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ORIGINAL PAPER

Inhibitory effect of bofutsushosan (fang feng tong sheng san) on glucose transporter 5 function in vitro

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Abstract
Bofutsushosan (BTS; fang feng tong sheng san in Chinese) is a formula in traditional Japanese Kampo medicine and Chinese medicine comprising eighteen crude drugs, and is used to treat obesity and metabolic syndrome. Fructose is contained in refreshing beverages as high-fructose corn syrup, and is associated with obesity. Fructose is absorbed via glucose transporter 5 (GLUT5) in the intestine. Therefore, the inhibition of GLUT5 is considered to be a target of obesity drugs. We evaluated the inhibitory effects of BTS extract and its constituents on fructose uptake using Chinese hamster ovary K1 cells, i.e., cells stably expressing GLUT5. Boiled water extract of BTS significantly suppressed GLUT5 function in a concentration-dependent manner without cytotoxicities. Among 18 components of BTS, the boiled water extracts of the rhizome of *Zingiber officinale*, the root and rhizome of *Saposhnikovia divaricata*, and the root of *Platycodon grandiflorum* exhibited significant inhibitory effects on fructose uptake with IC_{50} values of 314, 119 and 475 μg/ml, respectively. Among the constituents of the rhizome of *Z. officinale* extract, 6-gingerol significantly inhibited GLUT5 with an IC_{50} value of 39 μM, while 6-shogaol exhibited a significant but weak inhibition on GLUT5 at 100 μM. One of the mechanisms of action of BTS may be the inhibition of fructose absorption in the intestine, and one of the active components of BTS is the rhizome of *Z. officinale* and 6-gingerol.

Keywords Glucose transporter 5 · Fructose · Bofutsushosan · *Zingiber officinale* · 6-gingerol

Introduction

Bofutsushosan (BTS; fang feng tong sheng san in Chinese) is a formula in traditional Japanese Kampo medicine and Chinese medicine comprising eighteen crude drugs as shown in Table 1 [1]. In previous reports, BTS has been shown to ameliorate obesity induced by high-fat diet or diabetes in experimental animals, and some clinical trials have exhibited its effectiveness on obesity and metabolic syndrome [2–5]. Among several pathogeneses relating to obesity, diabetes, or metabolic syndrome, excessive fructose consumption has been identified as one of the contributors [6, 7]. Fructose is contained in refreshing beverages as high-fructose corn syrup, and sweetened beverage intake is associated with increased body weight and obesity [8]. In the small intestine, sugars in the diet are actively transported via glucose transporters, including sodium/glucose co transporter 1 (SGLT1) for glucose, glucose transporter 1 (GLUT1) for glucose and galactose, and glucose transporter 5 (GLUT5) for fructose [9]. GLUT5 expression levels and fructose uptake rates are significantly affected by diabetes and obesity [10]. GLUT5 is essential for the absorption of fructose in the intestine, and plays a fundamental role in the generation of fructose-induced hypertension [11]. Therefore, it is considered that the suppression of GLUT5 function is one of the targets of drug discovery to treat metabolic syndrome. We recently found that the natural compounds nobiletin and epicatechin gallate suppressed GLUT5 function in human intestinal epithelial Caco-2 cells [12].

In this study, we evaluated the inhibitory effects of BTS boiled water extract and its constituents on GLUT5. We found that Zingiberis Rhizoma, Saposhnikoviae Radix and Platycodi Radix contributed to the suppressive effect of BTS on GLUT5, and identified 6-gingerol in Zingiberis Rhizoma as one of the active ingredients in BTS.

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Table 1 The origin, distributor name, lot number of the sample, and the ratio yielded of crude drugs used

Latin name of crude drug	Origin	Distributor[a]	Lot #	Ratio yielded (%)[b]
Angelicae Radix	The root of *Angelica acutiloba*	Daiko	0H09M	40
Atractylodis Rhizoma	The rhizome of *Atractylodes japonica*	Daiko	0AJ0510	29
Cnidii Rhizoma	The rhizome of *Cnidium officinale*	Daiko	9I29M	22
Ephedrae Herba	The terrestrial stem of *Ephedra sinica*	Daiko	0I15M	16
Forsythiae Fructus	The fruit of *Forsythia suspensa*	Tsumura	19038951	14
Gardeniae Fructus	The fruit of *Gardenia jasminoides*	Daiko	9I11M	32
Glycyrrhizae Radix	The root and stolon of *Glycyrrhiza uralensis*	Daiko	9L21M	24
Gypsum	Natural hydrous calcium sulfate	Daiko	0I02M	–
Kasseki	Mineral composed of aluminum silicate hydrate and silicon dioxide	Daiko	2F23M	–
Menthae Herba	The terrestrial part of *Mentha arvensis* var. *piperascens*	Daiko	2F23M	34
Natrium Sulfricum	Mineral substance composed of sodium sulfate hydrate	Nacalai	M7P8998	–
Paeoniae Radix	The root of *Paeonia lactiflora*	Daiko	1I26M	38
Platycodi Radix	The root of *Platycodon grandiflorum*	Daiko	3G09M	44
Rhei Rhizoma	The rhizome of *Rheum palmatum*	Daiko	1F23	31
Saposhnikoviae Radix	The root and rhizome of *Saposhnikovia divaricata*	Daiko	2A25	21
Schizonepetae Spica	The spike of *Nepeta tenuifolia*	Tsumura	27042881	12
Scutellariae Radix	The root of *Scutellaria baicalensis*	Daiko	0J08M	42
Zingiberis Rhizoma	The rhizome of *Zingiber officinale*	Daiko	25021331	13

All crude drug samples met the grade standards of the Japanese Pharmacopoeia 17th edition [1]. The voucher specimens are deposited in the Department of Pharmacognosy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan

[a]Daiko is Daiko Shoyaku (Nagoya, Japan). Tsumura is Tsumura & Co. (Tokyo, Japan)

[b]Ratio yielded (%) is the ratio of the weight of boiled water extract to the weight of original crude drug

Materials and methods

Preparation of the extracts of BTS and each herbal component of BTS

All crude drugs used in this study met the grade standards of the Japanese Pharmacopoeia 17th edition (JPXVII) [1]. The daily dose of BTS for humans consists of 1.2 g of Angelicae Radix, 1.2 g of Paeoniae Radix, 1.2 g of Cnidii Rhizoma, 1.2 g of Gardeniae Fructus, 1.2 g of Forsythiae Fructus, 1.2 g of Menthae Herba, 0.3 g of Zingiberis Rhizoma, 1.2 g of Schizonepetae Spica, 1.2 g of Saposhnikoviae Radix, 1.2 g of Ephedrae Herba, 1.5 g of Rhei Rhizoma, 1.5 g of Sodium Sulfate, 2 g of Atractylodis Rhizoma, 2 g of Platycodi Radix, 2 g of Scutellariae Radix, 2 g of Glycyrrhizae Radix, 2 g of Gypsum, and 3 g of Kasseki [13]. The origins of these crude drugs are shown in Table 1. A mixture of the daily dose of BTS or 5 g of each botanical crude drug was boiled with 20 times its weight of water for 30 min and filtered. The decoctions were lyophilized to yield powdered extract. The weight of the BTS extract yield was 8.2 g (extraction ratio yielded was 29%), and the extraction ratios yielded of each botanical crude drug are shown in Table 1. The powdered extracts were stored in desiccated conditions until use.

The BTS extract (50 mg) was suspended with MeOH (1 ml) and sonicated for 30 min. The supernatant (30 µl) was injected to HPLC with the following conditions—system: Shimadzu LC–10A$_{VP}$ (Kyoto, Japan); column: TSK–GEL ODS–80$_{TS}$ (4.6 × 250 mm, Tosoh, Tokyo); mobile phase: 0.05 M AcOH–AcONH$_4$ buffer (pH 3.6)/CH$_3$CN 90:10 (0 min)–45:55 (40 min), linear gradient; flow rate: 1.0 ml/min; column temperature: 40 °C; and detection: 200–400 nm by a photodiode array detector. Some peaks were identified by the retention times and UV spectra of the standard compounds purchased from Wako Pure Chemical Industry (Osaka, Japan) except for wogonoside which was a gift from Tsumura (Tokyo, Japan). The fingerprint chromatogram of BTS extract is shown in Fig. 1. 6-Gingerol was purchased from Matsuura Yakugyo (Nagoya, Japan). 6-Shogaol, platicodin D and 4′-*O*-glucosyl-5-*O*- methylvisamminol were bought from Wako.

Quantification of marker compounds in the extract of Zingiberis Rhizoma

The content of 6-gingerol and 6-shogaol in the boiled water extract of Zingiberis Rhizoma was measured using an HPLC system consisting of a Shimadzu LC-10A$_{VP}$ unit with a SPD-M10A$_{VP}$ with photodiode array detector

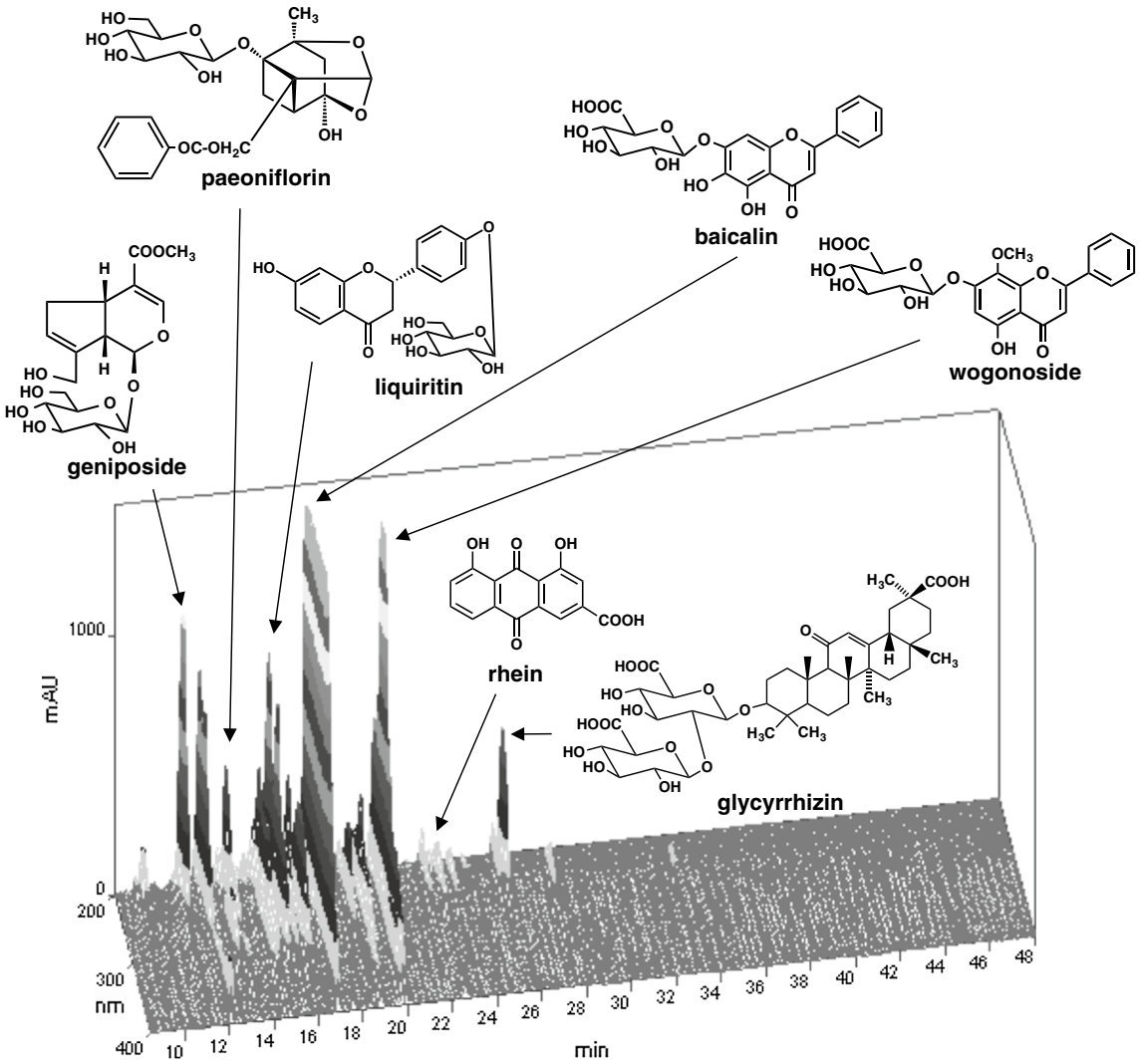

Fig. 1 HPLC fingerprint of BTS. BTS extract (50 mg) was suspended with MeOH (1 ml) and sonicated for 30 min. The supernatant (30 µl) was injected to HPLC with the following conditions—column: TSK-GEL ODS80$_{TS}$ (4.6 × 250 mm); mobile phase: 0.05 M AcOH–AcONH$_4$ buffer (pH 3.6)/CH$_3$CN 90:10 (0 min)–45:55 (40 min), linear gradient; flow rate: 1.0 ml/min; column temperature: 40 °C; detection: 200–400 nm by a photodiode array detector. Some peaks were identified by the retention times and UV spectra of the standard compounds

(Shimadzu, Kyoto, Japan) with the following conditions—column: Inertosil ODS-3 (4.6 × 250 mm, GL Science, Tokyo, Kapan); mobile phase: 65% MeOH; flow rate, 1.0 ml/min; column temperature: 40 °C; and detection: 210 nm. Standard solutions of 6-gingerol and 6-shogaol and the sample solution (10 mg/ml of Zingiberis Rhizoma extract) in MeOH were prepared, and 10 µl of each solution was injected. The retention times of 6-gingerol and 6-shogaol were 11.7 min and 28.0 min, respectively. Linear regressions of the concentration range of 6-gingerol (10.0–100 µg/ml) and 6-shogaol (0.20–2.0 µg/ml) were calibrated by the peak area using the least-squares method ($r^2 > 0.999$).

Evaluation of GLUT5 function

Chinese hamster ovary (CHO) K1 cells stably expressing human GLUT5 (CHO–GLUT5 cells) and their mock cells were established in our previous report [14]. These cells were cultured in Dulbecco's modified Eagle's medium (Nacalai Tesque, Kyoto, Japan) containing 10% FBS, 2 mg/ml G418 (Nacalai) at 37 °C in 5% CO_2 atmosphere. CHO–GLUT5 cells and mock cells were seeded in poly-L-lysine-coated 24-well plates (2×10^5 cells/well) and incubated for 24 h. Cells were preincubated for 10 min at 37 °C with 0.22 ml of Hanks' balanced salt solution (HBSS; 137 mM NaCl, 5.4 mM KCl, 1.3 mM $CaCl_2$, 1.0 mM $MgSO_4$,

0.25 mM Na_2HPO_4, 0.44 mM KH_2PO_4, 4.2 mM $NaHCO_3$, pH 7.2). [^{14}C]fructose (Eckert & Ziegler, Valencia, CA, USA) and the samples were diluted with HBSS to prepare sample solutions; the cells were then further incubated at 37 °C with 0.22 ml of each solution for 5 min. Since there are no standard GLUT5 inhibitors, we could not use a positive control. The surface of the cells was washed three times with 0.5 ml ice-cold phosphate-buffered saline (0.15 M, pH 7.2), and the contents of the cells were extracted with 100 µl of ethanol at room temperature for 10 min. For the uptake study of [^{14}C]fructose, ethanol extracts were transferred into vials containing 4 ml of Clearzol I (Nacalai), and radioactivities were measured using a liquid scintillation counter. To correct uptake values, 150 µl of 1 M NaOH was added to the residue and incubated for 12 h to lyse the cells. After neutralization by adding 150 µl of 1 M HCl, protein concentrations were measured using BCA™ Protein Assay kit (Thermo Scientific, Rockford, IL, USA).

To evaluate the cytotoxicity of the samples, CHO–GLUT5 cells were seeded in 96-well plates (5×10^4 cells/well) and incubated with different concentrations of the samples for 24 h. MTT (0.5 mg/ml; Sigma Aldrich, St. Louis, MO, USA) was added to the wells, and the cells were incubated for 10 min at 37 °C. The cells were lysed with 10% sodium lauryl sulfate, and the lysate optical densities were measured at 570 nm.

Statistical analysis

All statistical analyses were performed using the PASW Statistics version 18 (SPSS, IBM, Armonk, NY, USA). The statistical analysis was conducted using one-way analysis of variance (ANOVA) followed by Bonferroni/Dunnett's multiple *t* test for the differences among multiple groups. *P* values <0.05 were considered statistically significant.

Results and discussion

Fructose uptake into CHO–GLUT5 cells was reduced by the addition of BTS extract in media in a concentration-dependent manner (Fig. 2). BTS extract did not show any cytotoxicities at the concentrations shown when evaluated by MTT methods (data not shown). This result suggests that BTS extract has an inhibitory effect on GLUT5. The effective concentration of BTS extract that exhibited a statistically significant difference was 1 mg/ml (Fig. 2). The one-time dosage of BTS extract (3 times a day) is 2.7 g, and when patients take the extract with a cup of water (200 ml), the concentration of BTS extract solution is 14 mg/ml, which is 14-fold of the effective concentration of BTS extract. Although BTS extract in a cup of water would be diluted by intestinal fluid when taken orally by humans, a concentration

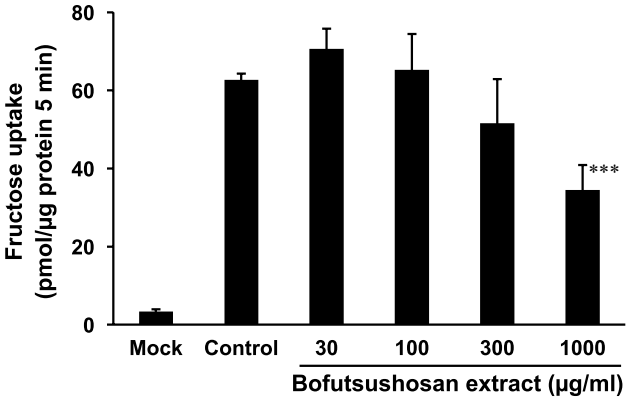

Fig. 2 Inhibitory effects of BTS extract on GLUT5 function. CHO–GLUT5 cells were incubated with buffer containing [^{14}C]fructose (4 µM) with bofutsushosan extract at 37 °C for 5 min. Mock cells and a control CHO–GLUT5 cell group were treated with buffer not containing BTS extract. The uptake of fructose into the cells was measured. Data are expressed as the mean ± SD ($n = 3$). ***$p < 0.001$ versus the control group by ANOVA and Bonferroni–Dunnett's multiple *t* test

of 1 mg/ml could conceivably appear in the human intestine if it is extrapolated from in vitro experiments to a clinical situation. Thus, BTS could exhibit an inhibitory effect on GLUT5 to reduce fructose absorption in humans.

In the next experiment, we tried to find the active components of BTS as crude drug levels. Since Gypsum, Kasseki and Natrium Sulfricum are derived from minerals and contain little organic compounds, we prepared boiled water extracts of 15 crude drugs as the components of BTS. Figure 3 shows the effect of these extracts on fructose uptake into CHO–GLUT5 cells at a concentration of 500 µg/ml. Among the 15 components of BTS, the extracts of Zingiberis Rhizoma, Saposhnikoviae Radix, Platycodi Radix, Menthae Herba and Gardeniae Fructus exhibited a significant ($p < 0.001$) inhibitory effect on fructose uptake, suggesting that these five crude drugs could contribute to the inhibitory effects of BTS extract on fructose uptake. We then confirmed the concentration dependency of the effects of these five crude drug extracts on fructose uptake into CHO–GLUT5 cells. These five crude drug extracts inhibited fructose uptake in a concentration-dependent manner, and the IC_{50} values of the extracts of Zingiberis Rhizoma, Saposhnikoviae Radix and Platycodi Radix were 314, 119 and 475 µg/ml, respectively (Fig. 4). Since the extracts of Saposhnikoviae Radix exhibited the strongest inhibitory effect, we tried to isolate the active ingredients from the extracts of Saposhnikoviae Radix. When the extract of Saposhnikoviae Radix was partitioned into ethyl acetate, water-saturated butanol, and a water layer, the active components transferred into the water layer, and we could not isolate the active ingredients (data not shown). We confirmed that the butanol layer contained 4′-*O*-glucosyl-5-*O*-methylvisamminol, the marker

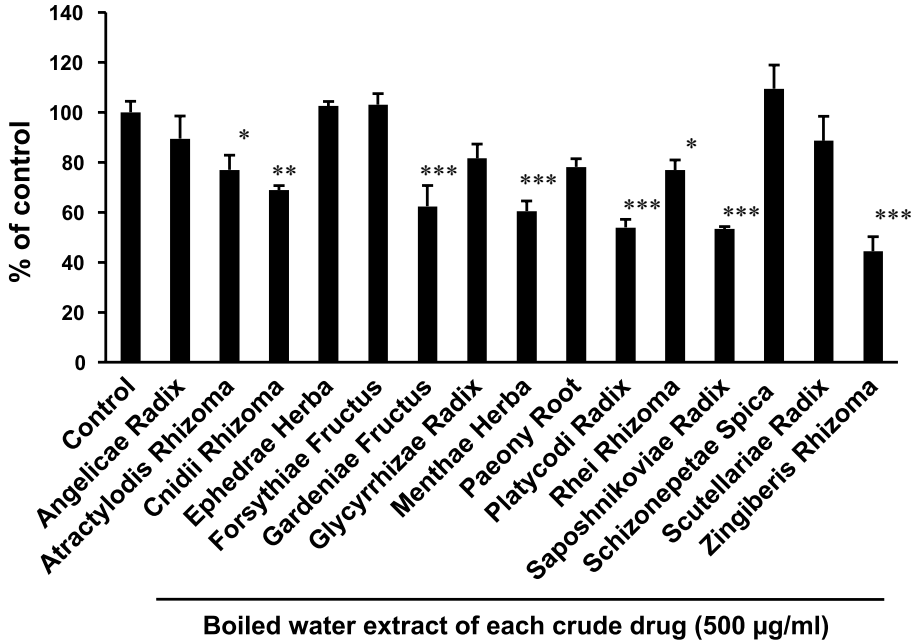

Fig. 3 Inhibitory effects of each extract of the component of BTS extract on GLUT5 function. CHO–GLUT5 cells were incubated with buffer containing [^{14}C]fructose (4 μM) with each extract (500 μg/ml) at 37 °C for 5 min. Mock cells and a control CHO–GLUT5 cell group were treated with buffer not containing the extracts. The uptake of fructose into the cells was measured. Data are expressed as % of control of the mean ± SD ($n = 3$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus the control group by ANOVA and Bonferroni–Dunnett's multiple *t* test

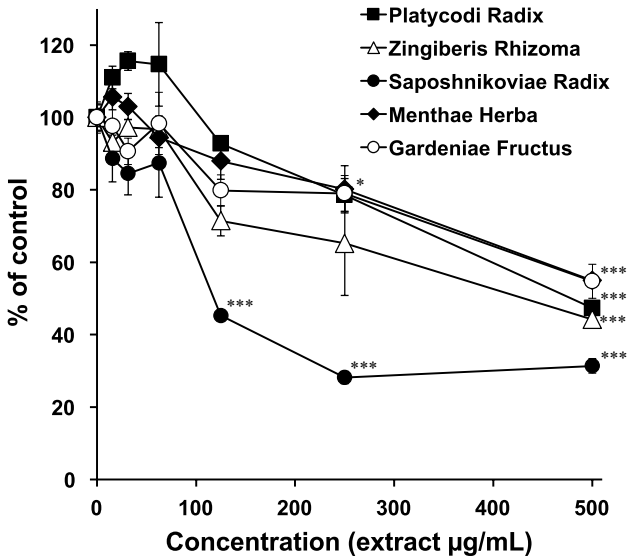

Fig. 4 Inhibitory effects of the extracts of Zingiberis Rhizoma, Saposhnikoviae Radix, Platycodi Radix, Menthae Herba and Gardeniae Fructus on GLUT5 function. CHO–GLUT5 cells were incubated with buffer containing [^{14}C]fructose (4 μM) with each extract at 37 °C for 5 min. Mock cells and a control CHO–GLUT5 cell group were treated with buffer not containing the extracts. The uptake of fructose into the cells was measured. Data are expressed as % of control of the mean ± SD ($n = 3$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus the control group by ANOVA and Bonferroni–Dunnett's multiple *t* test

compound of Saposhnikoviae Radix in JPXVII [1], by thin-layer chromatography, and this compound did not inhibit GLUT5 at a concentration at 125 μM (data not shown). Then, we tried to find the active ingredient from the second strongest crude drug extract of Zingiberis Rhizoma. 6-Gingerol and 6-shogaol are well-known pungent components in Zingiberis Rhizoma [15], and we evaluated the effects of these compounds on fructose uptake into CHO–GLUT5 cells. 6-Gingerol significantly inhibited fructose uptake into CHO–GLUT5 cells in a concentration-dependent manner, and its IC_{50} value was 39 μM. Compared with the effect of 6-gingerol, 6-shogaol showed a weak but significant inhibitory effect on fructose uptake into CHO–GLUT5 cells at 100 μM (Fig. 5). With regard to other crude drug extracts, we evaluated the effect of platicodin D, the marker compound of Platycodi Radix in JPXII [1]. However, this compound did not exhibit any effects at a concentration of 125 μM (data not shown).

The content of 6-gingerol and 6-shogaol in the extract of Zingiberis Rhizoma in the present study was 0.34 (w/w)% and 0.0037 (w/w)%, respectively. The IC_{50} value of Zingiberis Rhizoma extract in the present study was 314 μg/ml (contains 1.1 μg/ml = 3.6 μM of 6-gingerol). Therefore, it is predicted that approximately 9% of the inhibitory effect of Zingiberis Rhizoma extract on GLUT5 would be achieved by 6-gingerol.

It is reported that 60% of the ethanol extract of *Matricaria recutita* flower (German Chamomile) had an inhibitory effect on GLUT5 using Xenopus oocytes at a concentration of 0.5 mg/ml [16]. Chamomile contains several types of compounds belonging to flavonoids [17], and our previous study revealed that epicatechin gallate and nobiletin exhibited significant inhibitory effects on fructose uptake into Caco-2 cells derived from human epithelial colorectal adenocarcinoma in a concentration-dependent manner, with approximate IC_{50} values of 10 and 20 μM, respectively [12].

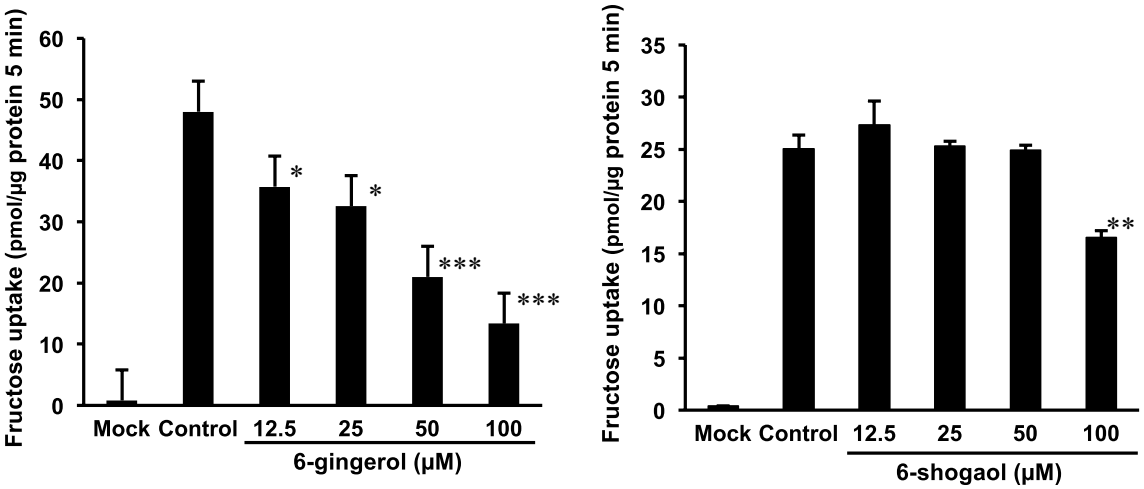

Fig. 5 Inhibitory effects of 6-gingerol and 6-shogaol on GLUT5 function. CHO–GLUT5 cells or mock cells were incubated with buffer containing [^{14}C]fructose (4 μM) with 6-gingerol or 6-shogaol at 37 °C for 5 min. A mock cell group and a control CHO–GLUT5 cell group were treated with buffer not containing these compounds. The uptake of fructose into the cells was measured. Data are expressed as % of control of the mean ± SD ($n = 3$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus the control group by ANOVA and Bonferroni–Dunnett's multiple t test

Although 6-gingerol has a much different chemical structure than flavonoids, the IC_{50} values of 6-gingerol on fructose uptake were similar to epicatechin gallate and nobiletin. Since the inhibitory effect of 6-shogaol was much weaker than that of 6-gingerol, the β-hydroxy carbonyl moiety in 6-gingerol plays an important role in exhibiting the inhibitory effect on GLUT5 function.

In conclusion, BTS is a formula in traditional Kampo medicine with a beneficial effect on obesity and metabolic syndrome, and one of its mechanisms of action is the inhibition of fructose absorption in the intestine. Among the components of BTS, Zingiberis Rhizoma, Saposhnikoviae Radix, Platycodi Radix, Menthae Herba and Gardeniae Fructus contribute to the effect of BTS, and one of the active constituents in Zingiberis Rhizoma is 6-gingerol.

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