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ORIGINAL CONTRIBUTION

Determination of the transient period of the EIS complex and investigation of the suppression of blood glucose levels by L-arabinose in healthy adults

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Abstract
Purpose L-Arabinose uncompetitively inhibits intestinal sucrase by forming an enzyme-inhibitor-substrate (EIS) complex. The transient period of the EIS complex affects the time span of inhibition. We determined the apparent transient period of the EIS complex of sucrase, L-arabinose, and sucrose both in vitro and in humans.
Methods Intestinal acetone powder (a source of sucrase), L-arabinose, and sucrose were mixed and injected into a dialysis membrane that was placed in a sucrose solution. The production rate of D-glucose and the release rate of L-arabinose from sucrase were determined. We also investigated the suppression of blood glucose levels by L-arabinose in 21 healthy volunteers. Sucrose (40 g) was ingested with or without L-arabinose (2 g), then blood glucose values were measured, which returned to steady-state conditions within 2 h. Volunteers were then given 90 g of commercial adzuki bean jelly containing 40 g sucrose as the sucrose load, and blood glucose values were measured again.
Results Addition of L-arabinose reduced the production rate of D-glucose compared to the rates measured in the absence of L-arabinose for several hours in vitro. L-Arabinose was released at a lower rate in the presence of sucrose than in its absence. Blood glucose values measured 2 h after sucrose was given with L-arabinose were significantly lower than those measured when L-arabinose was not given (Δ change in maximum value: with L-arabinose, 53.8 ± 19.7 mg/dL; without L-arabinose, 65.0 ± 17.7 mg/dL).
Conclusion The EIS complex of sucrase-L-arabinose-sucrose was maintained for several hours both in vitro and in humans.

Keywords L-Arabinose · EIS complex · Transient period · Second meal effect

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Introduction

L-Arabinose is one of the component sugars in plant cell wall material and is widely found in cereal fiber such as corn, wheat, barley, rye, or oats as arabinoxylan, which contains 30–40% [1–5] L-arabinose in its linked form. Beet pectin has a "hairy region," whose sugar composition is 75% [6] L-arabinose.

L-Arabinose selectively inhibits sucrase, an α-glucosidase found in the intestine. Experiments on rats and mice [7–9] have shown that intake of L-arabinose with sucrose reduced absorption of sucrose from the intestine and suppressed blood glucose levels. Inoue et al. [10, 11] reported that addition of L-arabinose to sucrose regulates blood glucose levels of both healthy adults and patients with diabetes mellitus.

When enzymes bind to their substrate, they form an enzyme–substrate (ES) complex. Sucrase forms a complex with sucrose, which is hydrolyzed into D-glucose and D-fructose. There are 3 types of enzyme inhibitors: competitive, uncompetitive, and noncompetitive. A competitive inhibitor is analogous to the substrate and binds to the active site, which blocks substrate binding. Noncompetitive inhibitors bind both to the free enzyme and to the

enzyme in the ES complex. While noncompetitive inhibitors do not inhibit formation of the ES or enzyme-inhibitor-substrate (EIS) complex, they inhibit formation and/or release of the product. An uncompetitive inhibitor binds only to the ES complex to form an EIS complex, which inhibits production and/or release of the product. L-Arabinose is an uncompetitive inhibitor of sucrase [7], and therefore, it forms an EIS complex.

For uncompetitive inhibitors, high levels of the ES complex result in high levels of the EIS complex, resulting in greater inhibition. In contrast, for competitive inhibitors, high levels of the ES complex cause low levels of inhibition. The K_i^{-1} value indicates the affinity of an inhibitor for an enzyme. The K_i^{-1} value affects the reaction rate of uncompetitive binding less than that of competitive binding; therefore, we cannot compare the strengths of different types of inhibitors using the K_i^{-1} value. Because the affinity of L-arabinose (an uncompetitive inhibitor) for sucrase is 12-fold higher than that of sucrose [7], L-arabinose likely can inhibit sucrase hydrolysis activity when high levels of the ES complex are present. The affinity of an uncompetitive inhibitor can be determined not only by the K_i^{-1} value, but also by the apparent transient period of the EIS complex. Matsuura et al. [12] reported that D-xylose and L-arabinose inhibit sucrase activity for 1 h in rats, indicating that their transient periods were fairly long, although the transient period of the EIS complex was not determined and data on suppression of blood glucose levels in humans were not recorded. Here, we aimed to determine the apparent transient period of the EIS complex in vitro and investigated the suppression span of blood glucose levels in healthy adults.

Materials and methods

Materials for in vitro tests

Superfine L-arabinose (Sanwa Cornstarch Co. Ltd.), which was >99% pure, was used. Intestinal acetone powder from rats was purchased from Sigma Co. Cellulose dialysis tubing (size, 2.5 mL/cm; MW cutoff, 25,000 Da) was purchased from Spectrum Labs. Other reagents of the highest grade were purchased from Wako Pure Chemical Industries, Ltd.

Determination of the inhibition effect in vitro

The method for determination of the inhibition effect in vitro is summarized in Fig. 1. Sucrose (2.0 g) and L-arabinose (0.1 g) were dissolved in 10 mL of 0.1 M maleic acid buffer (pH 6.0). Intestinal acetone powder (500 mg) from rats was added to the solution and was incubated at 37 °C for 1 h. After incubation, the suspension was transferred into dialysis tubing and labeled as "sucrase for reaction." "Sucrase for control" without L-arabinose was also prepared. Each sucrase was dialyzed in 90 mL of maleic acid buffer (pH 6.0) in which was dissolved 8.0 g of sucrose, and was incubated at 37 °C with stirring for 2 h. Aliquots (20 μL) of the maleic acid buffer were removed every 30 min, and the D-glucose concentration was measured using a Glucose CII Wako (Wako Pure Chemical Industries, Ltd.). The production rate of D-glucose was determined, and the production rate of "sucrase for reaction" was divided by that of "sucrase for control." The inhibition effect was calculated by subtracting this result

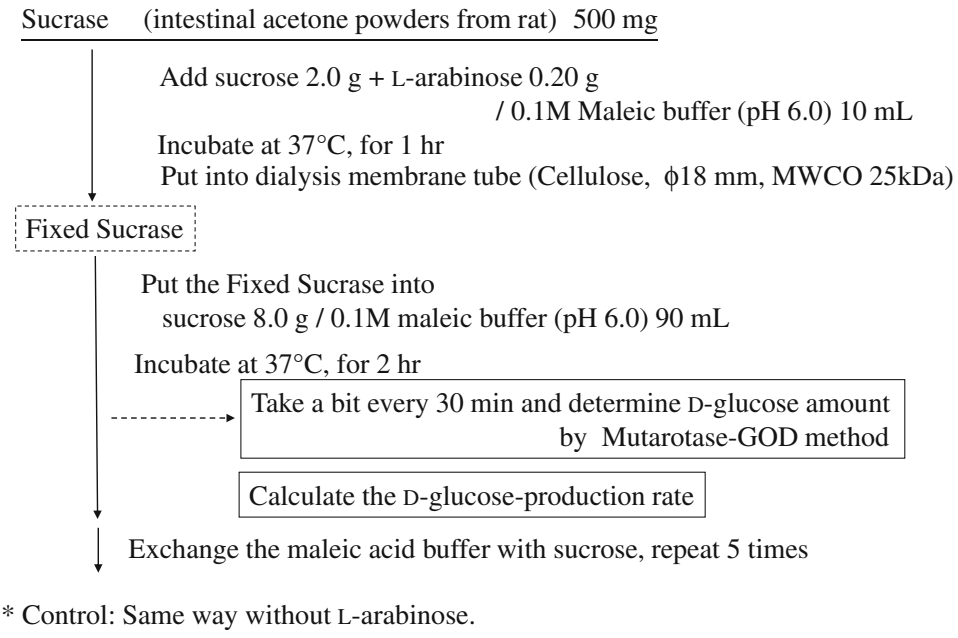
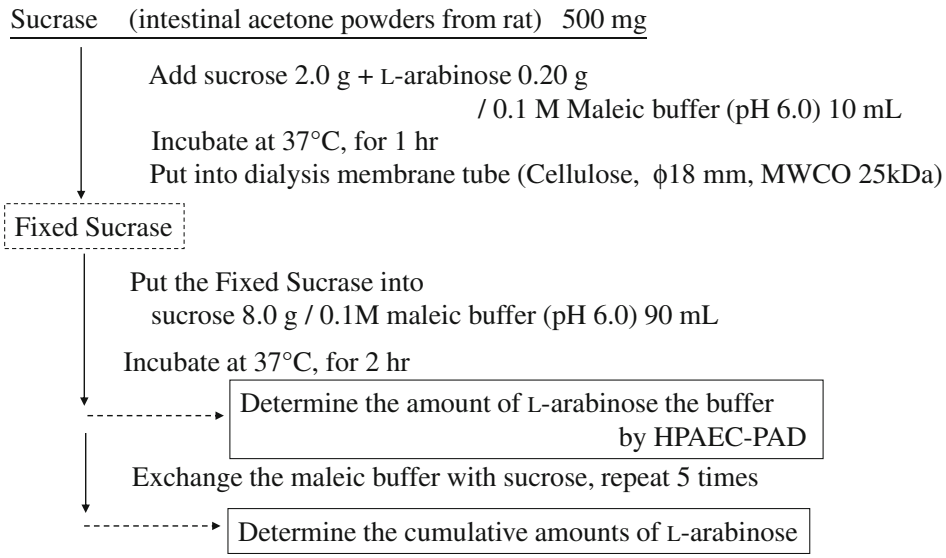


Fig. 1 The scheme for determination of inhibition effect in vitro. Amounts of produced D-glucose were determined by mutarotase-GOD method using Glucose C2 kit (Wako Pure Chemical Industries, Ltd.)



* Control: Same way without sucrose.

Fig. 2 The scheme for determination of apparent transient period of ESI complex in vitro. Amounts of released L-arabinose were determined by high-performance anion-exchange liquid chromatography with pulsed amperometric detector (HPAEC-PAD)

Table 1 Gradient program of eluent by HPAEC-PAD for determination of the amount of L-arabinose

Time (min)	Milli Q water (%)	0.5 M NaOH (%)	0.1 M NaOH (%)	0.1 M NaOH/ 1 M AcONa (%)
0	90	0	10	0
0.9	90	0	10	0
1.0	100	0	0	0
40.0	100	0	0	0
45.0	90	0	10	0
65.0	17.5	0	80	2.5
85.0	10	0	87	3
100.0	0	0	0	100
115.0	0	0	0	100
115.1	0	100	0	0
130.0	0	100	0	0
130.1	90	0	10	0
140.0	90	0	10	0

from 1. After 2 h, the maleic buffer with 8.0 g of sucrose was renewed and the measurements were repeated. These treatments were repeated 5 times for a total reaction time of 12 h.

Determination of the apparent transient period of the EIS complex in vitro

The method for determination of the apparent transient period of the EIS complex is summarized in Fig. 2. Sucrose (2.0 g) and L-arabinose (0.1 g) were dissolved in 10 mL of 0.1 M maleic acid buffer (pH 6.0), intestinal acetone powder (500 mg) was added, and the mixture was incubated at 37 °C for 1 h. The suspension was transferred into dialysis tubing and labeled "L-arabinose for determination" of the release rate. "L-Arabinose for control" without sucrose was also prepared. Each "L-arabinose" was dialyzed in 90 mL of maleic acid buffer (pH 6.0) in which was dissolved 8.0 g of sucrose and was incubated at 37 °C with stirring for 2 h. Every 2 h, the maleic acid buffer with 8.0 g of sucrose was renewed 5 times. The concentration of L-arabinose in maleic acid buffer was measured by high-performance anion-exchange chromatography with pulsed amperometric detector (HPAEC-PAD; DX-500, Dionex). The amount of released L-arabinose from the EIS complex in each time period was calculated from the integrated value of the HPAEC-PAD results.

HPAEC-PAD analysis

HPAEC-PAD analysis was performed using a DX-500 with a CarboPac PA1 separation column and a flow rate of 1.0 mL/min. Solvents were gradually changed as indicated in Table 1. Samples were added to the analyzer as 10-μL aliquots.

Materials for the sucrose tolerance test with L-arabinose in humans

Superfine L-arabinose, which was >99% pure, was used. Sucrose (Shinko Sugar Co. Ltd.) was used as the superfine sugar. The test meal, control meal, and sucrose-load meal were prepared as follows: sucrose (40 g) and L-arabinose (2.0 g) were dissolved in 108 g of deionized water as the test meal; 150 g of sucrose solution without L-arabinose

was used as the control meal. Commercial adzuki bean paste jelly (90 g neri-youkan; Sohonke Surugaya Co. Ltd.) was used for the sucrose-load meal, which corresponds to 40 g of sucrose as determined by the Japanese Agricultural Standards (JAS) method [13] of sucrose hydrolysis by invertase with the minor modification of using the Somogyi-Nelson method [14] for measuring increased reducing sugar.

Volunteers

This study was designed in compliance with the Helsinki declaration and approved by the local ethics committee, and volunteers were treated under the strict control of a qualified doctor responsible for the health of all volunteers. Volunteers for this study were healthy adult employees of Sanwa Cornstarch Co. Ltd. Volunteers were shown the detailed protocol for this study and gave written informed consent. Volunteers first underwent a sucrose tolerance test (40 g sucrose) by measuring blood glucose at 15, 30, 60, 90, and 120 min after intake using a blood glucose monitor (Medisafe mini GR-102; Terumo Co.). After prescreening, 21 volunteers (18 men and 3 women) who met the criteria of our study (Table 2) were selected. Before ingestion of sucrose, blood glucose was monitored and the stability of the value was observed 150 min after eating breakfast. Each volunteer was given the same breakfast on the day of the test.

Sucrose tolerance test with L-arabinose in humans

On the basis of their blood glucose levels in the prescreening, the 21 volunteers were classified into 2 phases: lower phase (increase in blood glucose level (ΔBlood Glc < 60 mg/dL) and higher phase (ΔBlood Glc > 60 mg/dL). Volunteers were then divided into two equal groups (test and control) with an approximately even distribution of blood glucose levels, age, sex, and body mass index (BMI).

Table 2 Selection and rejection standards of sucrose tolerance test

Selection standards

1. Adult male or female whose age is same to or higher than 20
2. Who is showed the protocol of this study in detail and gave written informed consent

Rejection standards

1. Who has higher blood glucose than 140 mg/dL at 120 min after ingestion in pretest
2. Who take any medicine for control blood glucose
3. Who is pregnant or lactating
4. Who is recommended to stop the test from the responsible doctor

Each group was subjected to the sucrose tolerance test with L-arabinose. On the day of the test, each volunteer finished breakfast before 7:30 am, started the test at 10:00 am, and consumed only the test meal or control meal, the sucrose-load meal, and deionized water. One group of volunteers ingested the test meal and the other group ingested the control meal in the first stage. In the second stage, their meals were reversed (crossover). Blood glucose levels were measured at 15, 30, 60, 90, and 120 min after intake of the test or control meal using a blood glucose monitor (Medisafe mini GR-102). We compared the values taken at 120 min to the values before intake of the test or control meal. If the value at 120 min was much higher than the initial value before intake of the test or control meal, we discontinued testing of the volunteer. After the blood glucose level had returned to the value measured before intake, the sucrose-load meal was ingested. Blood glucose levels were measured again at the same time intervals as after intake of the test or control meal. There was more than a 6-day interval between the first and second stage. All experiments were double blind.

Statistical analysis

All results of this study were analyzed using a paired Student's t test.

Results

Inhibition effect by L-arabinose in vitro

Plots of the amount of D-glucose in the maleic acid buffer at each time point were linear with a high coefficient of determination ($r^2 = 0.9970 \pm 0.0036$, mean $\pm$ SD, $n = 16$). The production rate of D-glucose was calculated by the slope of the curve for each "sucrase" at each time point (Table 3). The production rate of "sucrase for control" at each time point was similar, demonstrating that the activity of sucrase

Table 3 The production rate of D-glucose as slope of curve by each "sucrase" at each period in vitro test

Period (h)	Sucrase for reaction (mg/h)	Sucrase for control (mg/h)
0	9.8 ± 2.3	62.5 ± 2.2
2	12.3 ± 2.5	61.3 ± 1.7
4	19.0 ± 1.7	65.8 ± 3.9
6	30.4 ± 1.4	60.5 ± 3.0
8	48.7 ± 1.9	61.9 ± 2.8
10	52.0 ± 2.6	61.3 ± 3.6
12	56.7 ± 7.4	58.8 ± 1.9

Mean ± SD ($n = 3$)

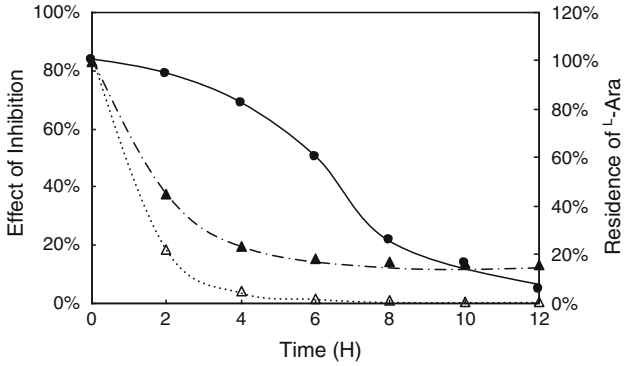


Fig. 3 Inhibition effect of L-arabinose and apparent transient period of ESI complex in vitro. *Closed circle* with *solid line*, inhibition effect of L-arabinose; *closed triangle* with *chain line*, the amount of released L-arabinose from sucrase with sucrose; *open triangle* with *dotted line*, the amount of released L-arabinose from sucrase without sucrose

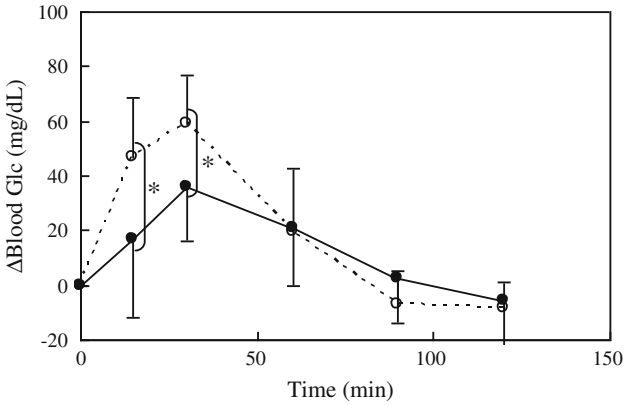


Fig. 4 Shifts of blood glucose levels at ingestion of 40 g of sucrose with and without 1 g of L-arabinose by 21 healthy adults. *Closed circle* with *solid line*, ingestion of sucrose with L-arabinose (test meal); *open circle* with *dash line*, ingestion of sucrose without L-arabinose (control meal). *Significantly different, $p < 0.05$

remained constant throughout the experiment. The production rate of "sucrase for reaction" increased, indicating that inhibition by L-arabinose decreased with increased dialysis time in the maleic acid buffer. The effect of inhibition was calculated using the following equation:

$$[\text{Effect of inhibition}] = 1 - \frac{[\text{D-Glc production rate with L-Ara}]}{[\text{D-Glc production rate without L-Ara}]}$$

D-Glc : D-glucose; L-Ara, L-arabinose

Results are shown in Fig. 3 with closed circles and a solid curve. These data indicate that L-arabinose with sucrose inhibited ~80% of the sucrase activity after 2 h, ~70% of the sucrase activity after 4 h, and ~50% of the sucrase activity after 6 h.

Apparent transient period of the EIS complex in vitro

Residual L-arabinose was calculated with and without sucrose at each time point by subtraction of the amount of L-arabinose released from the amount added. The residual ratio was also calculated as the ratio of the residual amount to the added amount. The residual ratios with and without sucrose are shown in Fig. 3 as closed triangles with a chain curve and open triangles with a dotted curve, respectively. These data indicate that the release rate of L-arabinose was reduced in the presence of sucrose. The apparent transient period of the EIS complex was 4–6 h, as indicated by the effect of inhibition and the residual amount of L-arabinose.

Suppression of blood glucose levels by L-arabinose in healthy adults

Blood glucose levels at each time period after ingestion of the test or control meal are summarized in Fig. 4. Open circles with a dashed curve represent intake of the control meal and closed circles with a solid curve, the test meal. Blood glucose levels at 15 and 30 min were suppressed significantly by intake of L-arabinose. The maximum elevated level of blood glucose and the area under the curve (AUC, mg min/dL) are summarized in Table 4. Both values with L-arabinose were significantly lower than values without L-arabinose.

Suppression span of blood glucose levels by L-arabinose in healthy adults

Two hours after the intake of the test meal or control meal, the sucrose-load meal was ingested. The blood glucose values were measured at 15–120 min after ingestion, and the results are shown in Fig. 5 as open circles with a dashed curve for intake of only sucrose 2 h before ingestion of the sucrose-load meal and closed circles with a solid line for intake of L-arabinose with sucrose 2 h before the sucrose-load meal. The elevated glucose value at 30 min was significantly inhibited by ingestion of L-arabinose. The maximum elevated glucose value and AUC were also significantly suppressed by the addition of L-arabinose (Table 4).

Discussion

L-Arabinose has been reported to suppress both the absorption of sucrose and elevated blood glucose levels in rats, mice, and humans [7–11]; our results agree with these reports. Lower AUC values in the presence of L-arabinose support the lower glycemic index of sucrose with L-arabinose. The proportion of unabsorbed sucrose was calculated to be 23% based on the suppressed AUC. Inoue et al. [10]

Table 4 Highest Δblood glucose values and area under the curves (AUC) after ingestion of the test or control meal, or sucrose-load meal by healthy adults ($n = 21$)

Meal	Highest Δblood glucose (mg/dL)	AUC (mg min/dL)
After ingestion of test or control meal		
Control meal	63.8 ± 17.9	2,680 ± 1,020
Test meal	40.3 ± 17.8*	2,070 ± 1,140*
After ingestion of sucrose-load meal		
Control meal	65.0 ± 17.7	3,680 ± 1,340
Test meal	53.8 ± 19.7*	2,680 ± 1,310*

Mean ± SD ($n = 21$), * Significant different, $p < 0.05$

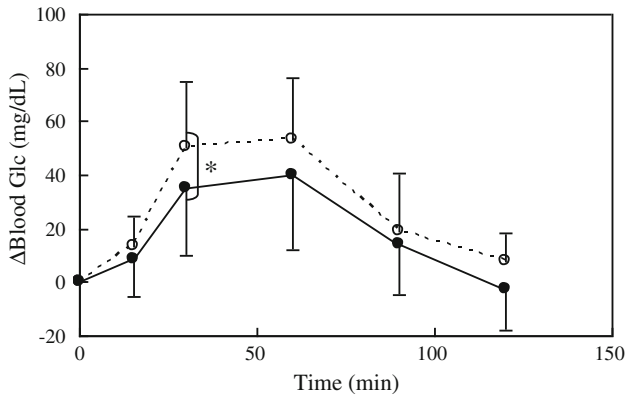


Fig. 5 Shifts of blood glucose level at ingestion of 90 g of commercial adzuki bean jerry as a sucrose-load meal by 21 healthy adults. *Closed circle* with *solid line*, ingestion of test meal 2 h before intake of sucrose-load meal; *open circle* with *solid line*, ingestion of control meal 2 h before intake of sucrose-load meal. *Significantly different, $p < 0.05$

demonstrated that AUC values were suppressed by 42 and 48% with addition of 3 and 4% L-arabinose to sucrose, respectively, although the values reported were not over 120 min but over 60 min. The decreased AUC values from 0 to 120 min observed in the present study were similar to previously reported values [10].

Because uncompetitive inhibitors only bind to the ES complex, the amount rather than the proportion of the substrate affects inhibition, although other modes of inhibition are directly affected by the proportion of the inhibitor to the substrate. Interestingly, an increase in the substrate might not cause a decrease in uncompetitive inhibition compared to other modes. In the present in vitro study, a small amount (only ~20%) of residual L-arabinose in the EIS complex suppressed ~50% of the inhibition (Fig. 3). In cases where the affinity of an uncompetitive inhibitor for the ES complex is higher than the affinity of the substrate for the enzyme, inhibitors released from EIS complexes would bind to free ES complexes. In other words, the concentration of the EIS complex would be dynamic rather than fixed. This may be because a small amount of the inhibitor prevents the reaction.

Based on the production rate of D -glucose and the release rate of L-arabinose in vitro (Fig. 3), ~20% of the sucrase appears to maintain formation of the EIS complex for 6 h. However, this type of inhibition could affect the proportion of substrate to enzyme; suppression of blood glucose in vivo and in humans could occur earlier than 6 h due to the lower amounts of sucrose ingested in ordinary intake. In this study, volunteers ingested 90 g of adzuki bean jelly and exhibited a 2-h suppression span for maximum changes to blood glucose levels and AUC (Fig. 5 and Table 4).

The suppressed proportion of the AUC after ingestion of the sucrose-load meal (27%) was similar to that for the test meal (23%) (Table 4), indicating that the inhibition effect was constant. This value agreed with the results in vitro, showing a similar inhibition effect at 0 h and 2 h (Fig. 3). These results indicate that L-arabinose can inhibit blood glucose for more than 2 h during ordinary intake.

After L-arabinose is released from the EIS complex, another L-arabinose molecule may bind the free ES complex to form another EIS complex. In this way, L-arabinose could remain in the small intestine for several hours. Alternatively, sucrose in the free ES complex may be hydrolyzed or a small amount of sucrose might be released from the ES complex without hydrolysis. Unprocessed sucrose cannot be absorbed from the small intestine but can flow from the small intestine into the colon and be consumed by microflora in the colon [15]. Osaki et al. [15] reported the decrease in the pH of the cecum contents when both sucrose and L-arabinose were ingested compared to when only glucose, fructose, or L-arabinose were ingested. Ultimately, all of the sucrose (and L-arabinose) would be released from the EIS complex; however, both hydrolysis and flow to the colon of the sucrose would continue to occur for several hours. Iwata et al. [16] and Ohki & Negishi [17] showed that intake of sucrose with L-arabinose activated microflora in rats and humans, which is consistent with a possible increase in the amount of sucrose in the colon. Iwata et al. [16] reported that intake of L-arabinose and sucrose significantly elevated the proportion of *Bifidobacterium* in the cecum of rats, while the microflora in humans did not increase as dramatically [17]. These differences may be due to differences in the amount of intake (rats eat ~100-fold higher amounts of sucrose with L-arabinose than humans based on proportional body weights [16, 17]) and species differences.

Matsuura et al. [12] reported that with continuous ingestion of sucrose, the ability of L-arabinose to inhibit elevated blood glucose levels was 60 min, which was a shorter time than observed for other inhibitors. However, their graphs for L-arabinose appeared to show similar

curves to D-xylose and D-glucurono-3,6-lactone, which were concluded to have longer inhibition times compared to L-arabinose. Therefore, the method for measuring the duration of the inhibitory effect may be too sensitive, as some inhibitors including L-arabinose may show shorter duration times. Acarbose and voglibose showed longer duration times in the study by Matsuura et al. [12], indicating that they have a higher affinity (lower K_i) for α-glucosidase [7, 18]. An uncompetitive inhibitor with a similar K_i would have a longer inhibitory effect than that of a competitive inhibitor. In fact, the K_i of L-arabinose (2.0 mM) was 1,800-fold higher than that of acarbose (1.1 μM) [7], although 50 mg/kg (only 33-fold the amount of acarbose) of L-arabinose had a similar inhibition effect to 1.5 mg/kg of acarbose, according to a traceability test with ^{14}C-labeled sucrose [9]. The higher degree of inhibition with a higher K_i value compared to a competitive inhibitor would also indicate loose binding of L-arabinose to the ES complex.

Based on the results of this study, we conclude that the EIS complex of sucrase-L-arabinose-sucrose is maintained for several hours both in vitro and in humans.

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