# Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers[1–3]

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**ABSTRACT** Quercetin is a dietary antioxidant that prevents oxidation of low-density lipoproteins in vitro. Intake of quercetin was inversely associated with coronary heart disease mortality in elderly Dutch men. However, the extent of absorption of quercetin in humans is unclear. The aim of this study was to quantify absorption of various forms of quercetin. Nine healthy ileostomy subjects were studied, to avoid losses caused by colonic bacteria. They followed a quercetin-free diet for 12 d; on days 4, 8, and 12 they received a supplement of fried onions at breakfast (rich in quercetin glucosides) equivalent to 89 mg aglycone, pure quercetin rutinoside (the major quercetin compound in tea) equivalent to 100 mg aglycone, or 100 mg pure quercetin aglycone, in random order. Subsequently, participants collected ileostomy effluent and urine for 13 h. In vitro incubations of quercetin or its glycosides with gastrointestinal fluids showed minimal degradation. Absorption of quercetin, defined as oral intake minus ileostomy excretion and corrected for 14% degradation within the ileostomy bag, was 52 ± 15% for quercetin glucosides from onions, 17 ± 15% for quercetin rutinoside, and 24 ± 9% for quercetin aglycone. Mean excretion of quercetin or its conjugates in urine was 0.5% of the amount absorbed; quercetin excretion in urine was negatively correlated with excretion in ileostomy effluent ($r = -0.78$, $n = 27$). We conclude that humans absorb appreciable amounts of quercetin and that absorption is enhanced by conjugation with glucose. *Am J Clin Nutr* 1995;62:1276–82.

**KEY WORDS** Quercetin, flavonoids, flavonols, dietary antioxidant, human absorption, excretion, ileostomy

## INTRODUCTION

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Flavonoids are categorized into flavonols, flavones, catechins, flavanones, and anthocyanidins (1). Quercetin (**Figure 1**), the major representative of the flavonol subclass, is a strong antioxidant (5) that prevents oxidation of low-density lipoproteins in vitro (6). Oxidized low-density lipoproteins are atherogenic and are considered to be a crucial intermediate in the formation of atherosclerotic plaques (7). This agrees with our observation that the intake of flavonols and flavones was inversely associated with subsequent coronary heart disease in both the Zutphen Elderly Study (8), a prospective cohort study, and in the Seven Countries Study (9), a cross-cultural study.

The average dietary intake of quercetin in the Netherlands is 16 mg/d (10), which is similar to that of vitamin E (7–10 mg/d), β-carotene (2–3 mg/d), and vitamin C (70–100 mg/d) (11). However, the extent of absorption of flavonoids is an important unsolved problem in judging their many alleged health effects (12). Indeed, it is often stated that flavonoids present in foods cannot be absorbed from the intestine because they are bound to sugars as glycosides (1). Only free flavonoids without a sugar molecule, the so-called aglycones, are considered to be able to pass through the gut wall, and no enzymes that can split these predominantly β-glycosidic bonds are secreted into the gut or present in the intestinal wall (1, 13). Hydrolysis only occurs in the colon by microorganisms, which at the same time degrade flavonoids (1). On the other hand, it was shown in one human study that the aglycone quercetin was not absorbed either (14). Nieder (15) suggested that flavonol glycosides from *Ginkgo biloba* were absorbed in human subjects, but no information on the extent of absorption was given.

A major problem in studying the absorption of quercetin in humans is its degradation by microorganisms in the colon. For that reason measurement of fecal excretion in normal human subjects would lead to an overestimate of the amount absorbed. We therefore studied quercetin absorption in healthy ileostomy subjects with complete small intestines. Ileostomy subjects with minimal ileal resection were successfully employed previously to determine absorption of minerals and trace elements (16), dietary starch and nonstarch polysaccharides (17), and cholesterol (18).

The present study was designed to determine absorption of quercetin from onions and of a major glycoside from tea, because tea and onions are the main dietary sources besides wine (10). Onions contain mainly quercetin glucosides (2, 3), whereas quercetin rutinoside predominates in tea (4) (Figure 1). Quercetin aglycone, ie, free quercetin with no sugar attached, was included as a model compound.

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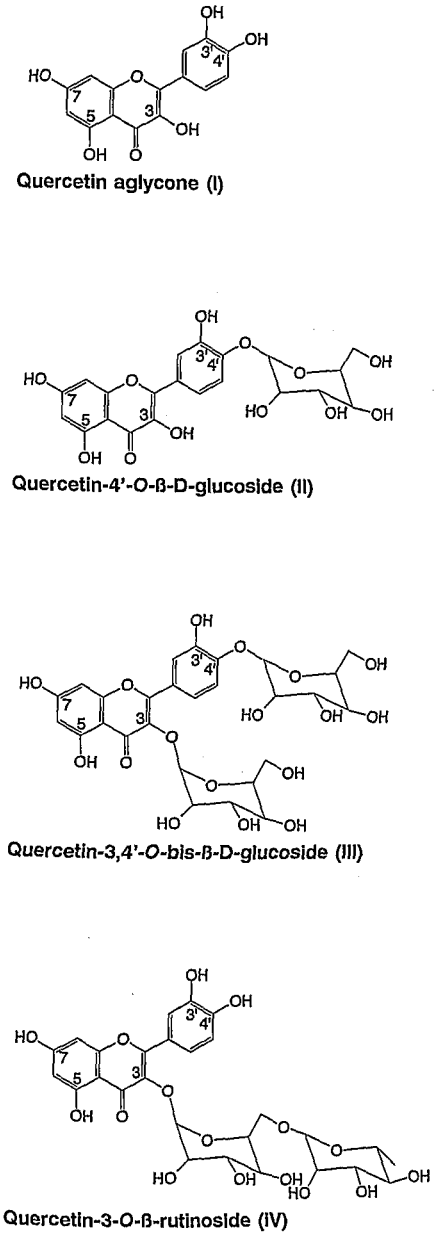


FIGURE 1. Structure of quercetin aglycone (I) and quercetin glycosides; II and III are the major species in onions (2, 3), and IV is the major species in tea (4).

## SUBJECTS AND METHODS

### Subjects

Ileostomy subjects have had their large intestine completely removed and the terminal ileum brought out onto the anterior abdominal wall as a fistula. We recruited nine subjects (five females, four males), aged ($\bar{x}$)45 y (range: 22–62 y), with a mean body mass index of 26 (range 21–33) kg/m$^2$. All had had total colectomies for ulcerative colitis or polyposis coli 13 y (range: 1–26 y) ago. In the operation an average of 8 cm (range: 0–40 cm) of the terminal ileum had been removed. None of the subjects had evidence of Crohn's disease or malabsorption, and all had well-functioning ileostomies. Subjects were not hospitalized and were leading normal, active lives. One subject was a psychologist, one was a clerk, one was a fruit farmer, one was a cleaner, one was a student, one was a retired civil engineer, and the other three were housewives. They were all judged healthy by a gastroenterologist on the basis of a medical questionnaire and had no record of gastric surgery. All subjects were unmedicated.

The protocol was approved by the Nijmegen University Hospital Ethical Committee and was fully explained to the participants, who gave their written informed consent.

### Study design, foods, and supplements

Subjects followed a quercetin-free diet for 12 d. On days 4, 8, and 12 we fed them three different quercetin-containing supplements in random order, at breakfast at the Department between 0745 and 0930. After the quercetin-rich breakfast, participants collected ileostomy effluent and urine for 13 h. Absorption was calculated as the difference between the amount of quercetin in the supplements and in the subsequent ileostomy effluent.

To ensure a quercetin-free diet, participants were given a list of vegetables and fruits containing > 15 mg quercetin/kg and of beverages with > 4 mg quercetin/L (19, 20) and were instructed not to consume any of them. Because proteins are known to bind polyphenols (21), the quercetin-supplemented breakfasts were low in protein; they consisted of protein-free bread, margarine, jams made from quercetin-free fruits, and other sweets such as chocolate sprinkles, coffee without milk, quercetin-free soft drinks, and mineral water. We fried 333 g yellow onions with 20 g margarine, 15 g tomato ketchup, and 1 g Italian herbs; 150 g of this dish, corresponding to 215 g raw yellow onions, constituted the onion supplement. It contained 89 ± 14 mg quercetin ($n$ = 9) as determined by HPLC (22). For the two other breakfasts 220 mg quercetin-3-*O*-ß-rutinoside (Rutosidum DAB, #339994; OPG Farma, Utrecht, Netherlands), equivalent to 100 mg aglycone, or 112 mg quercetin-dihydrate (#Q-0125; Sigma, St Louis), equivalent to 100 mg aglycone, were administered as capsules. The capsules also contained 80 mg *para*-aminobenzoic acid (#361334; OPG Farma). *Para*-aminobenzoic acid is completely absorbed and excreted with urine in humans (23). The onion breakfast was supplemented with a capsule containing 80 mg *para*-aminobenzoic acid. Subjects also ingested 25 radioopaque, barium-salt-impregnated plastic ringlets (outer diameter 3 mm) as a recovery marker. Subjects were instructed not to eat anything and to drink only water or coffee without milk after the experimental breakfasts until lunch.

Energy and nutrient intakes were calculated by using the Dutch food composition table (24). The breakfasts provided 1.52 ± 0.61 MJ (362 ± 145 kcal), with protein accounting for 2.0 ± 1.6% of energy, fat for 41.2 ± 12.6%, and carbohydrates for 56.4 ± 13.2%. The onion breakfast provided 3.8 ± 1.3% of energy from protein and the other breakfasts provided 1.0 ± 0.5%; no differences were found for fat and carbohydrates between the three breakfasts supplied. Average energy intake on days 3, 7, and 11, according to 24-h dietary recalls, was 11.26 ± 2.72 MJ, of which protein provided 14.6 ± 3.7% of energy, fat 37.7 ± 5.9%, and carbohydrates 47.2 ± 5.3%, with no differences between breakfast periods.

### Collection of samples

After the quercetin-rich breakfast, subjects returned home or went to work and collected urine and stoma effluent until they

went to bed between 2200 and 2345. On average, effluent and urine were collected for 13.4 ± 0.7 h. Subjects changed the ileostomy bags every 2–5 h (on average, 3.5 ± 1.5 h) according to their normal routine and immediately stored the bags in a polystyrene box containing dry ice. They collected urine in plastic bottles containing 0.1 g thimerosal (#T-5125; Sigma) and stored each bottle in dry ice immediately after voiding. Three of the subjects (nos. 1, 2, and 8) collected urine every 2 h, which allowed us to study the rate of excretion of quercetin.

### Sample preparation

The filled plastic ileostomy bags were kept frozen with liquid nitrogen, the bags were removed, and the frozen contents were freeze-dried, ground to pass through an 0.5-mm sieve, and stored at −20 °C until analyzed < 21 wk later. Urine samples were thawed in a water bath at 40 °C and mixed, and aliquots were taken within 30 min, frozen with liquid nitrogen, and stored at −40 °C until analyzed < 7 wk later.

Samples collected before breakfast (prebreakfast sample) and the final collection at the end of the day (final sample) were prepared separately, as were all samples from the three subjects who collected urine every 2 h. The other samples were pooled by subject and treatment day and thoroughly homogenized.

### Incubation of quercetin supplements with gastrointestinal fluids in vitro

Amounts of raw onions, quercetin-3-rutinoside, and quercetin corresponding to 3 mg quercetin aglycone were incubated with 3 mL human gastric juice (25) and 9 mL water at 37 °C for 0.5 and 2 h. This mimicked stomach contents after the experimental breakfasts (26). Similar amounts were also incubated with 1.5 mL human duodenal fluid (27) and 9 mL water at 37 °C for 1 and 4 h, corresponding to the average and maximal transit time in the small intestine, respectively (28).

The stability of quercetin in ileostomy fluid was studied as follows. About 6 mo after the experiments, three of the volunteers followed a quercetin-free diet for 2 d. At 1200 of the second day, they applied an ileostomy bag containing either 30 mg quercetin aglycone emulsified with 6.7 g margarine or 50 g finely ground fried onions prepared as described. Subjects allowed ileostomy fluid to drain into the bag for 3–4 h and kneaded the contents occasionally. The contents were then stored and studied as described above.

### Analytical methods

Quercetin glycosides and glucuronides were simultaneously extracted and hydrolyzed to the aglycone by using 2 mol HCl/L in aqueous methanol. By varying acid concentration and the duration of extraction and hydrolysis the following procedure was found to be optimal for urine: 12.5 mL methanol containing 2 g/L *tert*-butyl hydroxyquinone and 5 mL 10 mol HCl/L were added to 7.5 g urine, followed by mixing, the extract was refluxed at 90 °C for 2 h with regular swirling, allowed to cool, and subsequently brought to 50 mL with methanol. For ileostomy effluent, 40 mL 62.5% (by vol) aqueous methanol containing 2 g *tert*-butyl hydroxyquinone/L and 10 mL 10 mol HCL/L were added to 0.500 g freeze-dried effluent and then mixed. The extract was refluxed at 90 °C for 2 h with regular swirling, allowed to cool, and subsequently brought to 100 mL with methanol. Urine and effluent extracts were sonicated for 5 min and filtered through a 0.45-μm filter for organic solvents (Acrodisc CR PTFE; Gelman Sciences, Ann Arbor, MI) before HPLC analysis. We injected 10 μL onto an Inertsil ODS-2 (GL Sciences Inc, Tokyo) column (4.6 × 150 mm, 5 μm particle size) protected by an MPLC Newguard RP-18 (Brownlee; Applied Biosystems Inc, San Jose, CA) column (3.2 × 15 mm, 7 μm particle size) by using acetonitrile:0.025 mol phosphate buffer/L, pH 2.4 (31:69, by vol) as the mobile phase, at a flow rate of 1 mL/min. The columns were placed in a column oven set at 30 °C. The eluent was mixed with 0.4 mL/min 1.5 mol $Al(NO_3)_3$/L in methanol containing 7.5% (by vol) acetic acid in a postcolumn stainless steel reaction coil (0.25 mm × 15 m) placed in the column oven. The fluorescence of the ensuing quercetin-metal complex was measured at 490 nm with a Merck Hitachi F-1000 (Tokyo) fluorescence detector with the excitation wavelength set at 400 nm. Further details were described elsewhere (22).

The limit of detection, ie, the concentration producing a peak height three times the SD of the baseline noise, was 5 ng/g for urine and 2 μg/g for ileostomy effluent. Recovery of quercetin in onion extract, of pure quercetin-3-rutinoside, and of quercetin aglycone added at a quercetin concentration of 800 μg/g to freeze-dried ileostomy effluent free of quercetin was 91.6 ± 3.0%, 91.6 ± 0.3%, and 90.0 ± 0.1%, respectively ($n$ = 2). Addition of 0.5 μg quercetin aglycone/g urine yielded a recovery of 98.7 ± 8% ($n$ = 3).

All determinations were carried out in duplicate. We included a control sample of freeze-dried effluent in each series of analyses; all values were within 868 ± 103 μg/g ($\bar{x}$ ± 2 SD, $n$ = 18). For urine analyses a urine sample of the previous series was always included. The between-series CV was 4% ($n$ = 11). Quercetin absorption was calculated as the difference between the amount in the supplements and in the ileostomy effluent corrected for 9% analytical losses plus 5% degradation within the ileostomy bag (*see* Results).

*Para*-aminobenzoic acid was determined photometrically by using fluorescamine (#F-9015; Sigma) after hydrolysis with 0.1 mol HCl/L for 40 min in a boiling water bath (29). Addition of 0.15 mg *para*-aminobenzoic acid/g urine yielded a recovery of 94.2 ± 2% ($n$ = 6). A urine control sample was included in each series of analysis; values were within 66.8 ± 3.1 mg ($\bar{x}$ ± 2 SD, $n$ = 14).

### Statistical analysis

Because the amounts of quercetin excreted were expected to follow a log-normal distribution, values as proportions of intake were first converted to $\log_{10}$ values. The Shapiro-Wilk test for normality did not give evidence for nonnormality. Differences between treatments were tested by analysis of variance using the Statistical Package for Social Sciences, SPSS/PC+ (SPSS Inc, Chicago) with subject, type of breakfast, and previous type of breakfast as independent variables. The significance of differences was determined by paired $t$ test.

## RESULTS

### Stability of quercetin and glycosides in gastrointestinal fluids

Quercetin aglycone and glycosides were stable in vitro in gastric juice for ≥ 2 h and in duodenal fluid for ≥ 4 h

(**Table 1**). Incubation with ileostomy fluid for 3.25 h yielded a recovery of 86% (Table 1). The analytical recovery of quercetin added to freeze-dried ileostomy fluid was 91% (*see* Methods); therefore, the loss through degradation in an ileostomy bag carried on the body for 3.25 h was ≈5%.

### Compliance with the quercetin-free diet

The average quercetin intake from regular foods on days 3, 7, and 11 according to 24-h dietary recalls was 1.1 ± 1.4 mg. No difference in quercetin intake was observed between the three 4-d periods. Quercetin excretion in prebreakfast effluent samples was on average 3% of the total daily amount (**Table 2**) and on average 2% in prebreakfast urine (**Table 3**).

### Excretion of quercetin

The total amount of quercetin excreted in ileostomy effluent (**Figure 2**) was highly dependent on the type of supplement ($P < 0.01$). After correction for 14% analytical losses plus degradation during time in the ileostomy bag, average absorption was 52% for quercetin from onions, 17% for quercetin-3-rutinoside, and 24% for the pure aglycone (Table 2). No significant relation with the subject or with the supplement given in the previous period was found. Excretion of quercetin in urine was also significantly higher for quercetin from onions than for the aglycone, which was again higher than that for the rutinoside (Table 3). Again, no statistically significant relation with the subject or the supplement of the previous period was found. Still, one subject, depicted by ● in Figure 2 and **Figure 3** did excrete markedly less quercetin in ileostomy effluent after consumption of the quercetin-3-rutinoside and much more in urine than did the other subjects.

### Collection of effluent and urine

Of 25 radioopaque ringlets swallowed together with each supplement, on average 21 ± 8 were found after consumption of the onions, 17 ± 9 after the quercetin rutinoside, and 24 ± 2 after the quercetin aglycone supplements. On 7 of 27 person-days fewer than 22 of the 25 radioopaque ringlets ingested were recovered in the effluent. In the effluent of one subject no ringlets were found at all after two of the breakfasts but quercetin excretion in this subject was similar to that in the other subjects, indicating that all of the effluent was probably collected. A mechanical barrier in the connection between the ileum and the ileostomy bag may have caused the ringlets to be lost.

The final samples of effluent, collected just before bedtime, were analyzed separately. They contained on average 6% of the total amount of quercetin excreted after the onions and the aglycone breakfast and 15% after the quercetin-3-rutinoside breakfast (Table 2). This mean of 15% was caused by one subject, who excreted 88% of the total amount in this final sample. His ringlet recovery was only 7 of 25, which also indicated a long transit time. Thus, the total amount of quercetin excreted in effluent after quercetin rutinoside by this subject may have been even higher than the 86 mg recovered in 13 h, and the absorption correspondingly lower.

Urinary recovery of *para*-aminobenzoic acid was 85.5 ± 11.6%. Two volunteers showed recoveries of *para*-aminobenzoic acid between 64% and 82% for all treatments, but their urinary quercetin output was above average, which speaks against lack of compliance in collecting urine. The final sample of urine, collected just before bedtime, contributed 3% on average to the total daily output of quercetin (Table 3), which indicated that the peak of urinary quercetin excretion lay well within the 13-h period.

The three subjects (nos. 1, 2, and 8) who collected urine every 2 h (**Figure 4**) reached 90% of their cumulative excretion within 5.6 ± 0.3 h after the onion supplement, and within 7.8 ± 1.3 h after administration of quercetin aglycone. The rate of urinary quercetin excretion was significantly higher ($P < 0.05$) after the onion supplement. Administration of quercetin-3-rutinoside did not yield measurable amounts of quercetin in urine in these three subjects.

## DISCUSSION

We found that significant amounts of the quercetin glucosides present in onions and, to a lesser extent, of pure quercetin aglycone are absorbed by the human small intestine. This contradicts the widely held view that dietary flavonoids are poorly absorbed in humans and that the glycosides present in foods are especially poorly absorbed (1, 13). Absorption amounted to 52% for onions, 17% for quercetin-3-rutinoside, and 24% for quercetin aglycone. True absorption could be even higher if absorbed flavonoids are reexcreted with bile as was found in rats (13, 30). However, no data on reexcretion of flavonoids in human studies are available.

### Validity of the ileostomy model

We measured absorption as the difference between ingestion and excretion in healthy volunteers who lacked a colon. Jeju-

**TABLE 1**
Stability of quercetin recovered from various sources during incubation with human gastric juice or duodenal fluid in vitro, or ileostomy effluent ex vivo

| Source | Gastric juice | | Duodenal fluid | | Ileostomy effluent |
|---|---|---|---|---|---|
| | 0.5 h | 2 h | 1 h | 4 h | 3.25 ± 0.6 h |
| | % | % | % | % | % |
| Onions | 95.8[1] | 95.2 | 98.2 | 97.4 | 86.8 ± 4.5[2] |
| Quercetin-3-rutinoside | 91.9 | 92.7 | 95.7 | 94.7 | — |
| Quercetin aglycone | 94.9 | 88.7 | 98.8 | 108.4 | 85.9 ± 2.1 |

[1] $\bar{x}$ of duplicate determinations.
[2] $\bar{x}$ ± SD of incubations in ileostomy bags on the bodies of three volunteers. Analytical recovery after additions to freeze-dried effluent averaged 91.1 ± 2.1% ($n = 6$).

**TABLE 2**
Intake of quercetin at breakfast and subsequent mean cumulative excretion in ileostomy effluent over 13 h[1]

| Supplement (to breakfast) | Intake in terms of aglycone | Excretion in ileostomy effluent | | | Absorption[3] |
|---|---|---|---|---|---|
| | | Prebreakfast sample | Total[2] | Final (prebedtime) sample | |
| | *mg* | *mg* | *mg* | *mg* | *%* |
| Onions ($n$ = 9) | 89 ± 14 | 1.8 ± 1.1 | 37 ± 11 | 2.9 ± 3.3 | 52 ± 15 |
| Quercetin-3-rutinoside ($n$ = 9) | 100 ± 5 | 1.3 ± 0.9 | 72 ± 15 | 11 ± 25 | 17 ± 15 |
| Quercetin aglycone ($n$ = 9) | 100 ± 5 | 1.7 ± 1.3 | 66 ± 9 | 3.4 ± 5.5 | 24 ± 9 |

[1] $\bar{x}$ ± SD. Total excretion as a proportion of intake was significantly different ($P < 0.02$) among all three supplements after rejection of the outlying quercetin rutinoside results of subject 4 (●, in Figure 2).
[2] Includes the final but not the prebreakfast sample.
[3] Corrected for 9% analytical loss plus 5% degradation within the ileostomy bag.

noileal absorption in such subjects is probably equivalent to that in normal subjects with an intact colon, as indicated by their normal serum cholesterol concentrations (18) and absorption of *para*-aminobenzoic acid. Excluding the data of two subjects in whom recovery of *para*-aminobenzoic acid was low did not alter the results or conclusions.

It is unlikely that any quercetin disappeared through degradation in the stomach or duodenum because in vitro incubations with gastric juice or duodenal fluid mimicking normal conditions showed no loss of quercetin. Incubation of onions and quercetin in ileostomy fluid for 3 h produced an apparent loss of 14%. Some 9% of this was in fact due to analytical losses as shown by the in vitro recovery experiments (Methods). Thus, breakdown in the ileostomy effluent itself was only ≈5%. Degradation of sterols by microorganisms in ileostomy fluid was previously also reported to be small (18). Incomplete collection of ileostomy effluent by the volunteers is also unlikely in view of the high recoveries of the nonabsorbable marker and of the quercetin when fed as quercetin rutinoside.

Quercetin excretion in urine was strongly and negatively correlated with excretion in ileostomy effluent (**Figure 5**). This again suggests that low output of quercetin in stoma effluent was truly due to high absorption.

## Comparison with previous studies

Our results show that quercetin glucosides of onions are better absorbed than is the aglycone. Absorption of glycosides was also suggested by Nieder (15). However, no information about the nature of the glycosides was available.

Gugler et al (14) found no quercetin in urine or plasma after oral administration of 4 g quercetin aglycone to humans and concluded that < 1% could have been absorbed. The high limit of detection and the high dose could account for the difference in absorption (1% versus 24%) with the present study. Ueno et al (30) found that > 20% of orally administered [$^{14}$C]quercetin aglycone was absorbed in rats. The present study agrees with those results.

## Metabolism of quercetin

Figure 4 suggests that the rate of urinary excretion of quercetin was higher for the glucoside from onions than for quercetin aglycone, because the time to reach 90% of the cumulative excretion was ≈2 h shorter for the glucoside. This could be explained by more rapid absorption of the glucoside, assuming that the rate of elimination of the glucoside and aglycone are the same.

After the onion breakfast 41.1% was recovered in ileostomy fluid and 0.3% in urine. Thus, 58.6% went undetected, 2.5% of which may have been degraded in the ileostomy bag and another 3.3% was lost during sample preparation. Like many other compounds (31), absorbed quercetin is probably extensively modified before being excreted by the kidneys. Our assay would pick up quercetin glucuronides and similar conjugates, but *o*-methylated quercetin, a hepatic metabolite in rats (13, 30), would escape detection and so would metabolites in which the ring structure itself is altered. In addition to the formation of such undetectable metabolites an acute high dose such as was given here might also be partly stored and released slowly over subsequent days (32).

## Mechanisms of absorption

Quercetin glucosides from onions need to be liberated from the food matrix before being absorbed, whereas absorption of quercetin aglycone and quercetin rutinoside within the gut would probably be greater because these were administered as

**TABLE 3**
Intake of quercetin at breakfast and subsequent mean cumulative excretion of quercetin in urine over 13 h[1]

| Supplement (to breakfast) | Intake in terms of aglycone | Excretion in urine | | | |
|---|---|---|---|---|---|
| | | Prebreakfast sample | Total[2] | Final (prebedtime) sample | Total excretion as proportion of intake |
| | *mg* | *μg* | *μg* | *μg* | *%* |
| Onions ($n$ = 9) | 89 ± 14 | 1.2 ± 1.9 | 275 ± 129 | 5.7 ± 3.5 | 0.31 ± 0.14 |
| Quercetin-3-rutinoside ($n$ = 9) | 100 ± 5 | 3.6 ± 5.1 | 73 ± 190 | 1.7 ± 2.5 | 0.07 ± 0.19 |
| Quercetin aglycone ($n$ = 9) | 100 ± 5 | 1.0 ± 1.1 | 115 ± 75 | 4.4 ± 6.0 | 0.12 ± 0.08 |

[1] $\bar{x}$ ± SD. Total excretion as a proportion of intake was significantly different for all three supplements ($P < 0.02$).
[2] Includes the final but not the prebreakfast sample.

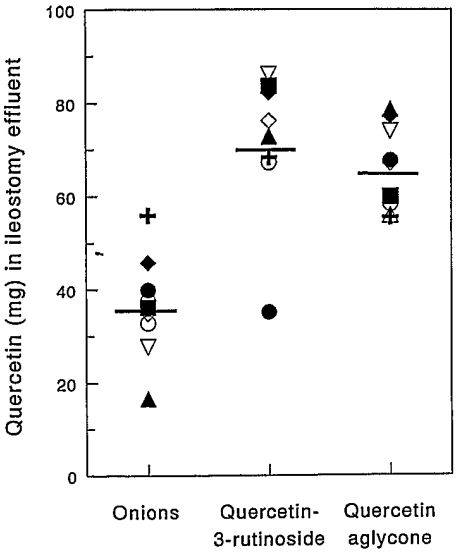


**FIGURE 2.** Total amount of quercetin excreted in daytime ileostomy effluent of nine subjects after consumption of various supplements. Each subject is depicted by a different symbol. Horizontal bars depict means.

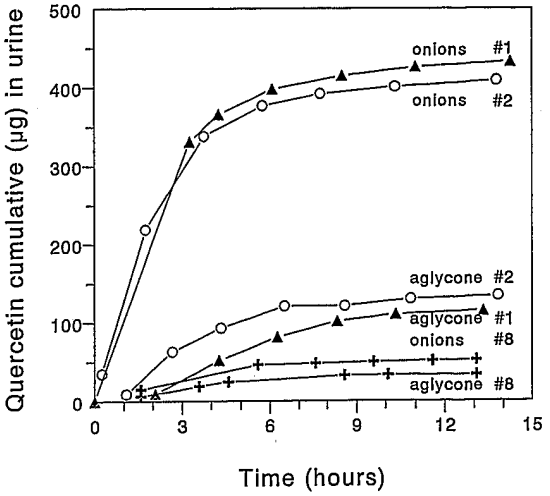


**FIGURE 4.** Cumulative amount of quercetin excreted in urine of subjects 1, 2, and 8 after consumption of onions and quercetin aglycone. Each subject is depicted by a different symbol. Time course of quercetin excretion after quercetin rutinoside is not shown because no measurable amounts were found.

powders. Poor solubility of quercetin rutinoside does not seem to be a major factor because it was well absorbed in subject 4. Thus, there is a predominant effect of the carbohydrate moiety on the absorption of quercetin. We speculate that intestinal sugar carriers may play a role in flavonoid absorption. Model studies by Mizuma et al (33) on the absorption of naphthol glycosides in everted small intestines of rats support such a mechanism. Absorption was higher for naphthol glucoside than for the galactoside, and higher for the β-anomer than for the α-anomer; also, the absorption of these glycosides was inhibited by the absence of $Na^+$, which is needed for active $Na^+$/glucose cotransport, and by the inhibitor of glucose transport phloridzin. Such active transport of β-glucosides of foreign compounds by the glucose transporter offers a possible explanation for the high absorption of quercetin from onions, in which it is present as β-D-glucosides. The quercetin group might thus be drawn into the enterocyte by its glucose moiety, which is transported by the glucose carrier. The aglycone (ie, free quercetin) would then fail to be absorbed because it lacks a sugar. However, experiments are needed to study the role of the active $Na^+$/glucose cotransporter in the absorption of quercetin glucosides. The poor absorption of quercetin rutinoside is puzzling, especially in view of indications that diosmin, the rutinoside of the flavone diosmetin, is absorbed in humans after oral administration (34). Studies of the absorption of rutinose

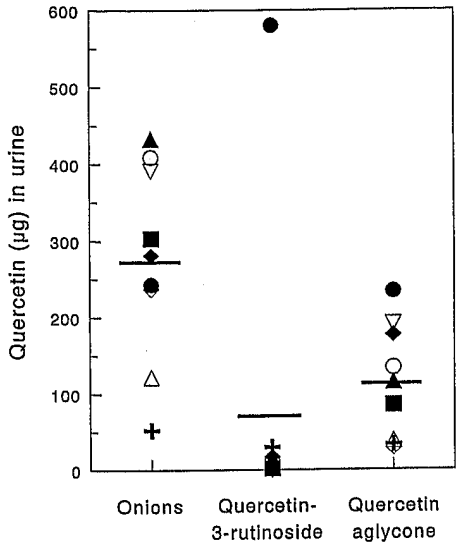


**FIGURE 3.** Total amount of quercetin excreted in daytime urine of nine subjects after consumption of various supplements. Each subject is depicted by a different symbol. Horizontal bars depict means.

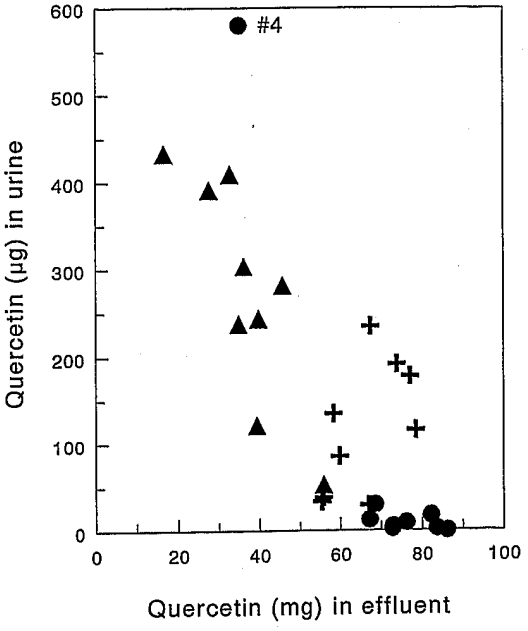


**FIGURE 5.** Correlation between total quercetin excreted in urine and in ileostomy effluent in nine subjects who consumed three supplements in random order; $r = -0.78$, $n = 27$ ($P < 0.0005$). ▲ onions; ● quercetin-3-rutinoside; + quercetin aglycone.

itself and of various rutinosides are required to solve this discrepancy.

In contrast with the other eight subjects, subject 4 showed low ileostomy and high urinary excretion after consumption of the quercetin-3-rutinoside (Figure 5). This may be due to a variant type of intestinal physiology; further studies of such subjects might yield clues to the mechanism of absorption of flavonoids. Rutinose is a disaccharide consisting of glucose and rhamnose (Figure 1). Possibly, subject 4 has a β-glycosidase in the small intestine that splits off rhamnose and transforms the rutinoside into a well-absorbable glucoside.

Thus, quercetin glucoside as present in onions is absorbed efficiently in humans. If the glucose transporter is involved in this then quercetin will enter the blood stream as the glucoside; this might affect its distribution, metabolism, and excretion. Quantitative data for separate quercetin glycosides in foods are needed for evaluation of the extent of absorption of quercetin from other foods such as tea.

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