Absorption of Dietary Licorice Isoflavan Glabridin to Blood Circulation in Rats

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Summary Bioavailability of glabridin was elucidated to show that this compound is one of the active components in the traditional medicine licorice. Using a model of intestinal absorption, Caco-2 cell monolayer, incorporation of glabridin was examined. Glabridin was easily incorporated into the cells and released to the basolateral side at a permeability coefficient of 1.70±0.16 cm/s×10⁵. The released glabridin was the aglycone form and not a conjugated form. Then, 10 mg (30 μmol)/kg body weight of standard chemical glabridin and licorice flavonoid oil (LFO) containing 10 mg/kg body weight of glabridin were administered orally to rats, and the blood concentrations of glabridin was determined. Glabridin showed a maximum concentration 1 h after the dose, of 87 nmol/L for standard glabridin and 145 nmol/L for LFO glabridin, and decreased gradually over 24 h after the dose. The level of incorporation into the liver was about 0.43% of the dosed amount 2 h after the dose. These detected glabridins were in the aglycone form and not conjugated forms. The bioavailability was calculated to be AUCₐᵣᵣ of 0.825 and 1.30 μM·h and elimination T₁/₂ of 8.2 and 8.5 h for standard glabridin and LFO, respectively. Adipocytokine levels were determined in the rats. The secreted amount of monocyte chemotactant protein-1 was significantly lower in the glabridin group compared to control vehicle group. Thus, dietary glabridin was at least partly incorporated into the body in an unchanged form, though most dietary flavonoids are converted to non-active conjugate forms during intestinal absorption.

Key Words dietary glabridin, licorice, intestinal absorption, bioavailability, MCP-1

Licorice (Glycyrrhiza glabra L.) is an authoritative medicinal plant and its root has been used for a traditional medicine since the Egyptian Era. The root extract includes flavonoids, glycyrrhizin, and saponin, among other compounds. The active compound in determining uptake efficiency is believed to be a flavonoid, glabridin. Glabridin has been reported to possess a strong antioxidant potency that can inhibit oxidation of low-density lipoprotein (1–5), nephritis (6), Helicobacter pylori activity (7), and melanogenesis and inflammation (8), and also to exhibit a modulating function on several proteins such as cytochrome P450 enzymes (9), peroxisome proliferators-activated receptor-γ (10), and regulatory proteins of serotonin re-uptake (11), blood glucose level (12), and bone disorders (13). This information on the bio-functions of glabridin attracted us to examine the bioavailability of dietary glabridin. The bio-functions of glabridin can not be supported without bioavailability data, because it needs to be shown that glabridin is incorporated into the body by itself without any metabolic conversions. However, the bioavailability of glabridin is still unclear.

Bioavailability of dietary factors is closely associated with susceptibility to conjugation during intestinal absorption. Non-nutrients such as polyphenols and flavonoids undergo conjugation in intestinal cells while nutrients are metabolized in the liver (14, 15). The conjugations mainly occur on functional groups such as hydroxyls with UDP-glucuronosyltransferase and/or phenol sulfotransferase, and consequently the conjugates do not exhibit bioactivities. Thus, highly bioavailable compounds are those which escape conjugation and can then exhibit a considerable range of bioactivities in the body. We have assumed that prenyl groups attached to functional groups occasionally resist the conjugation activity by obstructing the access of conjugation enzymes, and found that one prenyl phenol, artemipillin C, was incorporated in the active free form and exhibited a strong activity (16). An oral dose of artemipillin C clearly suppressed the formation of aberrant crypt foci (17) and induced tumor cells to arrest at G₀/G₁ by stimulating an expression of Cip1/p21 in the cells (18). Glabridin is a prenyl compound (Fig. 1), and may

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also escape conjugation. We have previously found that dietary glabridin appeared in human plasma in its free form (19). The reported obvious bio-functions may correlate with the high bioavailability of glabridin. To improve our understanding of the incorporation of dietary glabridin it is necessary to show whether glabridin is absorbed into the body unchanged in its active form or not by providing pharmacokinetic parameters.

In the present study, we examined the incorporation of glabridin first with a human colon adenocarcinoma cell line Caco-2, which has been used as a model of intestinal absorption. Then, glabridin was administered orally to rats, and glabridin itself but not the metabolized conjugates were determined in the blood.

MATERIALS AND METHODS

Chemicals. Glabridin of the highest grade was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). This was dissolved in dimethylsulfoxide (DMSO) for cell line experiments, or dissolved in medium-chain triglycerides (MCT) with a fatty acid composition of C8 : C10 = 99 : 1 at a concentration of 1% glabridin (w/w) for animal experiments. We also prepared a flavonoid extract from licorice as described previously (12). Briefly, licorice (Glycyrrhiza glabra L.) root was extracted with ethanol. This was used as the licorice-ethanol extract for cell line experiments after dissolving in DMSO at a concentration of 10% glabridin. The extract was filtered through a paper filter, condensed, and mixed with MCT. Removing insoluble materials by filtration, MCT was further added to adjust the concentration of glabridin to 1%. The MCT solution was used as licorice flavonoid oil (LFO) for animal experiments. Other chemicals were commercial products of the highest grade available.

Caco-2 cells. Caco-2 cells were kindly provided by Dr. Junji Terao (The University of Tokushima, School of Medicine, Japan), and cultured in Dulbecco’s modified Eagle’s medium (DMEM) (GIBCO BRL, NY), supplemented with 100 mL/L fetal bovine serum (Sigma Chemical), 10 mL/L non-essential amino acid solution (GIBCO), 25,000 units/L antibiotics penicillin, and 25 mg/L streptomycin (GIBCO). The cells were cultured as a monolayer under a humidified atmosphere of 95% air and 5% CO2 at 37°C. Subcultured until 80–90% confluent, they were harvested by trypsin treatment and then seeded on the apical side of a Transwell with a polycarbonate membrane 6.5 mm in diameter and 0.4 μm in pore size (Corning Costar Co., NY) at a density of 2.5 × 10⁵ cells/well. The cells on the Transwells were used to test the cellular uptake of glabridin. Alternatively, Caco-2 was seeded in 96-well plates at a density of 0.6 × 10⁶ cells/well, and after an overnight culture, was used for measuring cell viability.

Incubation of Caco-2 monolayers with glabridin. The Caco-2 cells at passages 55–61 were used for experiments 21–22 d postseeding in the Transwells according to the methods of Murota et al. (20). The monolayer was prepared from whole inserts by shaking slowly for 5 min. The monolayers were washed with Hank’s balanced salt solution (HBSS) pH 7.4, for 30 min, then incubated at 37°C, and then used in the cellular uptake experiments. Glabridin or LFO in DMSO was diluted with HBSS to 10 μM. The final concentration of solvent was 0.1% for DMSO. The HBSS containing glabridin (200 μL) was added to the apical side of the Caco-2 monolayer at a concentration of 10 μM glabridin (2 nmol/well) and incubated for up to 24 h. Following incubation at 37°C, the apical and basolateral solutions were collected. Cellular extracts were prepared from whole inserts by shaking slowly for 30 min with 100 μL methanol for the apical side and 700 μL for the basolateral side. The recovered solutions were submitted to solid-phase extraction by methanol with Sep-Pak (Vac 1 cc C8, Waters), and analyzed by HPLC (19).

With the transportation data, a permeability (Papp) coefficient of glabridin was calculated according to the method described previously (22) using the following equation:

\[ P_{\text{app}} = \frac{V}{A_{\text{C}} \cdot dC/dT} \]

where, V= the volume of the solution in the basolateral side, A=the membrane surface area, C0=the initial concentration in the apical side, and dC/dT=the change in glabridin concentration in the basolateral solution over time.

Cell viability. To establish the cytotoxicity of glabridin and LFO, Caco-2 cells in 96-well plates were incubated with these reagents, and the cell viability basically was evaluated with a MTS assay using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium according to the previously described method (23). Briefly, 10 μL MTS (2 mg/mL phosphate-buffered saline) was added to the wells and incubated at 37°C for 4 h, and then the difference in absorbance between 492 and 630 nm was measured with a Microplate reader MTP-120 (Corona Electric).

Animals and animal study. Male Crlj:CD(SD) rats (8 wk old) were purchased from Charles River Laboratories Japan Inc. The rats were housed in a temperature- and humidity-controlled room (23 ± 1°C and 60 ± 5% relative humidity) with a 12-h light-and-dark cycle, and were given free access to food (Rodent Lab diet® EQ, Shizuoka Laboratory Animal Center) and water. After 1-wk acclimation, 36 rats were randomly assigned to
three groups so that there were no significant differences in the starting body weight among the groups (318–367 g). One group received a single oral dose of 10 mg/kg body weight (30 μmol/kg) of glabridin in MCT by stomach tube, another group was given LFO in MCT containing 10 mg/kg body weight of glabridin, and the other group was given MCT alone to serve as a control for the following cytokine analysis. The rats were fasted for 8 h before the oral doses, and allowed free to access the diet and water after the doses. At regular intervals, blood was collected from the tail vein, and submitted to an analysis of glabridin. The rats were sacrificed 48 h after the oral doses. Mesenteric fat and kidney leaf fat were removed, and the feaces and urine were collected.

Another three groups of rats were treated similarly with oral doses of 30 μmol/kg and 15 μmol/kg body weight of glabridin in MCT and LFO containing 30 μmol/kg body weight of glabridin in MCT. Two hours later the rats were sacrificed, and the liver, kidney, mesenteric fat, and kidney leaf fat were taken for glabridin analysis.

All animal treatments in this study conformed to the “Guidelines for the Care and Use of Experimental Animals, Rokkodai Campus, Kobe University.”

Determination of glabridin by HPLC. Blood samples were treated with heparin and centrifuged, and the supernatant was extracted with 9-volumes of ethyl acetate 3 times. Liver, kidney, fats, urine, and feces were homogenized in 0.1 M sodium acetate buffer (pH 5.0) with a Teflon homogenizer and then extracted with ethyl acetate. These extracts were submitted to solid-phase extraction by methanol with Sep-Pak, and analyzed on a HPLC (Model LC-10AD VP, Shimadzu, Japan) equipped with an electrochemical detector (Coullochem III; analysis cell, Model 5010; ESA Inc., USA). The HPLC conditions were basically similar to those in our previous report: column, YMC J’Sphere ODS-H80 JH-3B; analysis cell, Model 5010; ESA Inc., USA). The detection limit of glabridin was 1.0 nmol/well glabridin.

RESULTS

Incorporation of glabridin in Caco-2 cells
Caco-2 monolayers have been frequently used as a model system of intestinal absorption, and were employed here to understand whether glabridin was able to be incorporated with or without metabolic conversion. Before the transportation experiments, the cytotoxicity of glabridin was examined (Fig. 2). Standard chemical glabridin did not affect cell viability at concentrations up to 25 μM after 24-h incubation. Licorice-ethanol extract at a concentration of 10 μM glabridin slightly decreased the cell viability after 24-h incubation. As a result, the standard chemical and licorice-ethanol extract were added at the concentrations of 10 μM (2.0 nmol/well) glabridin to the apical phase of the Caco-2 monolayer and the distribution of glabridin determined after 12 h (Fig. 3A). In the Caco-2 assay with standard glabridin, 1.80 nmol/well glabridin was recovered, and 47% was in the apical phase, 27% in the cells, and 26% in the basolateral phase. Similarly, 1.64 nmol/well was recovered in the cells treated with licorice-ethanol extract, and 38% was on the apical side, 36% in the cells, and 25% in basolateral phase. Glabridin of both standard chemical and licorice-ethanol extract was incorporated into intestinal cells and released to the basolateral side mostly without metabolic conversion. The time-dependent pass-through rate was determined in Caco-2 cells after the addition of 2 nmol/well of standard glabridin to the apical side (Fig. 3B). With increasing incubation time, apical glabridin decreased and basolateral glabridin increased. On the basis of the detection data, the $F_{app}$ coefficient of glabridin was determined using antibody kits obtained from Amersham Biosciences (Buckinghamshire, UK), Morinaga & Co. Ltd. (Yokohama, Japan), Amersham Biosciences, Morinaga & Co. Ltd., and Otsuka Phamacetical Co. Ltd. (Tokyo, Japan), respectively.

**Statistical analysis.** Data was expressed as the mean±SE. The significance of the difference was determined by Student’s t-test. Differences were considered significant when $p<0.05$.

Example figure caption:

**Fig. 2. Effect of glabridin on viability of Caco-2 cells.** Caco-2 cells were seeded at a density of 0.5×10^5 cells/mL and cultured overnight, and then incubated with the indicated amounts of standard glabridin (open circles) or licorice-ethanol extract (closed circles) in DMSO for 24 h. The cell viability was evaluated by an MTS assay and expressed as % of cells treated without glabridin. Values are means±SE, n=5.
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Glabridin from apical to basolateral sides in Caco-2 cells was calculated to be 1.70 cm/s. In these cells treated with standard and licorice-ethanol extract glabridin, the recovery of glabridin was 90 and 82%, respectively, and was the glabridin itself but not conjugates. These results clearly indicate that glabridin was incorporated into Caco-2 cells and released to the basolateral side mostly without metabolic conversion.

Standard and LFO glabridin were administered intragastrically to rats, and 30 min later blood was collected and analyzed by HPLC (Fig. 4). In rats dosed with both standard glabridin and LFO, a single peak was detected at around 16 min retention time (Fig. 4C and D) and coincided with the peak of authentic glabridin (Fig. 4B). This means that dietary glabridin at least partly appears in the blood circulation without metabolic conversion.

Incorporation of dietary glabridin in rats

The standard glabridin 30 μmol/kg body weight and LFO containing 30 μmol/kg body weight of glabridin were doses to rats intragastrically and blood from tail vein was collected at regular intervals (Fig. 5). The oral dose of 30 μmol/kg of standard glabridin showed a peak concentration of 87 nmol/L glabridin at 1 h after the dose, and decreased gradually thereafter. LFO glabridin was more easily incorporated into the blood and showed a peak of 145 nmol/L at 1 h after the dose and a shoulder peak of 56 nmol/L at 8 h after the dose. Both glabridin forms almost disappeared from the blood by 24 h after the doses.

The incorporation peaks of glabridin were observed at 1 h after the doses. Then, 15 μmol/kg and 30 μmol/kg of the standard glabridin and LFO containing 30 μmol/kg of glabridin were administered to another three groups and the accumulations were determined in liver, kidney, mesenteric fat, and kidney leaf fat 2 h after the doses (Fig. 6). A considerable amount of glabri-
Glabridin was detected in the liver, 23.0±2.3 nmol/liver in the 15 μmol/kg standard glabridin group, 53.6±5.2 nmol/liver in the 30 μmol/kg standard glabridin group, and 52.0±11.2 nmol/liver in the LFO group, representing about 0.37, 0.43 and 0.41% of the administered glabridin, respectively. The dose of 30 μmol/kg showed twice the amount of incorporation into the liver compared to the dose of 15 μmol/kg, but the incorporation rate was similar. Glabridin was also detected in the kidney, 1.14±0.13 nmol/kidney in the 15 μmol/kg group, 2.12±0.20 nmol/kidney in the 30 μmol/kg group, and 2.24±0.29 nmol/kidney in the LFO group, and were about 0.02, 0.02 and 0.02% of the doses, respectively (Fig. 6B). Lower amounts of glabridin occurred in mesenteric and kidney leaf fats (Fig. 6C and D). The mesenteric concentrations of around 1 nmol/rat were similar in the three groups regardless of the doses. In kidney fat, 0.13±0.05 nmol/rat in the 15 μmol/kg group, 0.60±0.16 nmol/rat in the 30 μmol/kg group, and 1.80±0.59 nmol/rat in the LFO group were detected and were around 0.002, 0.005 and 0.014% of the administered amounts, respectively. These results showed that dietary glabridin was partly incorporated into the blood and liver in an unchanged form. After a short time in the circulation glabridin was excreted through the kidney and barely accumulated in adipose tissues.

Changes in cytokine secretions following with the dose of glabridin

In our previous paper (24), we showed that dietary glabridin suppresses body weight gain and fat accumulation in obese C57BL/6J mice. Therefore, in the present study, adiposis related cytokines, insulin, leptin, adiponectin, MCP-1, and TNF-α were determined in the blood collected from the rats in Fig. 5. The cytokine levels were compared to those in an MCT-dosed group as a control (Fig. 7). Insulin secretion increased in all three groups, which is considered to be due to resumption of feeding after 8-h fasting for the oral doses. Adiponectin was almost unchanged in the three groups and TNF-α showed similar changes in all three groups. Leptin

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Fig. 6. Accumulation of dietary glabridin in liver (A), kidney (B), mesenteric fat (C), and kidney leaf fat (D) 2 h after the doses of glabridin or LFO. Values are mean±SE of glabridin concentration in organ and tissues of each rat, n=12.

Fig. 7. Changes in secretions of insulin, adiponectin, leptin, TNF-α, and MCP-1 after oral doses of standard glabridin (open circle), LFO glabridin (closed circle), or vehicle MCT (triangle) as a control. Asterisks show a significant difference from the value of MCT group.
secretion was a little lower in the LFO group than in the MCT control and the standard glabridin groups, but was not significant. MCP-1 secretion in standard glabridin group was significantly lower at 8–24 h after the dose than in the MCT group.

**DISCUSSION**

Licorice flavonoid glabridin has been expected to possess a high bioavailability, because glabridin is a prenyl compound and refractory from undergoing conjugations, although most flavonoids are inactivated by conjugation during intestinal absorption. In the present study, we have shown that dietary glabridin was at least partly incorporated into the body in the aglycone form using Caco-2 monolayer and rat studies.

In the Caco-2 monolayer study, glabridin was easily incorporated into the cells and released to the basolateral side, and furthermore the released glabridin was in the free aglycone form not in conjugated forms (Fig. 3). Recovery of glabridin from the Caco-2 cells was around 90%. This means that most glabridin added to the apical side passed to the basolateral side without conversion. The $P_{app}$ coefficient of glabridin from the apical to basolateral side in Caco-2 cells was $1.70 \text{ cm/s} \times 10^5$. Though the value is lower compared to the $P_{app}$ of $2.7 \text{ cm/s} \times 10^5$ of another prenyl phenol artepillin C (14), it is clear that glabridin gradually passes-through intestinal cells and glabridin itself is incorporated into the blood stream. In addition, glabridin was detected in the blood unchanged in form when orally dosed to rats (Fig. 4). These results show that dietary glabridin also appears by itself in animal blood.

The fate of dietary glabridin was determined in rats dosed with 30 $\mu$mol/kg body weight of standard chemical glabridin and LFO glabridin (Fig. 5). Standard glabridin gave a peak of 87 nmol/L for the maximum concentration in blood 1 h after the dose. LFO glabridin showed a peak concentration of 145 nmol/L at 1 h after the dose accompanied by a shoulder of 56 nmol/L at 8 h after the dose. Both forms of glabridin decreased gradually and almost disappeared 24 h after the doses. At the end of experiments 48 h after the doses, the rats were sacrificed and glabridin accumulation determined. In liver, kidney, mesenteric fat, and kidney leaf fats, glabridin was under the detection limit (data not shown). This means that dietary glabridin is partly incorporated into the blood circulation and easily excreted by 24 h after the doses without accumulation.

Glabridin was also determined in feces and urine collected throughout the experiments until 48 h after the doses. In feces of both groups glabridin was detected at a similar ratio, around 37% of the administered amounts. Urine glabridin was trace in both groups, at less than 2 nmol/rat. This suggests that glabridin did not show entero-hepatic circulation. The pharmacokinetic parameters of dietary glabridin, the maximum concentration in plasma ($C_{max}$), time required to reach the maximum concentration ($T_{max}$), area under the curve (AUC$_{inf}$), total clearance (Cl/F where F denotes bioavailability), and elimination half-life ($T_{1/2}$) were calculated using WINNONLIN software (version 1.1, SCI, Morrisville, NC) from the results in Fig. 5 (Table 1). Standard glabridin gave AUC$_{inf}$ of 0.825 $\mu$M-h, $T_{1/2}$ of 8.2 h, and Cl/F of 37.4 L/h. LFO glabridin had values of 1.30 $\mu$M-h, 8.5 h, and 23.7 L/h, respectively. We also determined the $T_{1/2}$ of plasma glabridin in humans using LFO glabridin, and found it to be about 10 h (25). This parameters that dietary glabridin shows a similar elimination profile in humans and rats. Comparing the parameters between standard and LFO glabridin, AUC$_{inf}$ and $C_{max}$ values were greater in LFO than for standard glabridin, while $T_{max}$ and $T_{1/2}$ values were similar. This indicates that LFO glabridin is more easily incorporated than standard glabridin. Both forms of glabridin were dissolved in the same solvent, MCT, and LFO is a mixture of various licorice flavonoids as mentioned in “Material and Methods.” Probably the coexistent components facilitate the incorporation of glabridin in LFO.

Pharmacokinetic data has been reported for various flavonoids. The most abundant flavonoid in our food is quercetin (26). Hollman et al. (27, 28) determined that the AUC of quercetin was 18.8 $\mu$M-h and its elimination $T_{1/2}$ was 16–17 h when about 200 $\mu$mol of quercetin glucoside was ingested in humans. Conquer et al. (29) showed that the blood concentration of quercetin was less than 1.5 $\mu$M when a 1 g quercetin capsule was supplied daily. These findings indicate that quercetin enters the blood more easily than glabridin. However, the chemical form of endogenous quercetin is mostly conjugates of glucuronide or sulfate (30, 31). The conjugates fail to produce bioactivity because they are the excretion form and cannot enter body cells (14, 32, 33).

Table 1. Pharmacokinetic parameters of glabridin in rats.*

<table>
<thead>
<tr>
<th>30 $\mu$mol/kg body weight of:</th>
<th>AUC$_{inf}$ (nM-h)</th>
<th>$C_{max}$ (nM)</th>
<th>$T_{1/2}$ (h)</th>
<th>$T_{max}$ (h)</th>
<th>Cl/F (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard glabridin</td>
<td>825</td>
<td>87</td>
<td>8.2</td>
<td>1</td>
<td>37.4</td>
</tr>
<tr>
<td>LFO glabridin</td>
<td>1.301</td>
<td>145</td>
<td>8.5</td>
<td>1</td>
<td>23.7</td>
</tr>
</tbody>
</table>

*Mean values of plasma glabridin profiles in each group were analyzed using non-compartmental model.
glabridin circulates in the blood stream mainly as the aglycone form. These strongly indicate that glabridin possesses a higher bioavailability than the other flavonoid such as quercetin.

Using another three groups of rats, the incorporation of glabridin in organs and tissues was measured 2 h after the dose (Fig. 6), since the maximum concentration in blood appeared at 1 h after the dose in Fig. 5. Glabridin was incorporated into the liver, kidney, and kidney leaf fat, and was double in amount in the groups with 30 μmol/kg of standard or LFO glabridin compared to the group of 15 μmol of standard glabridin. Thus, glabridin seems to be incorporated dose-dependently, and the incorporated amount in liver was calculated to be around 0.37–0.43% of the dose. Previously, we showed that dietary glabridin suppressed the gene expression of lipogenesis-related enzymes and stimulated gene expression of β-oxidation enzymes in the liver of C57BL/6j mice (24). Adiposis-related cytokines were measured in the blood pooled from the glabridin-treated rats in Fig. 5 (Fig. 7). Adipocyte growth is considered to correlate with the secretions of insulin, leptin, adiponectin, TNF-α, and other cytokines (35), and described to accompany inflammation and increasing secretion of TNF-α (36). MCP-1 which contributes to macrophage infiltration has been reported to increase in obese diabetic mice (37). In the present study, the oral dose of glabridin did not accompany clear changes of insulin, adiponectin, or TNF-α levels. Leptin secretion showed a tendency to be lowered in the LFO group, and MCP-1 was significant lower in the standard glabridin group. These indicate that dietary glabridin can mitigate inflammation through suppressing MCP-1 secretion. However, the suppressing effect was not observed in the LFO group. LFO includes various licorice flavonoids other than glabridin, such as glabrene and isoliquiritigenin (1, 13). Glabrene has a strong estrogen-like activity (38, 39), and isoliquiritigenin exhibits a reducing effect of prostaglandin E2 and nitric oxide (40, 41). These flavonoids probably offset the effect of glabridin in the present experiments.

The bioactivity of LFO should be examined more thoroughly, but one of the ingredients, glabridin, clearly possessed a high bioavailability in the present study. Prenyl flavanone glabridin escaped conjugation during the intestinal absorption process (Figs. 3 and 4) and existed in the free aglycone form in the blood and liver (Figs. 5 and 6). Free aglycones have been well recognized to exhibit strong bioactivity, but the conjugate forms have low bioactivity. Prenyl flavonoids have been found to possess a higher bioactivity, which is probably attributable to the higher affinity of hydrophobic prenyl groups to biomembranes (42). Glabridin should be one of candidate factors in the diet for preventing degenerative diseases.

REFERENCES


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