-free diet

The average intake of quercetin from regular foods according to 24-h dietary recalls on the third day of each of the three diet periods was 5 ± 3 μmol (1.5 ± 0.9 mg). No difference in quercetin intake from the background diet was observed between the three diet periods. Plasma quercetin concentration before breakfast was on average 0.017 ± 0.013 μM. Thus, compliance with the quercetin-free diet was excellent.

3.4. Completeness of collection of urine

Urinary recovery of *para*-aminobenzoic acid was 87.3 ± 10.0%, indicating acceptable compliance in collecting urine [20]. On six out of 27 person-days subjects reported not to have swallowed the *para*-aminobenzoic acid capsule at dinner, so compliance of these subjects at evening could not be checked. As quercetin was almost completely excreted in urine within the first 10 h after the supplemented breakfasts, this uncertainty is of minor importance.

4. Discussion

Our data show that the dietary antioxidant quercetin is found in the circulation after consumption of major dietary sources of quercetin. Bioavailability and absorption kinetics

Table 2
Intake of quercetin at breakfast and subsequent mean cumulative excretion of quercetin in urine over 24 h

Supplement (to breakfast)	Quercetin intake (μmol)	Quercetin excretion in urine	
		Amount (μmol)	Proportion of intake (%)
Onions	225 ± 43	3.22 ± 1.60	1.39 ± 0.49[a]
Apples	325 ± 7	1.45 ± 0.71	0.44 ± 0.22[b]
Rutinoside	331 ± 7	1.17 ± 1.34	0.35 ± 0.41[b]

Each of the nine subjects received each supplement in random order at 14-day intervals.
Data are means ± S.D. for nine subjects.
[a,b]Results with a different superscript letter differ significantly ($P < 0.001$).

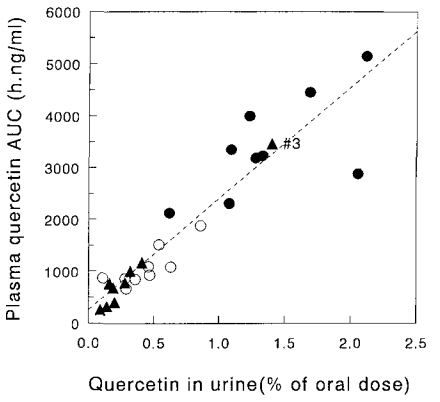

Fig. 3. Correlation between the area under the concentration-time curve (AUC) of quercetin in plasma and the 24-h excretion in urine of nine subjects who consumed onions, apples or quercetin rutinoside. The area was standardized to an intake of 331 μmol quercetin glycosides; urinary excretion is expressed as a percentage of the ingested dose. Each subject received each supplement in random order at 14-day intervals. Values are means for nine subjects for each supplement. The correlation coefficient (r) was 0.93 for 27 data points. ●, onions; ○, apples; ▲, rutinoside.

differed widely between sources. A major difference between these sources is the type of glycoside. Quercetin from onions, which contain only glucosides, was rapidly absorbed, whereas pure quercetin-3-rutinoside, the major species in tea, showed a markedly delayed absorption. The absorption rate from apples, which contain a variety of glycosides, was intermediate. Thus, these results point to a predominant role of the sugar moiety in the bioavailability and absorption of dietary quercetin in the human body. However, it cannot be ruled out that differences between apples and onions in cell wall structures, location of glycosides in cells, or their binding to cell constituents also affect the liberation of quercetin from these foods in the gastrointestinal tract.

4.1. Pharmacokinetics

The biphasic concentration profile in the elimination of quercetin from plasma (Fig. 2) indicates a rather fast distribution and elimination followed by a slow final elimination. Because most of the urinary quercetin is excreted within the first 12 h, urinary excretion contributes to this first rather fast decrease, and is only of minor importance in the second final phase. We only can speculate on the elimination mechanisms in the final phase. Biliary recirculation, as described in rats [24], offers a possible explanation: quercetin eliminated in the first fast phase may be reabsorbed in the colon thus slowing down elimination. It also possible that quercetin slowly penetrates into tissues where it is subsequently metabolized into compounds that escape our assay. However, conjugates with various pharmacokinetic properties formed upon or after absorption also may cause such a biphasic profile.

After consumption of a single portion of onions and apples, a considerable fraction of the absorbed quercetin was present in plasma throughout the day as is indicated by the elimination half-lives of about 24 h. The plasma time curve after consumption of the rutinoside indicates a similar slow elimination. A more accurate estimation of half-lives would require plasma samples to be taken for 3 days. The long half-lives implicate that repeated intake of onions, apples, and possibly tea would lead to a build-up of quercetin in plasma. The different rates of absorption of quercetin measured after ingestion of the various supplements will cause quercetin to enter the plasma continuously for a few hours following a mixed meal containing a variety of quercetin sources. We earlier found a peak plasma concentration of 0.75 μM or 225 ng/ml after administration of a single high dose of dietary quercetin equivalent to 4 times the average Dutch daily intake [2]. Concentrations of the dietary antioxidant β-carotene in human plasma are similar to this value [25]. Thus in subjects who regularly eat onions, plasma quercetin levels may approach those of β-carotene.

24-h Urinary excretion of quercetin predicted the area under the plasma concentration-time curve ($AUC_{0\rightarrow 36h}$) very well (Fig. 3). Thus, the bioavailability of quercetin from foods can be predicted from its 24-h excretion in urine, which obviates the need for repeated blood sampling.

Our quercetin assay in plasma and urine measured the sum of free quercetin, quercetin glycosides, and any glucuronides and sulfates formed by conjugation in the liver or the small intestine [26]. Methylated quercetin formed in the liver [24] escaped our assay, because it would not be hydrolyzed. Quercetin glucuronides, sulfates and glycosides, if present in plasma, might each show a somewhat different distribution and elimination. In addition, for apples each separate glycoside probably is absorbed at its own rate. Thus, the pharmacokinetic parameters calculated reflect the summed absorption and disposition of various conjugates.

4.2. Comparison with previous studies

Absorption profiles of flavonols in plasma were determined in two subjects by Nieder [10] after administration of an unspecified type and amount of flavonol glycosides from *Ginkgo biloba*. Peak concentrations of flavonols in plasma were reached after 2–2.5 h. Quercetin glycosides were detected in plasma of two unsupplemented volunteers [27]. Quercetin aglycone could not be detected in plasma of human subjects by Gugler et al. [9] after oral administration of even 4 g of quercetin aglycone. However, their assay, which had a limit of detection of 0.33 μM (100 ng/ml), would not have detected quercetin present as conjugates. The elimination half-lives of 2–4 h measured by Nieder [10] after oral, and Gugler et al. [9] after intravenous administration were much shorter than those reported here, possibly because in both studies the plasma concentration was not measured for long enough. Most likely these authors mistook the distribution phase for the elimination phase.

4.3. Mechanisms of absorption

The short time to reach peak levels after onion glucosides points to absorption from the stomach or small intestine, whereas the prolonged time needed for the rutinoside to reach its peak suggests that it transits the small intestine and is absorbed from the colon. We previously showed that intact glucosides are absorbed well [12]. The presence of quercetin glycosides in human plasma [27] suggests that intact glycosides may be absorbed. However, hydrolysis of the rutinoside may be necessary before absorption can occur. Because the rutinoside is a β-glycoside, only microorganisms in the colon can mediate hydrolysis, but at the same time they will also degrade the liberated aglycone [1]. In contrast with the present study in volunteers with a complete gastro-intestinal tract, we found practically no urinary excretion of quercetin or its con-

jugates after administration of the rutinoside to ileostomy subjects, who lack a colon [12]. This again provides evidence for a role of the colon in the absorption of quercetin rutinoside, the major species in tea. The present study suggests that the sugar moiety has a predominant effect on the absorption and plasma levels of quercetin.

We found that quercetin glycosides present in major food sources of flavonols are absorbed, and that they are eliminated slowly throughout the day. Quercetin could thus contribute significantly to the antioxidant defences present in blood plasma.

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