Human Nutrition and Metabolism—Research Communication

Bioavailabilities of Quercetin-3-Glucoside and Quercetin-4′-Glucoside Do Not Differ in Humans[1,2]

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ABSTRACT The flavonoid quercetin is an antioxidant which occurs in foods mainly as glycosides. The sugar moiety in quercetin glycosides affects their bioavailability in humans. Quercetin-3-rutinoside is an important form of quercetin in foods, but its bioavailability in humans is only 20% of that of quercetin-4′-glucoside. Quercetin-3-rutinoside can be transformed into quercetin-3-glucoside by splitting off a rhamnose molecule. We studied whether this 3-glucoside has the same high bioavailability as the quercetin-4′-glucoside. To that end we fed five healthy men and four healthy women (19–57 y) a single dose of 325 μmol of pure quercetin-3-glucoside and a single dose of 331 μmol of pure quercetin-4′-glucoside and followed the plasma quercetin concentrations. The bioavailability was the same for both quercetin glucosides. The mean peak plasma concentration of quercetin was 5.0 ± 1.0 μmol/L (±SE) after subjects had ingested quercetin-3-glucoside and 4.5 ± 0.7 μmol/L after quercetin-4′-glucoside consumption. Peak concentration was reached 37 ± 12 min after ingestion of quercetin-3-glucoside and 27 ± 5 min after quercetin-4′-glucoside. Half-life of elimination of quercetin from blood was 18.5 ± 0.8 h after ingestion of quercetin-3-glucoside and 17.7 ± 0.9 h after quercetin-4′-glucoside. We conclude that quercetin glucosides are rapidly absorbed in humans, irrespective of the position of the glucose moiety. Conversion of quercetin glycosides into glucosides is a promising strategy to enhance bioavailability of quercetin from foods. J. Nutr. 130: 1200–1203, 2000.

KEY WORDS: • quercetin glucosides • flavonols • bioavailability • metabolism • humans

Flavonoids are polyphenolic compounds that occur in foods of plant origin. The average daily intake of the flavonoid subclasses of flavonols and flavones in The Netherlands is 23 mg (expressed as aglycones) of which quercetin supplies 16 mg (Hertog et al. 1993b). Quercetin is an antioxidant in vitro because it can scavenge radicals, inhibit lipid peroxidation and chelate metals (Rice Evans et al. 1996). Quercetin was able to inhibit oxidation of LDL in vitro at a concentration as low as 0.25 μmol/L, which is in the physiological range (de Whalley et al. 1990, Manach et al. 1998). Therefore quercetin might contribute to the prevention of cardiovascular disease (Hertog et al. 1993a). However, to induce these health effects in humans, quercetin must enter the systemic circulation. Quercetin in foods is bound to sugars, mainly as β-glycosides, and the bioavailability of these various quercetin glycosides is affected by their sugar moiety (Hollman et al. 1995, 1996a and 1999). Quercetin-3-rutinoside and quercetin-4′-glucoside are important forms of quercetin in foods (**Fig. 1**). Quercetin-3-rutinoside accounts for ∼40% of quercetin in black tea (Engelhardt et al. 1992), and consumption of black tea contributes about 48% to the total flavonol and flavone intake in The Netherlands (Hertog et al. 1993b). Quercetin-4′-glucoside accounts for ∼45% of quercetin in onions (Kiviranta et al. 1988), and consumption of onions contributes another 29% to the total flavonol and flavone intake (Hertog et al. 1993b). Although the intake of quercetin-3-rutinoside is twice that of quercetin-4′-glucoside, the absorption of quercetin-3-rutinoside is only 17% of ingested dose, whereas the absorption of quercetin-4′-glucoside is 52% of ingested dose (Hollman et al. 1995). Furthermore, the bioavailability of quercetin-3-rutinoside is only 20% of that of quercetin-4′-glucoside (Hollman et al. 1999). Therefore it would be interesting to attempt to increase the bioavailability of quercetin-3-rutinoside. Rutinose is a dimer of glucose and rhamnose; therefore quercetin-3-rutinoside can be transformed into quercetin-3-glucoside by splitting of the rhamnose molecule with the enzyme alpha-L-rhamnosidase (Bokkenheuser et al. 1987, Gunata et al. 1988, Kurosawa et al. 1973). The resulting quercetin-3-glucoside differs only from the highly bioavailable quercetin-4′-glucoside in the position of the glucose moiety on the quercetin aglycone. However the bioavailability of quercetin-3-glucoside is unknown. Therefore we tested whether the position of the glucose moiety affected the bioavailability of quercetin glucosides in humans.

MATERIALS AND METHODS

Subjects. The protocol was approved by the Ethical Committee of Nijmegen University Hospital. All subjects were fully informed about the study and signed an informed consent form. Five women and five men started with the study, but one woman was excluded because of problems with blood sampling. Mean age of the remaining nine subjects was 25 y (range 19–57 y) and mean body mass index was 21.3 kg/m² (range 19.8–24.8 kg/m²). All subjects were healthy based on a medical questionnaire—the absence of protein and glucose in urine and normal values for blood hematocrit, hemoglobin concentration and leukocyte and platelet counts. Subjects were not
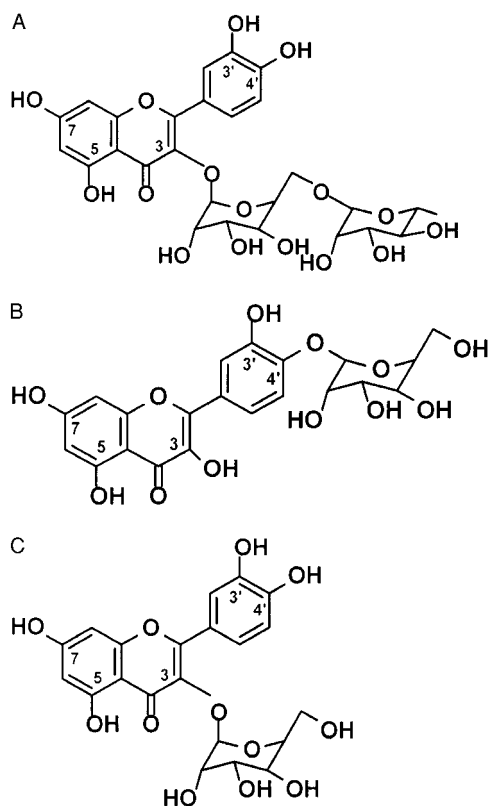
FIGURE 1 Structure of quercetin glycosides: *A*: quercetin-3-rutinoside, *B*: quercetin-4′-glucoside, and *C*: quercetin-3-glucoside.

allowed to use any medicine during the study, except for acetaminophen (paracetamol) and oral contraceptives.

Study design and supplements. The subjects ingested quercetin-3-glucoside or quercetin-4′-glucoside (Fig. 1) on two different days in random order, and subsequently we measured quercetin in blood over 72 h and in urine over 24 h. Subjects consumed a low quercetin diet from d 3 to 16, having been given a list of fruits and vegetables which contained >15 mg quercetin/kg and of beverages with >4 mg quercetin/L (Hertog et al. 1992 and 1993c) which they were instructed not to consume. During the mornings of d 7 and of d 13, the subjects came to the University Hospital Nijmegen after they had fasted overnight. Five of the subjects ingested 325 μmol (151 mg) quercetin-3-glucoside (#011095; Extrasynthese, Genay, France) on d 7 and 331 μmol (154 mg) quercetin-4′-glucoside (#4564; Carl Roth, Amsterdam, The Netherlands) on d 13. The other four subjects received the same supplements in reverse order. Each supplement was dissolved in 10 mL ethanol plus 200 mL of hot water (5% v/v alcohol concentration). Subjects ingested 2 g of sodium chloride dissolved in 10 mL of water just before they ingested the supplement because the sodium glucose cotransporter might play a role in the absorption of quercetin glucosides, and sodium is necessary for the active transport of glucose. During the first 3 h after ingestion of the supplements, subjects were allowed to consume water only. We checked compliance with the dietary guidelines with a 24-h recall for d 6 and 12. We calculated intakes with the Dutch food composition table. Average energy intake was 13.4 ± 0.9 (SE) MJ, of which protein provided 14.8 ± 0.5%, fat 34.7 ± 2.8% and carbohydrates 49.8 ± 3.2%. The mean daily quercetin intake from regular foods during the study was not different between supplement periods and was 7.6 ± 2.3 μmol. Because this was about 2% of the dose of the supplements, we conclude that intake of quercetin from regular foods did not affect our results.

Collection of blood and urine samples. We took venous blood samples (10 mL blood per blood sample) into vacuum tubes containing EDTA once before subjects ingested the supplement, and at 15 min, 30 min, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h after ingestion. Platelet-poor plasma was prepared by centrifuging the

blood for 10 min at 2500 × g at 4°C. The plasma was stored at −80°C until analysis. On d 7 and 13, subjects collected urine for 24 h in plastic bottles, one for each voiding, with thymol (#8167; Merck, Amsterdam, The Netherlands) dissolved in isopropanol as preservative. They stored each bottle in dry ice immediately after voiding. At the laboratory we thawed the urine bottles in a water bath of ∼40°C, pooled and mixed urine per subject and per supplement day, froze aliquots of urine in liquid nitrogen and stored the urine samples at −80°C until analysis. Subjects took 300 μmol lithium chloride dissolved in 10 mL of water every morning from d 1 until d 14. Urinary recovery of lithium was 94.4 ± 17.2% (means ± SD), which indicates that collection of urine was complete (Sanchez-Castillo et al. 1987a and 1987b).

Analytical methods. Quercetin, isorhamnetin (3′-methoxyquercetin) and their conjugates with glycosides, glucuronic acid or sulfates in plasma or urine were simultaneously extracted and hydrolyzed to their aglycones with 2 mol/L HCL in aqueous methanol (Hollman et al. 1997). We measured the aglycones by HPLC with fluorescence detection (Hollman et al. 1996b). The limit of detection, i.e., the concentration producing a peak height three times the standard deviation of the baseline noise was 0.007 μmol/L (2 ng/mL) for quercetin in plasma and 0.01 μmol/L (3 ng/mL) for quercetin in urine (Hollman et al. 1997). The limits of detection for isorhamnetin were one-third of those for quercetin (Hollman et al. 1996b). Lithium was measured in undiluted, acidified urine by atomic absorption spectrophotometry (Anonymous 1976).

Data analysis. We used a two-compartment model to describe the pharmacokinetics of quercetin and isorhamnetin. We calculated peak plasma concentration, time to reach peak plasma concentration, elimination half-life and area under the plasma concentration vs. time curve (AUC$_{0→72h}$)[4] with the MW/Pharm computer package (Proost and Meijer 1992). We calculated the AUC$_{0→72h}$ with the linear trapezoidal rule. Differences between results after ingestion of quercetin-3-glucoside and after quercetin-4′-glucoside were tested for significance by paired t test with a significance level of $P < 0.05$ (SAS Institute, Cary, NC).

RESULTS

The time course of the quercetin (measured as the quercetin aglycone) concentration in blood after ingestion of quercetin-3-glucoside was not different from that after ingestion of quercetin-4′-glucoside (**Fig. 2**). The plasma kinetic variables

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[4] Abbreviation used: AUC$_{0→72h}$, area under the plasma concentration vs. time curve.
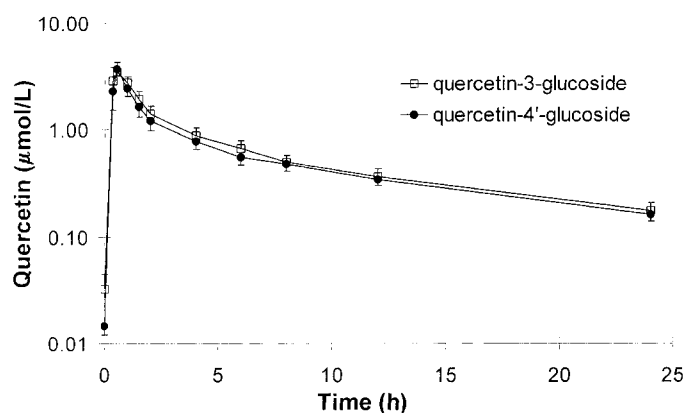

FIGURE 2 Total quercetin concentration in plasma of nine human subjects after ingestion of 325 μmol (151 mg) quercetin-3-glucoside (means + SE) or 331 μmol (154 mg) quercetin-4′-glucoside (means − SE). Each subject received each supplement in random order at a 6-d interval.

TABLE 1

Kinetic variables of quercetin absorption and elimination in plasma of human subjects after one-time ingestion of quercetin-3-glucoside or quercetin-4-glucoside[1]

	Supplement[2]	
Variable	Quercetin-3-glucoside	Quercetin-4-glucoside
Plasma total quercetin		
Peak concentration		
μmol/L	5.0 ± 1.0	4.5 ± 0.7
ng/mL	1526 ± 315	1345 ± 212
Time to reach peak concentration, *min*	37 ± 12	27 ± 5
Elimination half-life, *h*	18.5 ± 0.8	17.7 ± 0.9
Area under the plasma concentration vs. time curve ($AUC_{0\to72h}$)		
$h \times \mu$mol/L	19.1 ± 2.9	17.5 ± 2.4
$h \times$ ng/mL	5775 ± 876	5276 ± 730

[1] Values are means ± SE, $n = 9$. None of the variables differed significantly between supplements.

[2] Subjects ingested 325 μmol (151 mg) of quercetin-3-glucoside or 331 μmol (154 mg) of quercetin-4-glucoside. Each subject received each supplement in random order at a 6-d interval.

of the two glucosides also did not differ, as did the bioavailability, as indicated by the similar $AUC_{0\to72h}$ (**Table 1**).

The concentration of quercetin in plasma rose rapidly after ingestion of quercetin-3-glucoside as well as after ingestion of quercetin-4'-glucoside. The mean peak plasma concentration of quercetin, the time to reach peak concentration, and the elimination half-life of quercetin in plasma did not differ when subjects consumed quercetin-3-glucoside or quercetin-4'-glucoside (Table 1).

The amount of quercetin excreted in 24-h urine after intake of the 3-glucoside was not different from that after intake of the 4'-glucoside (**Table 2**). Only about 3% of the ingested quercetin was excreted in urine as quercetin aglycone or its conjugates, which indicates that quercetin is extensively metabolized in the human liver and other organs and by the colonic microflora. One of the metabolites of quercetin is isorhamnetin (3'-methoxyquercetin) (Manach et al. 1998,

TABLE 2

Excretion of quercetin and isorhamnetin in urine of subjects during the first 24 h after one-time ingestion of quercetin-3-glucoside or quercetin-4'-glucoside[1]

		Excretion in urine	
Supplement[2]	Intake	Quercetin	Isorhamnetin
	μmol	% quercetin glucoside intake	
Quercetin-3-glucoside	325	3.0 ± 0.3	0.61 ± 0.08
Quercetin-4'-glucoside	331	2.6 ± 0.4	0.53 ± 0.07

[1] Values are means ± SE, $n = 9$. None of the variables differed significantly between supplements.

[2] Subjects ingested 325 μmol (151 mg) of quercetin-3-glucoside or 331 μmol (154 mg) of quercetin-4'-glucoside. Each subject received each supplement in random order at a 6-d interval.

Morand et al. 1998). We found isorhamnetin in plasma and urine after ingestion of both quercetin supplements. Peak concentration of isorhamnetin did not differ between the glucosides and was reached in 51 ± 19 min after the quercetin-3-glucoside and in 32 ± 5 min after the quercetin-4'-glucoside. Other kinetic variables of isorhamnetin also did not differ between the quercetin glucosides (data not shown). In urine, ~0.6% of the ingested quercetin glucosides was recovered as isorhamnetin (Table 2).

DISCUSSION

The bioavailability of quercetin-3-glucoside is similar to that of quercetin-4'-glucoside. We found that the time to reach peak concentrations was ~30 min for both quercetin glucosides and the peak concentration was ~5 μmol/L. This corresponds well with the peak concentration of 3.5 μmol/L for quercetin-4'-glucoside, reported by Hollman et al. (1999), who also found that the bioavailability of quercetin-3-rutinoside was 20% of that of quercetin-4'-glucoside. Therefore our results suggest that enzymatic conversion of quercetin-3-rutinoside into quercetin-3-glucoside will increase bioavailability. Quercetin-3-glucoside itself also occurs commonly in foods such as tea, tomatoes and apples (Engelhardt et al. 1992, Herrmann 1976 and 1988). We may now conclude that this naturally occurring 3-glucoside has the same high bioavailability as the 4'-glucoside.

Quercetin glucosides are absorbed more rapidly than other quercetin glycosides (Hollman et al. 1997 and 1999). The mechanism for quercetin absorption is not known. Hollman et al. (1995 and 1999) speculated that the intestinal sodium-glucose cotransporter is able to transport glucose attached to quercetin through the intestinal cell wall. This idea was supported by the results of Aziz et al. (1998), who found the quercetin-4'-glucoside in human plasma after volunteers had consumed onions. If the sodium-glucose cotransporter plays a role in the absorption of quercetin glucosides, our results would suggest that the absorption of glucose is not affected by its position on the attached quercetin. However, transport of quercetin glucosides by the glucose cotransporter has not been proven yet in vivo. For the interpretation of the bioactivity of quercetin from foods in humans, it is important to know in what form quercetin actually circulates in blood. From the results in this study, it is unclear in what form quercetin circulates in blood because we measured the concentration of quercetin after hydrolysis to the quercetin aglycone. With regard to bioactivity of various forms of quercetin, quercetin conjugated with glycosides, glucuronic acid or sulfates also has antioxidant activity in vitro, although the antioxidant activity is lower than that of the quercetin aglycone (Manach et al. 1998, Williamson et al. 1996).

In addition to bioavailability data, our study also provided information on the metabolism of quercetin into isorhamnetin (3'-methoxyquercetin). Of the ingested quercetin glucosides, ~50% is absorbed in the small intestine and subsequently metabolized, for example into isorhamnetin, in the liver and in other organs. The 50% of ingested quercetin which is not absorbed in the small intestine is metabolized by the colonic microflora into quercetin aglycone and phenolic acids which might be absorbed from the colon (Hollman and Katan 1998, Hollman et al. 1995, Manach et al. 1998). Only 3% of the ingested quercetin is recovered in urine as aglycone or its conjugates. The quercetin in urine might originate from quercetin absorbed in the small intestine and from quercetin absorbed in the colon. Metabolites of quercetin may also be biologically important, because they have antioxidant activity

in vitro (Manach et al. 1998, Rice Evans et al. 1996) and might exert antioxidant effects in humans. In this study we measured isorhamnetin as a metabolite of quercetin. Isorhamnetin concentration in plasma peaked shortly after the quercetin concentration peak. This suggests that both quercetin glucosides are methylated into isorhamnetin immediately after absorption. Methylation of the catechol group of quercetin produces isorhamnetin, and it is catalyzed by the enzyme catechol-*O*-methyltransferase in the liver (Zhu et al. 1994). In quercetin-4'-glucoside the 4' position is occupied by a glucose, and thus there is no catechol group available for methylation. Deglucosylation of the 4'-glucoside is needed to release the catechol group. Because the time to reach peak concentrations of isorhamnetin after intake of the 3-glucoside was the same as after intake of the 4'-glucoside, this could imply that deglucosylation of the 4'-glucoside is not rate-limiting for isorhamnetin formation. Furthermore, isorhamnetin is not an important final metabolite of quercetin because only 0.6% of the ingested quercetin glucosides was excreted in urine as isorhamnetin.

This study shows that it might be possible to increase or decrease bioavailability of quercetin, and maybe of other components in foods and of drugs, by attaching or detaching a glucose molecule. Specifically, treatment of the poorly absorbed quercetin-3-rutinoside from tea with rhamnosidase would transform it into the highly bioavailable quercetin-3-glucoside. Recent research has reinforced the evidence for an inverse association between the intake of flavonoids and death from coronary heart disease (Yochum et al. 1999). If intake of quercetin and related flavonols can indeed be proven to reduce coronary heart disease risk, then production of foods with a more highly bioavailable form of quercetin might become a realistic proposition.

ACKNOWLEDGMENTS

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