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Absorption and Urinary Excretion of Quercetin, Rutin, and αG-Rutin, a Water Soluble Flavonoid, in Rats

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Quercetin, rutin, αG-rutin (a water soluble flavonoid), and a mixture of rutin and αG-rutin were administered to rats by a single gastric intubation, and their absorption and urinary excretion were examined. The plasma and 24 h urinary levels of aglycons (quercetin and tamarixetin/isorhamnetin) were measured by HPLC after deconjugation with β-glucuronidase/sulfatase treatment. αG-rutin was absorbed more rapidly than quercetin or rutin, and the plasma concentrations of quercetin and tamarixetin/isorhamnetin reached the highest peak level 30 min after dosing. Quercetin, rutin, and the mixture of rutin and αG-rutin showed the first peak level 8 h, 8 h, and 30 min after dosing, respectively. The area under the concentration−time curve (AUC) for quercetin in rats administered αG-rutin was approximately 4.5- and 2-fold higher than those in rats administered quercetin and rutin, respectively, and was almost the same as that in rats administered a mixture of rutin and αG-rutin. The highest 24 h urinary excretion was observed in αG-rutin-administered rats. These results suggest that αG-rutin is absorbed more efficiently than either quercetin or rutin and that a high plasma concentration can be maintained by supplying rutin and αG-rutin in combination.

KEYWORDS: Quercetin; rutin; αG-rutin; urinary excretion; absorption; AUC

INTRODUCTION

Flavonoids occur naturally in vegetables, fruits, and tea. Epidemiological studies have shown that the dietary intake of flavonoids is associated with a lower incidence of cardiovascular disease and cancer (*1*). These correlations may implicate in part the antioxidant activity including scavenging radicals, inhibition of lipid peroxidation, and chelating metals. Flavonoids could inhibit low-density lipoprotein oxidation and platelet aggregation (*2*, *3*). Anticarcinogenic effects of flavonoids have been reported to include the modulation of enzymatic activation, detoxification of carcinogens (*4*), and inhibition of the growth of various cancer cells (*5*).

Quercetin, a flavonol, usually occurs in glycosylated forms in many vegetables such as onions. αG-rutin has been used as an antioxidant and a colorant for processed foods and beverages in Japan. It is formed by enzymatic transglycosylation (*6*) and contains mainly 4^G-α-D-glucopyranosylrutin (81.8%) and isoquercitrin (13.4%). The structures of 4^G-α-D-glucopyranosylrutin, rutin, isoquercitrin, and quercetin are shown in **Figure 1**. We have reported that αG-rutin inhibited lipid peroxidation induced by Fe-NTA/H_2O_2 and Fe^{2+}/H_2O_2 in a concentration-dependent manner and that preadministration of αG-rutin by gastric intubation 30 min before γ irradiation reduced the frequency of micronucleated reticulocytes (MNRETs) in mouse peripheral blood (*7*). Also, we have previously demonstrated that absorbed αG-rutin prevents oxidative renal damage in mice treated with Fe-NTA either by scavenging reactive oxygen species or by chelating ferric ions (*8*). αG-rutin has been shown to act as an antioxidant in rodents against free radical-caused oxidative damage of DNA and proteins (*9*).

The bioavailability of flavonoids needs to be determined to clarify whether the absorbed flavonoids function in vivo. Manach et al. demonstrated that dietary rutin was recovered in a substantial concentration in rat plasma as two conjugated metabolites and was absorbed more slowly than quercetin (*10*). Rutin can be hydrolyzed by the intestinal microflora with α-rhamnosidase and β-glucosidase to isoquercitrin (quercetin 3-glucoside) and quercetin (*11*, *12*). Then quercetin is absorbed, and the absorbed quercetin is excreted into the bile and urine as glucuronide and sulfate conjugates within 48 h (*13*). It has been reported that quercetin is further degraded as phenolic acids such as 3-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid through B-ring fission by intestinal bacteria (*14*−*17*). On the other hand, Hollman et al. reported that humans absorb appreciable amounts of quercetin and that quercetin glycosides from onion were absorbed more efficiently than the aglycon form in ileostomy patients (*17*, *18*). Day et al. (*19*) showed that lactase phlorizin hydrolase, a β-glucosidase,

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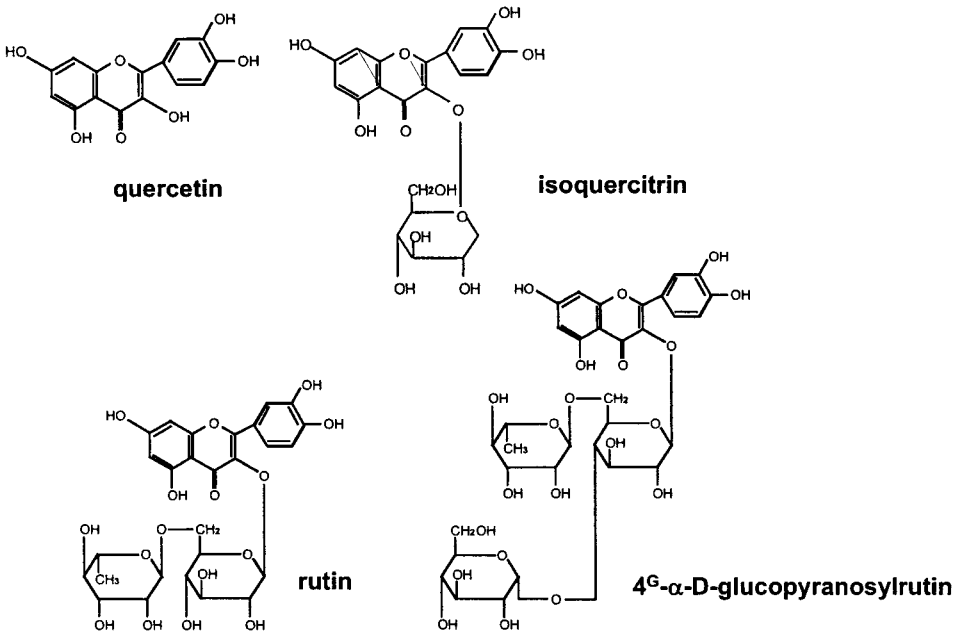

Figure 1. Chemical structures of 4^G-α-D-glucopyranosylrutin, rutin, isoquercitrin, and quercetin.

presents on the brush border membrane. Isoquercitrin is hydrolyzed to quercetin during transport across the intestinal membrane. However, there is little information concerning absorption and metabolism of αG-rutin.

In this study, we compared the absorption of quercetin, rutin, and αG-rutin in rats and examined the effect of their supply in combination on the maintenance of plasma concentration of their metabolites.

MATERIALS AND METHODS

Chemicals. αG-rutin was from Toyo Sugar Refining Co. Ltd., Tokyo, Japan. Quercetin, rutin, and β-glucuronidase/sulfatase were purchased from Sigma (St. Louis, MO). Isorhamnetin and tamarixetin were from Extrasynthese (Genay, France).

Animals and Diets. Male Sprague−Dawley rats (6 weeks old, Charles River Japan Inc., Atsugi, Japan) weighing 145−176 g were housed in an air-conditioned room (22 ± 3 °C) under 12 h dark/12 light cycles, with free access to tap water and AIN-76A diet (Oriental Yeast Co., Tokyo, Japan). Four rats were assigned to each experimental group.

Sample Preparation of Blood and Urine. Rats fasted overnight were administered quercetin, rutin, αG-rutin, or a mixture of rutin and αG-rutin [50 μmol/kg in 0.5% carboxymethyl cellulose sodium (CMC-Na)] by gastric intubation. Blood (1.2 mL) was withdrawn from the cervical vein into heparinized tubes at various times after dosing. Blood collection from one rat was carried out twice (for example, 0.5 and 10 h after dosing). Plasma was obtained by centrifugation (4 °C, 3000 rpm, 10 min). Urine samples were collected for 24 h using metabolic cages, and each excretion volume was measured. These samples were stored at −80 °C until use.

HPLC Analysis. HPLC analysis was performed according to the method described previously with some modification (*20*). Plasma (0.5 mL) and urine were acidified with the same volume of 1 M acetate buffer (pH 4.5) and preincubated for 2 min at 37 °C. Solutions were treated with 5.4×10^2 units/mL β-glucuronidase and 0.2×10^2 units/mL sulfatase for 20 min at 37 °C, and then 0.5 mL of 0.01 M oxalic acid was added. The mixtures were centrifuged for 5 min at 8000 rpm. Supernatants were applied to a Sep-Pak C_{18} cartridge. After the cartridge had been washed with 0.01 M oxalic acid and distilled water, the methanol eluate was obtained. The eluate was evaporated to dryness, and the residue was dissolved in 100 μL of methanol. After centrifugation for 2 min at 0 °C at 15000 rpm, the supernatants were analyzed chromatographically by a JASCO HPLC system (PU-1580, CO-1565 and As-1559, Tokyo, Japan) using a 250 × 4.6 mm i.d. Capcell Pak C_{18}-UG120 column (Shiseido, Tokyo, Japan) and UV detection at 372 nm (multiwavelength detector MD-1510, JASCO, Tokyo, Japan). The mobile phase contained the following: solvent A, 10% methanol with 1% acetic acid; solvent B, 70% methanol with 1% acetic acid. Gradient conditions were as follows: A/B = 100−70/30 for 0−15 min; 70/30−65/35 for 15−20 min; 65/35−50/50 for 20−30 min; 50/50−0, for 30−45 min; 0 for 45−55 min; 0−100 for 55−55.1 min; 100 for 55.1−65 min. The column temperature was maintained at 35 °C, and the flow rate was 1 mL/min. The retention time of tamarixetin was almost the same as that of isorhamnetin under these HPLC conditions. Therefore, quercetin and tamarixetin (as a methylated quercetin) were quantified by measuring the peak areas based on calibration plots of the peak area of standard quercetin and tamarixetin at various concentrations. The recovery with this method using a standard was >95%.

RESULTS

Figure 2 shows representative HPLC profiles of standard quercetin and tamarixetin (A), extract of plasma from a control rat (B), and extracts of plasma (C) and 24 h urine (D) from rats administered αG-rutin (a water soluble flavonoid) after hydrolysis of conjugates with β-glucuronidase/sulfatase. Peaks a and b were quercetin and tamarixetin, respectively. Their identity was confirmed by LC-MS analysis.

The concentrations of quercetin in rat plasma with time after administration of quercetin, rutin, αG-rutin, and a mixture of rutin and αG-rutin in 0.5% CMC-Na by gastric intubation (50 μmol/kg) are shown in **Figure 3A**. All plasma samples were treated with β-glucuronidase/sulfatase. The concentration of quercetin in rat plasma increased to the first and second peak levels 30 min (4.35 ± 0.98 nmol/mL) and 8 h (2.41 ± 0.84 nmol/mL) after dosing with αG-rutin. Quercetin and rutin were absorbed slowly and reached the highest plasma levels of 0.85 ± 0.14 and 1.30 ± 0.33 nmol/mL at 8 h after dosing, respectively. The mixture of rutin and αG-rutin showed three peaks of 0.87 ± 0.14, 2.07 ± 0.78, and 2.96 ± 1.80 nmol/mL at 30 min, 8 h, and 12 h after dosing, respectively. The concentration of quercetin in rat plasma was lower in rats administered quercetin or rutin than in those administered

Table 1. Urinary Excretion and Total Area under the Plasma Concentration–Time Curve of Quercetin and Methylated Quercetin in Rat Administered Quercetin and Its Glycosides

supplement	metabolite	urinary excretion (nmol/24 h urine)	excretion/ingestion (%)	AUC 0 → 24 h (nmol/h)
quercetin	quercetin	32.4 ± 14.1	0.38 ± 0.16	4.13
	methylated quercetin	50.7 ± 20.2	0.6 ± 0.23	1.91
rutin	quercetin	59.1 ± 10.3	0.75 ± 0.12	9.97
	methylated quercetin	173.4 ± 40.2	2.2 ± 0.50	9.75
αG-rutin	quercetin	95.3 ± 41.3	1.16 ± 0.52	20.25
	methylated quercetin	248.3 ± 100.8	3.03 ± 1.28	73.3
αG-rutin and rutin	quercetin	92.8 ± 28.8	1.2 ± 0.40	25.44
	methylated quercetin	232.2 ± 69.2	2.99 ± 0.97	71.62

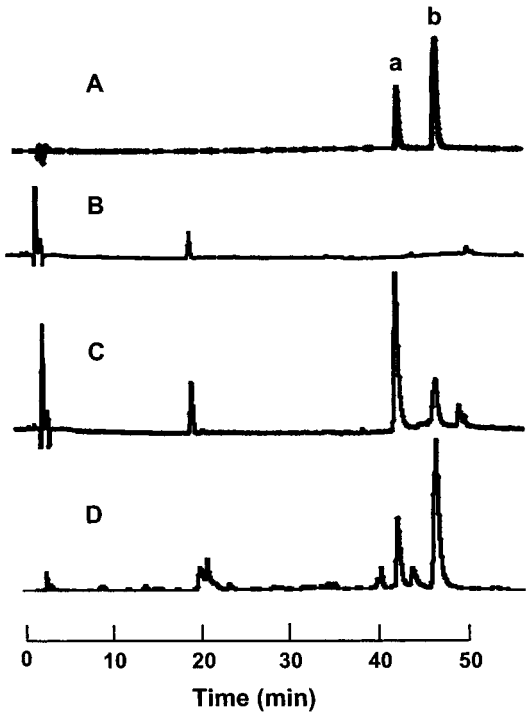

Figure 2. Representative HPLC profiles of standard quercetin and tamarixetin (A), extract of plasma from a control rat (B), and extracts of plasma (C) and 24 h urine (D) from rats administered αG-rutin after hydrolysis of conjugates with β-glucuronidase/sulfatase. UV detection at 372 nm. Peak a, quercetin, 42.7 min; peak b, tamarixetin, 46.9 min

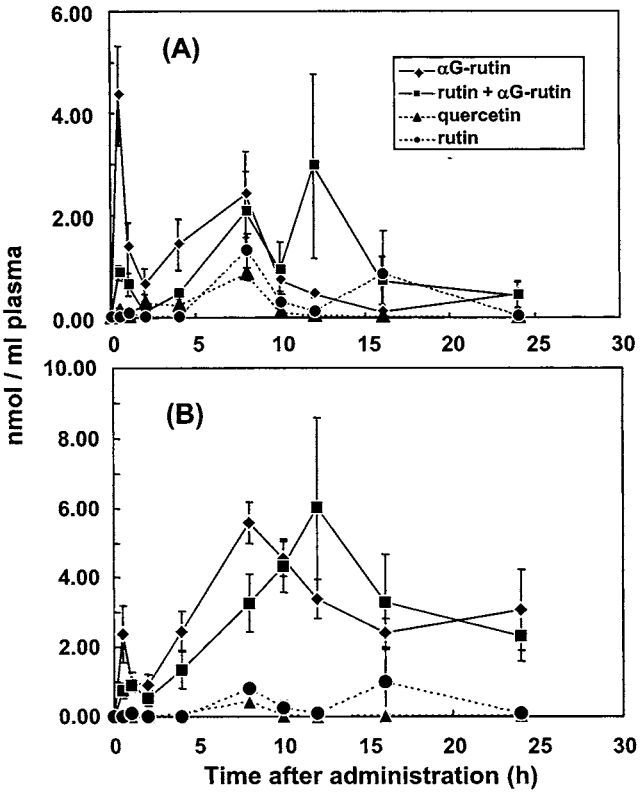

Figure 3. Changes in the concentration of quercetin (A) and methylated quercetin (B) in rat plasma after administration of quercetin, rutin, αG-rutin, and a mixture of rutin and αG-rutin. These flavonoids were suspended in 0.5% CMC-Na and given to rats by gastric intubation (50 μmol/kg). Obtained plasma samples were treated with β-glucuronidase/sulfatase. Methylated quercetin was determined using tamarixetin as a standard. Results are means ± SE ($n = 4$).

αG-rutin or a mixture of rutin and αG-rutin at all time points. The plasma level of methylated quercetin (as tamarixetin) showed a change similar to that of quercetin in all four groups (**Figure 3B**). The levels of αG-rutin at 30 min and 8 h after dosing with were 2.38 ± 0.82 and 5.58 ± 0.58 nmol/mL, respectively.

As shown in **Table 1**, the mean 24 h urinary excretions of quercetin, rutin, αG-rutin, and a mixture of rutin and αG-rutin (means ± SE, $n = 4$) were 32.4 ± 14.1, 59.1 ± 10.3, 95.3 ± 41.3, and 92.8 ± 28.8 nmol as quercetin, respectively, and 50.7 ± 20.2, 173.4 ± 40.2, 248.3 ± 100.8, and 232.2 ± 69.2 nmol as tamarixetin, respectively. The area under the concentration–time curve (AUC) for quercetin in rats administered αG-rutin was approximately 4.5- and 2-fold higher than those in rats administered quercetin and rutin, respectively, and was almost the same as that in the rats administered a mixture of rutin and αG-rutin. The ratio of excretion to ingestion in each group demonstrated that αG-rutin was absorbed more efficiently than either quercetin or rutin. The supply of rutin and αG-rutin in combination resulted in the maintenance of a high plasma concentration of quercetin metabolites.

DISCUSSION

Dietary intake of polyphenols including flavonoids, their bioavailability, and the factors controlling their bioavailability have been reviewed (*21*). There have been many studies reporting that flavonoids in a free form or a glycosylated form are absorbed from the intestinal tract and are metabolized to glucuronide or sulfate conjugates. These metabolites circulate in the blood and are excreted into bile and urine. Quercetin has been reported to be completely converted to conjugates and methylated conjugates in rat or human plasma after administration (*22*–*24*). Manach et al. further demonstrated that conjugated metabolites accumulate in the plasma after ingestion of quercetin glucosides in humans (*25*). Recently, Moon et al. also found that quercetin conjugates accumulate in human plasma after periodic ingestion of quercetin glucoside-rich onions (*26*). Therefore, we measured the plasma level of quercetin aglycon

after deconjugation with β-glucuronidase/sulfatase to compare absorption profiles of quercetin, rutin, αG-rutin, and a mixture of rutin and αG-rutin, a powder of which was suspended in 0.5% CMC-Na. The solubilities of quercetin, rutin, and αG-rutin in 0.5% CMC-Na were 2.4 μg/mL, 51 μg/mL, and >1 g/mL, respectively. αG-rutin is very water soluble. The highest plasma level of quercetin was observed 8 h after administration of quercetin and rutin. Piskula and Terao (*27*) reported that a rapid absorption was observed when propylene glycol was used as vehicles. The highest plasma level of quercetin was observed 30 min after administration. We also showed that luteolin dissolved in propylene glycol was absorbed rapidly (*20*). These results indicate that the extent of quercetin absorption depends on the solubility in the vehicle used for the administration. Quercetin and rutin are insoluble in water. Therefore, it takes more time for quercetin and rutin suspended in 0.5% CMC-Na to be absorbed from the digestive tract. As αG-rutin is water soluble, it was rapidly absorbed.

On the other hand, as shown in **Figure 3**, rutin was absorbed into the circulation more slowly than quercetin. In humans, Hollman et al. (*28*) have reported that peak levels were reached 9 h after ingestion of rutin. Conjugated quercetin metabolites were found in plasma from rats fed a rutin diet (*10*). Griffiths and Barrow have reported that no aglycons were detected in the feces of germ-free rats (*29*). Intestinal microflora with α-rhamnosidase and β-glucosidase hydrolyzed flavonoid glycosides (*11*, *12*). These results indicated that enzymatic conversion of rutin to quercetin by intestinal bacteria is required for intestinal absorption of rutin. The concentration of quercetin in rat plasma increased to the first and second peak levels 30 min and 8 h after dosing with αG-rutin. αG-rutin consists of 4^G-α-D-glucopyranosylrutin and isoquercitrin. 4^G-α-D-Glucopyranosylrutin dissolved in propylene glycol showed a markedly delayed absorption in F344 rats, and rutin and quercetin were detected in the intestinal tract (data not shown). Murota et al. have reported that quercetin aglycon was taken up into Caco-2 cells and metabolized to its conjugated forms more efficiently than its glucosides (*30*). In contrast, the glucosylated forms of quercetin, isoquercitrin, and quercetin 4′-glucoside were more efficiently absorbed than quercetin and showed high bioavailability (*18*, *31*). Lactase phlorizin hydrolase, a β-glucosidase, which presents on the brush border membrane, hydrolyzes isoquercitrin to quercetin during transport across the intestinal membrane (*19*). Whether the sodium-dependent glucose transport is involved or not in the mechanism for their rapid absorption is unclear (*32*, *33*). Therefore, the first peak of quercetin in rat plasma may have derived from isoquercitrin, and 4^G-α-D-glucopyranosylrutin may have been orderly hydrolyzed by intestinal bacteria to rutin and quercetin. The plasma concentration of quercetin and methylated quercetin increased 16 h after administration of rutin again. This seems to be due to enterohepatic circulation. When the metabolites of quercetin are excreted in the bile, they are secreted into the duodenum and deconjugation occurs by microflora (*34*). The deconjugated quercetin and methylated quercetin may be reabsorbed again.

In this study, quercetin, rutin, and αG-rutin were orally administered to rats at the same molar dose as quercetin. However, the AUC for quercetin in rats administered αG-rutin was approximately 4.5- and 2-fold higher than those in rats administered quercetin and rutin, respectively; the mean 24 h urinary excretion was in the same order. These results indicate that αG-rutin is absorbed more efficiently than either quercetin or rutin due to its water solubility. The absorption profile of methylated quercetin in each group was similar to that of quercetin, whereas the AUC for methylated quercetin in rats administered αG-rutin and a mixture of rutin and αG-rutin was higher than those in rats administered quercetin or rutin. Similar results were observed in urinary excretion. These results suggests that methylated quercetin is excreted to the bile more efficiently than quercetin and that subsequent biliary recirculation may occur. The combined administration of rutin and αG-rutin showed a triphasic absorption profile and could maintain to some extent the plasma level of quercetin and methylated quercetin in conjugated form.

ABBREVIATIONS USED

AUC, area under the concentration−time curve; CMC-Na, carboxymethyl cellulose sodium; Fe-NTA, ferric nitrilotriacetate; MNRETs, micronucleated reticulocytes.

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