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Brief communication

Comparison of bioavailability of quercetin and its structural analogs in mice

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ABSTRACT

Flavonoids are thought to provide beneficial effects on health. However, there are still uncertainties regarding their bioavailability. In this study, we investigated the bioavailability of 6 flavonoids, galangin, kaempferol, quercetin, myricetin, fisetin, and luteolin, by oral administration to mice. Analysis of plasma concentrations of free flavonoids after deconjugation by LC-MS/MS revealed that all flavonoids were rapidly absorbed after administration. Among 6 flavonoids, kaempferol and fisetin showed high absorbed amounts in blood plasma. With the LogP value of the two flavonoids as the maximum value, the amount absorbed decreased for both lower and higher LogP values. The results of the tissue distribution of galangin, kaempferol, and quercetin suggested that the order of fastest movement from the stomach to the small intestine was kaempferol > quercetin > galangin. In addition, the amount of kaempferol and quercetin distributed in the liver was greater than that of galangin. These results suggest that the bioavailability of flavonoids varies with the slight structural differences, possibly due to differences in their rapid accessibility to the small intestine that is the primary site of absorption and metabolism within the body.

1. Introduction

Flavonoids are natural polyphenolic compounds widely found in plants [1]. The structure of flavonoids is represented by the C6–C3–C6 model. Flavonoids are thought to have beneficial effects on health such as antioxidant and anti-inflammatory properties. Quercetin, one of the major flavonoid aglycones, has been extensively studied by many researchers for its activities, and is particularly well-known for its antioxidant properties directly or via signal transduction. In addition to the activities, quercetin has also been well studied for its bioavailability. Quercetin is mainly metabolized by some drug-metabolizing enzymes such as uridine 5′-diphosphate-glucuronosyltransferase, sulfotransferase, and/or catechol *O*-methyltransferase (COMT) to form glucuronides and sulfates with or without methylation [2–4]. Quercetin aglycone was hardly detected in the human plasma [5,6].

Regarding other flavonoids, galangin, kaempferol and myricetin, which differ from quercetin in the number of OH groups in the B-ring, have also been reported to have antioxidant activities [7]. In addition, fisetin and luteolin, which have the same number of OH groups on the B-ring as quercetin, but differ in that on the A or C rings, also exhibit antioxidant activities [8,9]. There are differences in the degree of effectiveness of these flavonoids even at the same concentration. On the other hand, research on the bioavailability of flavonoids is less extensive than that of quercetin. The absorption of flavonoids into the body is considered one of the prerequisites for the expression of physiological activities. However, there are still uncertainties regarding their bioavailability. In this study, we investigated the bioavailability of 5 flavonols and 1 flavone, galangin, kaempferol, quercetin, myricetin, fisetin, and luteolin, by oral administration to mice.

2. Materials and methods

2.1. Chemicals

Galangin, kaempferol, quercetin, myricetin, fisetin, luteolin, and isorhamnetin were obtained from Tokyo Chemical Industry (Tokyo,

Abbreviations: G, galangin; K, kaempferol; Q, quercetin; M, myricetin; F, fisetin; L, luteolin.

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Japan). Diosmetin was purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). 3′-Methoxy-3,7,4′-trihydroxyflavone (methylated fisetin) was obtained from Biosynth (Berkshire, UK). Glucuronidase/sulfatase derived from *Helix pomatia* (Sulfatase type H-1) was purchased from Sigma Chemical Company (St. Louis, MO, USA). All other chemicals were of analytical grade.

2.2. Animals and study design

The study protocol was approved by the Institutional Animal Care and Use Committee of Okayama University (permission number OKU-2022169, OKU-2023664). ICR mice (male, 7-9 weeks old) housed by a previously described method were used [10]. After overnight fasting, except for free access to tap water, each flavonoid solubilized with propylene glycol (1 mg/mL) was administered into the intragastric administration as 5 mg flavonoid aglycone/kg body weight (e.g. a dose of 150 μL per 30 g of body weight). All flavonoids were completely dissolved in propylene glycol. For blood plasma collection, peripheral blood was collected from the tail vein using heparinized capillaries before and at 0.5, 1, 3, and 6 h after administration. For tissue collection, mice were euthanized at each time point and then tissues were collected. The samples were stored at −20 °C until use.

2.3. Analysis of quercetin and its metabolites in the biological sample

To determine the apparent total levels of flavonoids before and after administration of the sample, the obtained blood plasma was analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS, Xevo TQD, Waters) with deconjugation treatment using glucuronidase/sulfatase (Sulfatase type H-1). The obtained tissues were homogenized and analyzed with or without deconjugation treatment. After the treatment, each flavonoid was extracted with ethyl acetate as previously described [11,12]. HPLC separation was done by a gradient system using solvent A (0.1% formic acid) and solvent B (acetonitrile) using a ACQUITY UPLC BEH C18 column (1.7 μm, Waters) at the flow rate of 0.4 mL/min. The gradient program was 0 min (A 95%), 0.5 min (A 95%), 5 min (A 5%), 5.5 min (A 5%), 5.6 min (A 95%), and 6.5 min (A 95%). The detection limit of all flavonoids was 20 fmol/2 μL injection (10 nM). The peak area of each flavonoid was corrected by the area of the internal standard, chalcone. In spike recovery experiments, the extraction efficiency of flavonoids using ethyl acetate from blood plasma were nearly equivalent in the range of 0.5 to 50 μM (each $n \geq 3$, galangin (80-85%), kaempferol (79-85%), quercetin (81-85%), myricetin (79-85%), fisetin (81-82%), luteolin (80-83%)). The accuracy of all flavonoids was less than 10% deviation at all tested concentrations. In addition, 50 μM Q3GA and Q3S added to the blood plasma were below the detection

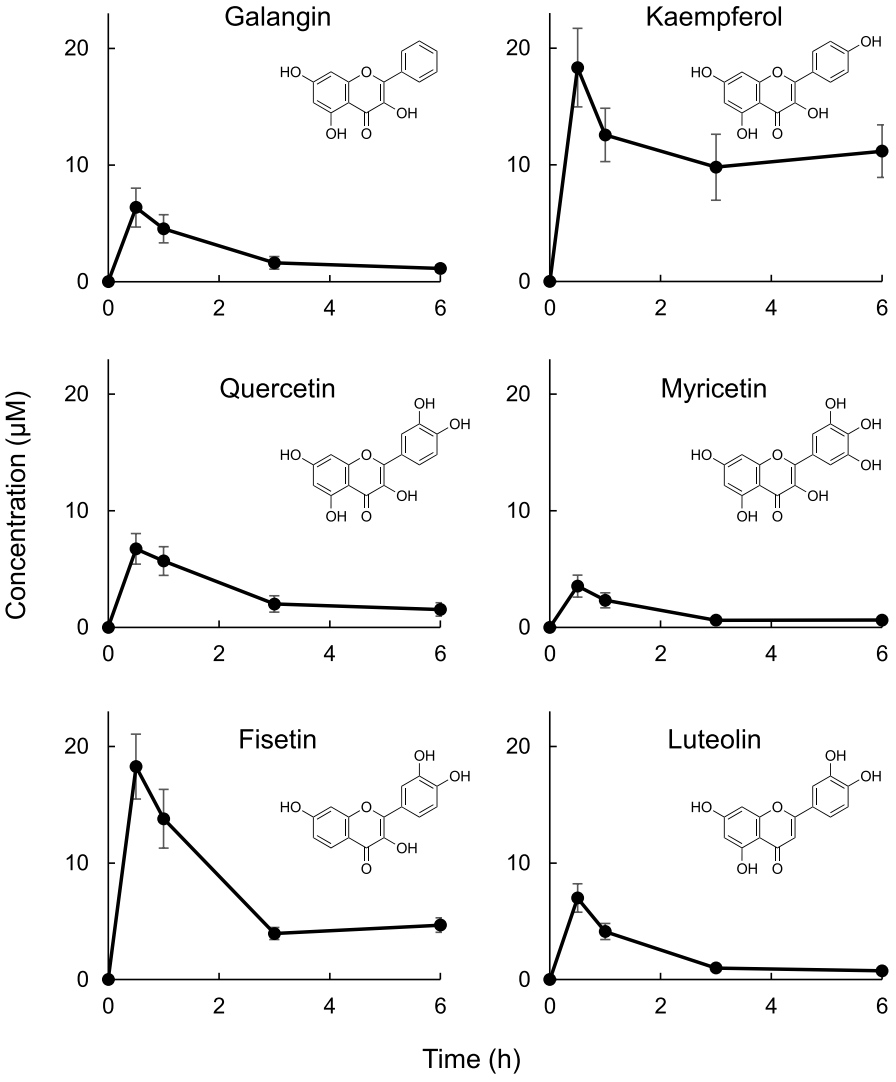

Fig. 1. Time-dependent changes of the flavonoid levels in the plasma. Peripheral venous blood was collected at the desired time points before and at 0.5, 1, 3, and 6 h after administration. The collected samples were treated with deconjugation enzymes before analysis.

limit after sulfatase treatment.

2.4. Statistical analyses

All values are presented as means ± standard error (S.E.) ($n > 3$). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Tukey. The data were considered significant at $P < 0.05$.

3. Results

3.1. Total plasma concentration of flavonoids in mice after oral administration

We first quantified the total plasma levels of the flavonoids as free forms using LC-MS/MS. After deconjugation treatment, flavonoid aglycones were detected in the blood plasma of the mice after the administration of flavonoids (Fig. 1). The maximum concentration (C_{max}) of all 6 flavonoids in the plasma was achieved 0.5 h after administration. Among them, kaempferol and fisetin were well absorbed, and kaempferol maintained relatively high blood concentrations even 6 h after administration. Interestingly, a correlation was observed between the area under the curve (AUC) and LogP values from ChemDraw 22.2.0 (Fig. 2). With the LogP value of the two flavonoids as the maximum values, the amount absorbed decreased for both lower and higher LogP values. These results implied that the absorption of flavonoids in the small intestine was influenced by their hydrophobicity.

3.2. A comparison of the tissue distribution of galangin and kaempferol

Next, we focused on galangin, kaempferol, and quercetin, which have different numbers of OH groups in the B-ring, and confirmed their distribution in the stomach, small intestine, large intestine, and liver. Comparing the three compounds, galangin and quercetin tended to remain in the stomach longer than kaempferol, while kaempferol reached the small intestine in greater amounts than galangin and quercetin at 0.5 h after administration (Fig. 3). No difference was observed in the amount of either compound in the large intestine. In addition, the amount of kaempferol and quercetin distributed in the liver was greater than that of galangin. Noteworthy, most of the galangin and kaempferol, but not quercetin, were detected as aglycones in the small intestine and liver (Fig. 4). It is suggested that quercetin is metabolized more readily and undergoes enterohepatic circulation compared to the other two compounds, as detected by the higher amounts of its methylated form (Fig. 2).

4. Discussion

In the present study, we demonstrated the bioavailability of flavonoids by oral administration to mice. Although there are the reports showing the bioavailability of flavonoids, information regarding which flavonoids are readily absorbed is very limited. Understanding the

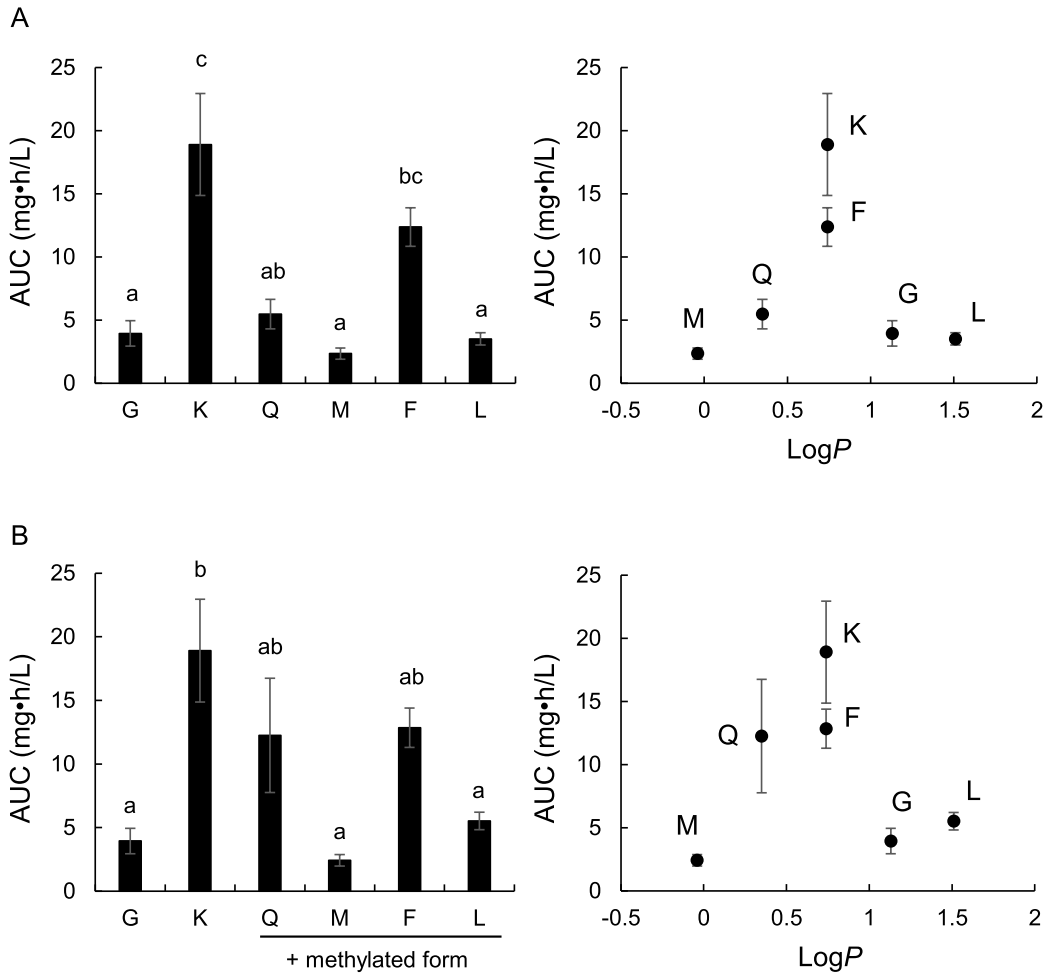

Fig. 2. The AUC values of flavonoids in blood plasma and the correlation between AUC value and LogP value of flavonoids. (A) The AUC values of flavonoid aglycones (B) the AUC values including their methylated forms. G, galangin; K, kaempferol; Q, quercetin; M, myricetin; F, fisetin; L, luteolin. Values are means ± S.E. Different letters above the bars indicate significant differences among the treatments ($p < 0.05$).

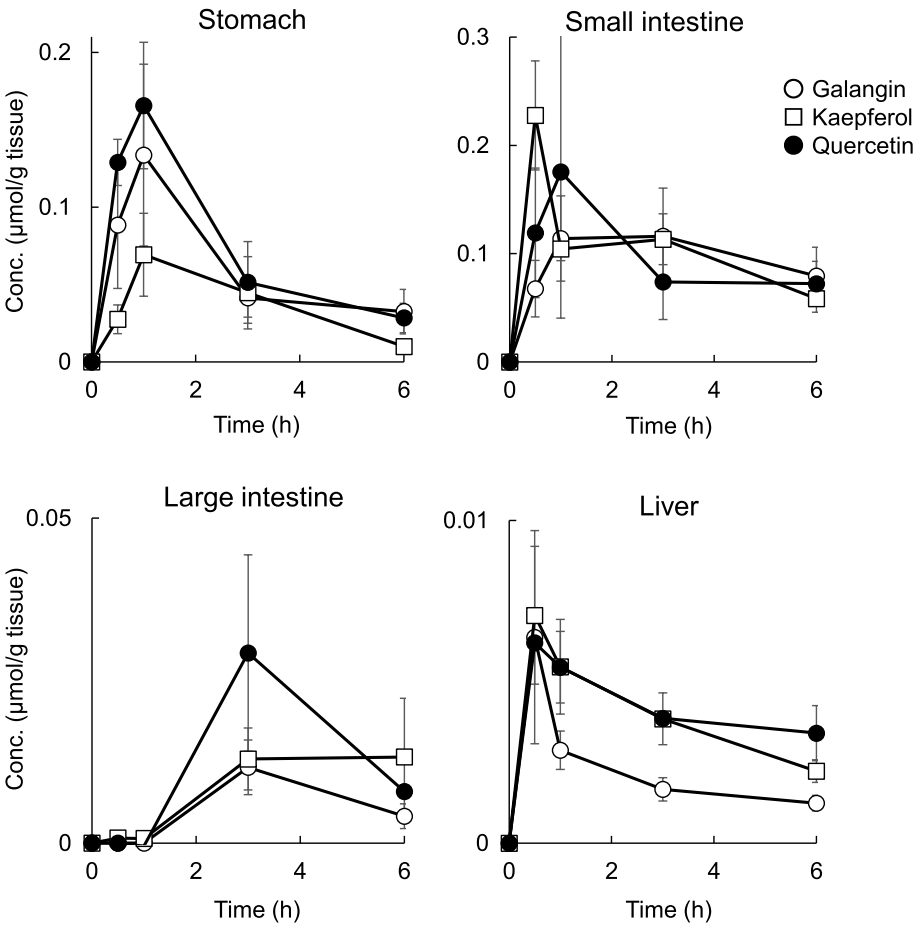

Fig. 3. Time-dependent changes of the flavonoid levels in the stomach, small intestine, large intestine, and liver. Tissues were collected at the desired time points before and at 0.5, 1, 3, and 6 h after administration. The collected samples were treated with or without deconjugation enzymes before analysis.

bioavailability of flavonoids is important for comprehending their effects in the body. A previous study indicated that the bioavailability of quercetin di-glucoside was lower than that of a mixture of its mono-glucoside and α-oligoglucosides, which is more hydrophobic than quercetin di-glucoside [11]. However, there are no reports on the relationship between the bioavailability of flavonoids and their hydrophobicity. This report, to the best of our knowledge, is the first report to clarify the differences in the absorption levels of six types of flavonoids, and is the first to demonstrate the correlation between the hydrophobicity of flavonoids and their bioavailability (Figs. 1 and 2).

The bioavailability of each flavonoid, particularly that of quercetin, by oral administration has been well reported. In our previous study, quercetin in blood plasma was detected micromolar range at 0.5 h after oral administration to mice [12]. Another experiment using Wistar/ST rats, quercetin was also detected almost same levels after administration into the duodenum [13]. Regarding other flavonoids, galangin [14], myricetin [15], fisetin [16], and luteolin [17,18] have also been reported to be rapidly absorbed into the blood circulatory system after oral administration, followed by gradual decreased in their plasma concentration. On the other hand, kaempferol has been reported to maintain relatively high concentrations for an extended period post-administration compared to quercetin [19]. The data obtained in this study were largely consistent with previous reports. The previous report indicated that solubility of flavonoid can change when the flavonoids dissolved in propylene glycol is combined with water [20]. In this study, flavonoids except for galangin were dissolved in propylene glycol with combination of equal volume of water. The low absorbed amount of galangin may be attributed to its reduced solubility within the digestive tract.

The methylated forms of fisetin, luteolin and quercetin, which possess a catechol group in the B-ring, were generated, possibly through the action of COMT. For fisetin and luteolin, the total amount of aglycones and their methylated forms showed little change, in contrast to that of quercetin (Fig. 2). Flavonoids are mainly metabolized by uridine 5′-diphosphate-glucuronosyltransferase. It has been reported using rodent microsomes that luteolin tends to form glucuronide conjugates at the 3′- and 4′-positions of the hydroxyl group compared to quercetin [21]. The reason why the concentration of methylated luteolin in plasma was not high may be due to the blocking of the catechol group by glucuronic acid. As the total concentration of fisetin in plasma showed relatively high values after deconjugation enzyme treatment, the metabolism of fisetin to its methylated form may have been suppressed similarly to that of luteolin. In addition, triphenols such as pyrogallol and gallic acid are also the substrates for mammalian COMT [22]. Since myricetin acts as an inhibitor of COMT [23], it is presumed that methylated myricetin was scarcely detected in this study.

Regarding tissue distribution, a previous study indicated the bioavailability of quercetin 4′-glucoside using its radiolabeled form [24]. However, there are no reports on the distribution of other flavonoids in the digestive tract. This study suggested that, based on the amounts detected in the small intestine, the order of fastest movement from the stomach to the small intestine was kaempferol > quercetin > galangin (Fig. 3). It has been reported that galangin can inhibit ATP-dependent K^+ ($K_{ir}6.1$) channels activity, which play a central role in the regulation of resting membrane potential, membrane excitability and, consequently, of gastric motility [25]. As a result of this inhibitory effect, galangin may have reached the small intestine later than the other two compounds. In addition, kaempferol is

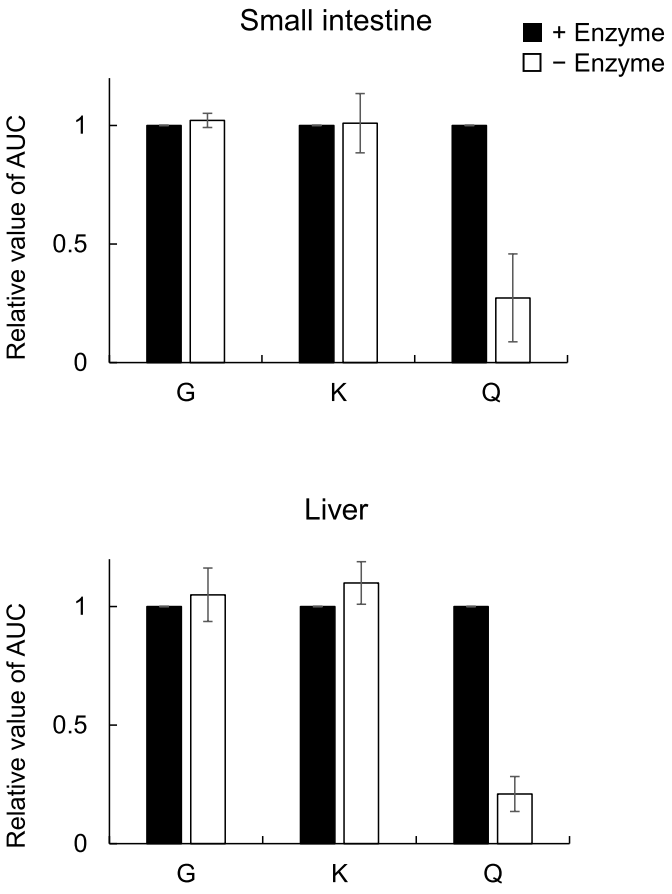

Fig. 4. The AUC values of flavonoids. Small intestine and liver were collected at the desired time points before and at 0.5, 1, 3, and 6 h after administration. The collected samples were treated with or without deconjugation enzyme before analysis. Filled bars denote the AUC values of flavonoid aglycones after deconjugation enzyme treatment, and open bars denote the values without deconjugation enzyme treatment. G, galangin; K, kaempferol; Q, quercetin. Values are means ± S.E.

more readily absorbed in the body compared to galangin and quercetin (Fig. 3). Kaempferol has been reported to inhibit or downregulate the activity, protein expression, and mRNA levels of multidrug resistance-associated protein 2 (MRP2), a member of the ABC transporter family [26]. Inhibition of MRP2 has also been shown to increase plasma concentrations of methylated quercetin [26]. Therefore, the absorbed kaempferol itself may regulate MRP2, thereby suppressing its excretion from the body. In this study, the total amounts of galangin, kaempferol and quercetin detected in four tissues 1 h after administration were only 42%, 34% and 49%, respectively. There are many possible reasons for this, such as absorption into the body, degradation within the digestive tract, interaction with biomolecules, or distribution to other tissues. All three compounds were detected at relatively high levels in the small intestine even 6 h after administration (Fig. 3). The sustained exposure in the small intestine may explain why plasma kaempferol concentrations remained at relatively high levels in plasma even 6 h after administration. On the other hand, galangin and quercetin gradually decreased in the plasma (Fig. 1). Quercetin is thought to be metabolized into its methylated form. This is because only small amounts of quercetin aglycone are detected in the small intestine and liver (Fig. 4), and because the AUC for the sum of quercetin and its methylated form was higher than that for quercetin alone (Fig. 2). Regarding galangin, its absorption may be limited due to regulation by certain metabolism-related proteins expressed in the small intestine, as indicated by its low levels in the liver.

Flavonoids are known to be converted into conjugates such as glucuronides and sulfates, and mainly exist as conjugates in blood plasma. These conjugates generally exhibit weaker biological activity than the aglycones. In this study, galangin and kaempferol were detected as aglycones in the small intestine and liver (Fig. 4). It is speculated that galangin and kaempferol were converted into conjugates in the small intestine and subsequently deconjugated in the liver to become free forms. These two compounds are thought to exert beneficial effects in the liver more effectively than quercetin.

In conclusion, the bioavailability of the six flavonoids differed despite the slight structural differences. The absorption of flavonoids in the small intestine may be influenced by their hydrophobicity. Therefore, it is important to note not only the biological activity of flavonoids but also their bioavailability. On the other hand, the rodent model has several limitations, particularly in that it does not reflect human characteristics. Additionally, flavonoids are normally present in the diet in the form of glycosides such as monoglucosides and diglycosides. A previous study has indicated that quercetin aglycone and its monoglucoside are absorbed in similar amounts in the body [13]. However, flavonoid diglycosides such as rutin and scolymoside reach the large intestine, where they are deglycosylated before being absorbed. Future efforts will be related to clarify the precise bioavailability of flavonoids, including glycosides, in human. In addition, the mechanism for differences of flavonoid bioavailability would need to be clarified.

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CRediT authorship contribution statement

Nozomi Maeda: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Atsushi Hashimoto:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Ryosei Morita:** Formal analysis, Investigation, Methodology. **Shintaro Munemasa:** Validation. **Yoshiyuki Murata:** Validation. **Yoshimasa Nakamura:** Data curation, Validation, Writing – original draft, Writing – review & editing. **Toshiyuki Nakamura:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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