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스트렙토조토신 유도 당뇨병 쥐에서 돼지감자 추출물과 이눌린의 혈당과 인슐린 분비에 대한 영향

김승희[1], 김병기[1], 박부연[1], 김정민[1], 이영직[2], 이미경[3], 이성태[4], 강미연[1]
성가롤로병원 [1]내과, [2]병리과, 국립순천대학교 [3]식품영양학과, [4]약학과

Effects of Jerusalem Artichoke Extract and Inulin on Blood Glucose Levels and Insulin Secretion in Streptozotocin Induced Diabetic Mice

Seung Hee Kim[1], Byung Ki Kim[1], Boo Yeun Park[1], Jung Min Kim[1], Young Jik Lee[2], Mi Kyung Lee[3], Sung-Tae Yee[4], Mi Yeon Kang[1]
[1]Department of Internal Medicine,
[2]Department of Clinical Pathology, St. Carollo Hospital,
[3]Department of Food and Nutrition,
[4]Department of Pharmacy, Sunchon National University, Suncheon, Korea

Abstract

Background: To determine the effects of Jerusalem Artichoke extract (JAE) and inulin on blood glucose levels and insulin secretion in streptozotocin (STZ)-induced diabetic mice.
Methods: Thirty four mice were divided into a normal control group and three experimental groups: diabetic control, JAE, and inulin. STZ (50 mg/kg) was injected intraperitoneally to induce diabetes in the three experimental groups. The JAE and inulin groups were fed 10 g/kg JAE or fed 1 g/kg inulin, respectively, for 6 weeks. Fasting glucose was checked weekly. After 6 weeks, the oral glucose tolerance test (OGTT) was performed, and the insulin level was checked.
Results: Four mice from the JAE group (n = 9) died and autopsies revealed inflammation and ulceration of skin lesions on the chest areas. Fasting glucose levels were not decreased in the inulin or JAE group relative to diabetic control group. In the OGTT at 60 minutes and 120 minutes, the serum glucose levels

Corresponding author: Mi Yeon Kang
Division of Endocrinology and Metabolism, Department of Internal Medicine, St. Carollo Hospital, 221 Sungwang-ro, Suncheon 57931, Korea, E-mail: leerabin@hanmail.net

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were significantly higher in the inulin group (572.6 ± 52.0 mg/dL and 555.8 ± 72.9 mg/dL, respectively) than in diabetic control group (484.3 ± 81.6 mg/dL and 467.3 ± 111.1 mg/dL, respectively). Insulin levels were not increased in the inulin group relative to the diabetic control group.
Conclusion: These results indicate that JAE and inulin might not be useful therapeutic strategies for diabetes mellitus and indiscreet intake of Jerusalem Artichoke could exacerbate to diabetes.

Keywords: Diabetes mellitus; Glucose; Helianthus; Insulin; Inulin

INTRODUCTION

Diabetes mellitus (DM) is a non-curative chronic disease with a high social cost owing to a number of DM-related complications. The incidence of microvascular and macrovascular complications can be reduced by controlling serum glucose. Thus, the significance of serum glucose control is well known [1-3].

However, the results of studies on the glucose control status of patients with DM in Korea are not satisfactory. According to data from the Korea National Health and Nutrition Examination Survey (2011~2016), the control rate among people with diabetes is 25.1% for a glycemic target goal of HbA1C < 6.5%, or 52.6% of HbA1C < 7.0% [4].

The causes of uncontrolled glucose can include lack of education of patients with DM and treatment compliance issues [5]; the compliance rate for diabetic patients continuing medication more than 360 days was only 21.8% [6].

Diabetic patients attempt various traditional folk remedies while refusing medications. DM itself was shown to be an independent prognostic factor for the degree of dependence on complementary alternative medicine [7], and silkworm powder was the most commonly used folk remedy among Korean patients with DM in 1998 [8].

Recently, Jerusalem Artichoke has been preferred as an alternative treatment for diabetic patients. Jerusalem Artichoke is a perennial plant of the family Asteraceae with North American origins, and its main component is inulin, a type of fructosan that is not digested by human digestive enzymes but is fermented by microorganisms in the large intestine. Inulin fermentation, results in enhancement of the intestinal environment without increasing serum glucose levels as it is broken down into fructose on degradation [9]. A previous study found that insulin secretion was significantly increased compared to the control group when Jerusalem Artichoke extract (JAE) and inulin were added to the pancreatic beta cell line; HIT-T15 [10], and the fasting glucose levels decreased in a previous study performed with non-diabetic subjects [11].

Although the effect of Jerusalem Artichoke on serum glucose reduction has not been proven [12]; and the safety of the medications at different dosages has not been established, many patients indiscreetly consume JAE. Thus, this study was designed to investigate the effect of JAE and inulin on serum glucose and insulin levels in streptozotocin (STZ)-induced diabetic mice and to identify any adverse effects of the dosage of Jerusalem Artichoke indiscreetly taken by patients.

MATERIALS AND METHODS

1. Manufacturing JAE

Jerusalem Artichoke powder (100 g) was diluted 10-fold in distilled water and was heated and extracted at 80℃ for 4 hours and then filtered using Whatman filter papers (GE Healthcare, Chicago, IL, USA). The extract was concentrated under reduced pressure using a rotary evaporator and cryodesiccated, and its yield was 45.63%.

2. Experimental design and sample collection

This study's protocol was approved by the Institutional Animal Care and Use Committee of Sunchon National University (SCNU IACUC-2014-04).

For DM experimental animals, 8-week-old male ICR mice were purchased from Orient Bio Inc. (Seoul, Korea). Mice were adapted with solid diets for 5 days and classified into a normal group (n = 8) and DM group according to a randomized block design. For the induction of DM, 50 mg/kg STZ (Sigma, St. Louis, MO, USA) dissolved in 0.1 M citrate buffer (pH 4.2) was intraperitoneally injected at the same time daily for 4 consecutive days. After 2 days, fasting serum glucose was measured and mice with greater than 200 mg/dL were classified into the diabetic control group (n = 9), Jerusalem Artichoke group (10 g/kg, n = 9), or inulin group (1 g/kg, n = 8) (Sigma). Each mouse was raised in an individual polycarbonate cage for 6 weeks. The amount of JAE (10 g/kg) was the indiscreet dosage taken by patients.

Mice were fed solid diets, and experimental agents were dissolved in purified water and administered orally at the same time each day. An equal amount of distilled water was orally administered to apply the same stress to the normal group and diabetic control group.

The environment of the animal breeding room was controlled at constant temperature (20 ± 2℃), constant humidity (50 ± 5%), and 12-hour interval light-period (08:00~20:00). All mice received food and water ad libitum.

After 6 weeks, experimental animals were fasted for 12 hours before euthanization. Mice were anesthetized with ether, and blood samples were obtained via the inferior vena cava. The drawn blood was maintained at room temperature for 30 minutes to allow the blood cells to settle and then centrifuged at 3,000 rpm (4℃) for 15 minutes to separate the serum. Insulin and GLP-1 were measured in the separated serum using a multiplex detection kit (Bio-Rad, Hercules, CA, USA). The organs of experimental animals were extracted immediately after blood draw and; washed with phosphate buffered saline (PBS) solution several times, and the surface water was removed. Tissues were immediately frozen with liquid nitrogen and stored at −70℃.

3. Measurement of body weight, diet intake and serum glucose

Body weight and diet intake were measured and recorded at the same time daily, during the breeding period. To investigate the effects of JAE administration on the serum glucose levels of DM animal models, serum glucose was measured weekly using a glucose monitoring device (G-Doctor; Allmedicus, Anyang, Korea) with blood drawn from a tail vein after 8 hours of fasting.

4. Oral glucose tolerance test (OGTT)

The OGTT was performed at week 6. JAE (10 g/kg) and inulin (1 g/kg) were orally administered 10 minutes

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before the administration of glucose solution. The same amount of distilled water was orally administered to the normal and diabetic controls group. At 0, 30, 60, 90, and 120 minutes after administration of 1 g/kg glucose solution, blood was drawn from a tail vein and the glucose level was measured using a glucose monitoring device (G-Doctor).

5. Statistical analysis

The study results were presented as the mean ± standard deviation using the SPSS statistics program (ver. 10; SPSS Inc., Chicago, IL, USA) for each experimental group. The statistical significance of the means of each group was tested by one-way ANOVA, and the difference between multiple groups was tested with a significance level of $P < 0.05$ using Duncan's multiple range test.

RESULTS

1. Effect on body weight and diet intake

The change of body weight was significantly lower in the diabetic control, Jerusalem Artichoke, and inulin groups than in the normal group beginning in week 2 ($P < 0.05$). However, there were no differences in body weight change among the diabetic control, Jerusalem Artichoke, and inulin groups (Supplementary Fig. 1).

Although diet intake was significantly greater in the diabetic control group and inulin group throughout the entire experimental period, there was no difference in the diet intake between diabetic control group and inulin group. The diet intake was significantly lower in the Jerusalem Artichoke group than in the diabetic control and inulin groups at week 4 (Supplementary Table 1).

2. Effect on serum glucose

The mean serum glucose level on the first week for the normal group, diabetic control group, Jerusalem Artichoke group, and inulin group was 136.3 ± 17.8 mg/dL, 235.2 ± 75.5 mg/dL, 170.3 ± 58.1 mg/dL, and 257.5 ± 78.4 mg/dL, respectively, indicating reduction of serum glucose in the Jerusalem Artichoke group compared to the diabetic control and inulin groups. However, the serum glucose of the Jerusalem Artichoke group and diabetic control group was significantly higher at weeks 2 and 3 than in the normal group ($P < 0.05$). Although serum glucose at week 4 in the Jerusalem Artichoke group was lower than in the diabetic control group and higher than in the normal group, the differences were not statistically significant. After week 4, due to the death of four mice and chest inflammation of one mouse in the Jerusalem Artichoke group, it was determined that comparison analysis for the Jerusalem Artichoke group would not be possible (Table 1, Fig. 1).

The serum glucose was higher in the inulin group than in to normal group throughout the entire period. Serum glucose in the inulin group was also higher beginning at week 3 than in the diabetic control group, with the difference reaching statistical significance at weeks 5 and 6 (week 5: 397.4 ± 103.6 mg/dL vs 301.0 ± 105.2 mg/dL; week 6: 394.9 ± 134.3 mg/dL vs 262.4 ± 80.9 mg/dL, respectively) (Table 1, Fig. 1).

3. Effect on the OGTT

The OGTT was significantly lower in the normal group than in the diabetic control group and inulin group at 30, 60, 90, and 120 minutes after glucose administration. Although there was no significant difference in serum

Table 1. The blood glucose levels in normal, diabetes, Jerusalem Artichoke, and inulin group

Week	Normal (mg/dL)	Diabetes (mg/dL)	Jerusalem Artichoke (mg/dL)	Inulin (mg/dL)
0	139.6 ± 15.4[a]	230.8 ± 28.7[b]	223.8 ± 17.9[b]	225.9 ± 22.7[b]
1	136.3 ± 17.8[a]	235.2 ± 75.5[b]	170.3 ± 58.1[a]	257.5 ± 78.4[b]
2	125.8 ± 12.2[a]	278.3 ± 69.0[b]	241.4 ± 98.1[b]	278.8 ± 83.8[b]
3	131.9 ± 22.0[a]	313.9 ± 124.4[bc]	243.8 ± 112.3[b]	361.8 ± 131.9[c]
4	131.8 ± 9.5[a]	315.9 ± 141.5[b]	298.0 ± 146.9[ab]	356.6 ± 112.3[b]
5	127.4 ± 10.4[a]	301.0 ± 105.2[b]		397.4 ± 103.6[c]
6	119.6 ± 26.0[a]	262.4 ± 80.9[b]		394.9 ± 134.3[c]

Values are presented as mean ± standard deviation.
[a,b,c]Means in the same row not sharing a common superscript are significantly different among groups ($P < 0.05$).

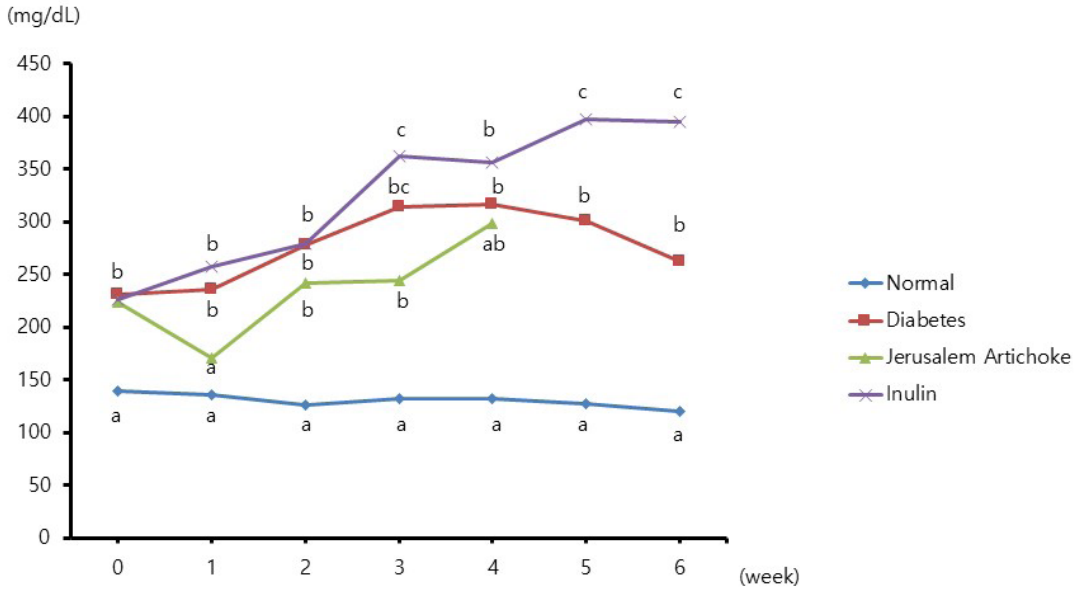

Fig. 1. The blood glucose levels in normal, diabetes, Jerusalem Artichoke, and inulin group.
[a,b,c]Means not sharing a common letter are significantly different among groups ($P < 0.05$).

glucose between the diabetic control group and inulin group at 30 minutes and 90 minutes after glucose administration, it was significantly lower in the diabetic control group than in the inulin group at 60 minutes and 120 minutes (60 minutes: 484.3 ± 81.6 mg/dL vs 572.6 ± 52.0 mg/dL; 120 minutes: 467.3 ± 111.1 mg/dL vs 555.8 ± 72.9 mg/dL, respectively) (Table 2, Fig. 2).

4. Effect on insulin and GLP-1

Although insulin and GLP-1 were high in the normal group, there was no significant difference among the normal

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Table 2. The result of oral glucose tolerance test in normal, diabetes, and inulin group

Time (min)	Normal (mg/dL)	Diabetes (mg/dL)	Inulin (mg/dL)
0	166.6 ± 20.3[a]	314.4 ± 85.8[b]	411.0 ± 127.3[c]
30	248.9 ± 40.6[a]	487.6 ± 59.2[b]	537.1 ± 104.6[b]
60	217.1 ± 52.2[a]	484.3 ± 81.6[b]	572.6 ± 52.0[c]
90	207.9 ± 50.7[a]	491.3 ± 112.7[b]	560.9 ± 67.0[b]
120	187.9 ± 39.6[a]	467.3 ± 111.1[b]	555.8 ± 72.9[c]

Values are presented as mean ± standard deviation.
[a,b,c]Means in the same row not sharing a common superscript are significantly different among groups ($P < 0.05$).

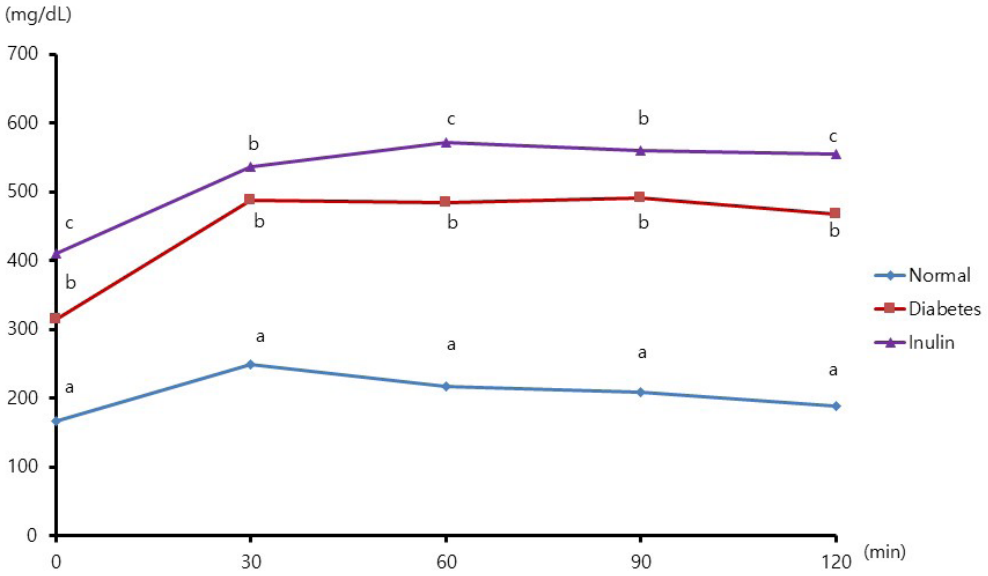

Fig. 2. The result of oral glucose tolerance test (OGTT) in normal, diabetes, and inulin group.
[a,b,c]Means not sharing a common letter are significantly different among groups ($P < 0.05$).

group, diabetic control group and inulin group (Fig. 3).

5. Adverse effects in the Jerusalem Artichoke group

Four of nine mice in the Jerusalem Artichoke group died during the study, and adverse effects occurred in one mouse. One mouse in the Jerusalem Artichoke group died on the day 2 of week 4, the three other mice died after another 2, 5, 6 days. One mouse developed a rash and edema on the left side of the chest 5 days after the first mouse died. The dead mice exhibited rash and swelling on the left side of the chest and autopsies reveled pus underneath the skin. Biopsies revealed severe inflammation and ulcer (Fig. 4). The spleen of the surviving mouse exhibiting adverse effects was enlarged three fold relative to the spleen of a normal mouse.

DISCUSSION

Because tight control of serum glucose from the early

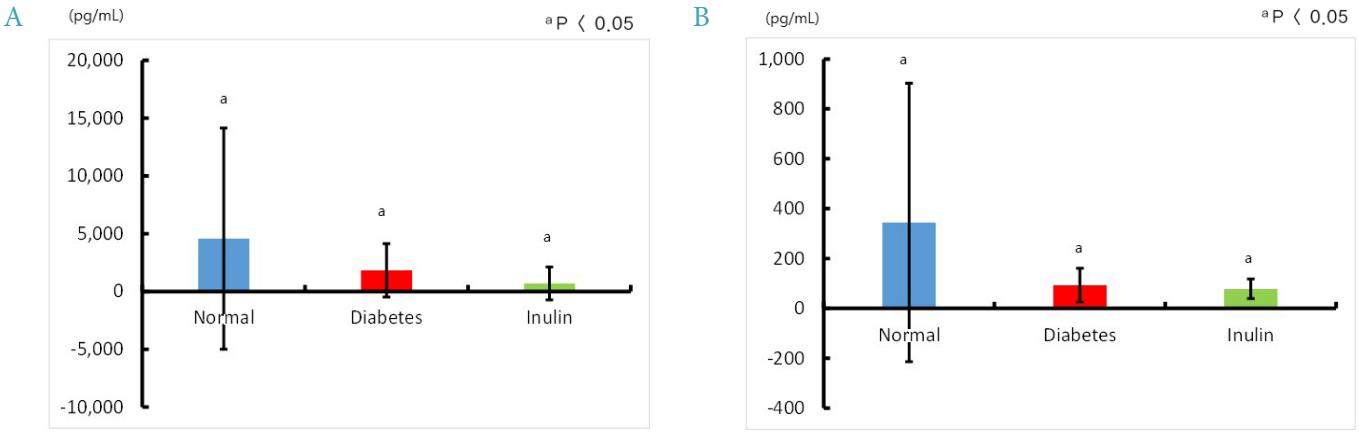

Fig. 3. Insulin (A) and GLP-1 (B) levels in normal, diabetes, and inulin group.
GLP-1, glucagon-like peptide-1.
[a]Means not sharing a common letter are significantly different among groups ($P < 0.05$).

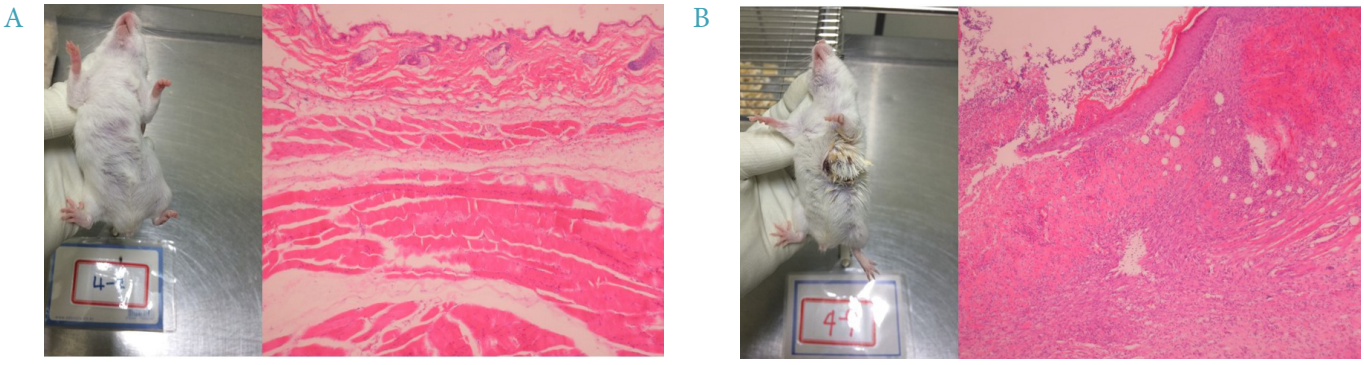

Fig. 4. Normal group mouse (A) vs Jerusalem Artichoke group mouse with complications (B). (A) Normal group mice showed normal skin, subcutaneous tissue and muscle. (B) Jerusalem Artichoke group mice macroscopically showed swollen skin and microscopically showed skin ulcer and inflammatory cells infiltration into subcutaneous tissue and skeletal muscle. H&E stain, ×40 (A, B).

stage reduces the complications of DM, treatment with insulin or an oral glucose lowering agent in addition to life-style modification including diet control and exercise is recommended beginning at the time of diagnosis of DM [13].

However, many diabetic patients indiscreetly rely on folk remedies without supporting evidence of their efficacy and safety. According to the a survey regarding the use of folk remedies by Korean patients with DM in 1998, 53.4% of respondents utilized at least one of 54 folk remedies including the most common type, silkworm powder. Most folk remedies were encountered based on recommendations from friends or relatives or media such as TV, newspapers, and magazines [8]. Unlike in the past, our recent experience indicates that patients most commonly use Jerusalem Artichoke and bitter gourd as folk remedies, and these are mainly encountered TV or internet advertisements.

Some articles have previously reported the effects of inulin, which is a main component of JAE and Jerusalem Artichoke, on serum glucose. Jerusalem Artichoke was reported to reduce serum glucose by inhibiting α-glucosidase activity, and this effect was associated

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with inulin [14,15]. In an 8-week study of 52 diabetic female patients, 27 received 10 g inulin, and 25 received 10 g maltodextrin. The fasting glucose, glycosylated hemoglobin, interleukin-6, tumor necrosis factor-α, and plasma lipopolysaccharide levels were found to be significantly reduced in the inulin group compared to the malodextrin group. Thus, the authors reported that inulin reduced serum glucose and exhibited an anti-inflammatory effect [16]. In another study of STZ-induced DM mice administered JAE for 4 weeks, serum glucose and triglycerides levels significantly decreased in the JAE group compared to the diabetic control group, and the reduction of body weight was small compared to the diabetic control group [17].

Inulin and JAE were reported to increase insulin secretion in the pancreatic beta cell line HIT-T15 [10], and insulin secretion measured by hyperglycemic clamp was shown to significantly increase in both the first and second phases in DM mice administered Jerusalem Artichoke and soybean (Chung-Guk-Jang) compared with the diabetic control group [18].

However, in this study fasting serum glucose was significantly higher in the inulin group than in the diabetic control group as of week 5, and serum glucose was significantly higher in the inulin group than in the diabetic control group in the OGTT at 60 minutes and 120 minutes after administering glucose, indicating that inulin increased the serum glucose. In addition, inulin did not increase the secretion of insulin and GLP-1, and there was no effect on body weight. These results suggest that inulin would have no benefit in DM.

Although fasting serum glucose significantly decreased during the first week in the Jerusalem Artichoke group, there was no significant difference compared to the diabetic control group between 2 and 4 weeks. Moreover, we identified several severe adverse effects: four of nine mice died in the Jerusalem Artichoke group after week 4, and one mouse developed inflammation on the chest. Because mice were randomly classified into groups, all mice were kept in the same animal breeding room, all groups received identical diet and water, and all mice in the other groups were normal until the end of the experiment, the severe adverse effects in the Jerusalem Artichoke group are likely associated with JAE administration and not viral or bacterial infection. Therefore, the indiscreet administration of Jerusalem Artichoke might lead to severe risk for patients.

Consistent with these results, postprandial glucose and serum triglycerides were found to increase with Jerusalem Artichoke administration in patients with type 2 diabetes [19]. Analysis of the results of 13 randomized clinical trials testing the effects of fructan administration on serum glucose in diabetic patients revealed a lack of evidence that fructans, such as inulin, significantly reduced serum glucose [12]. Furthermore, there has been no long-term study testing whether fructan is beneficial to diabetic patients [20].

Potassium is the most abundant mineral component of Jerusalem Artichoke at 2,489 mg%, accounting for 79.6% of all minerals [21]. According to Jang et al. [22], the potassium content of superior potato was 317 mg%, that of rose potato was 493 mg%, and that of Jasim potato was 432.68 mg%, and potassium was the most abundant mineral component. Thus, the potassium content of Jerusalem Artichoke was 7.9-, 5-, and 5.8-fold those of superior potato, rose potato, and Jasim potato, respectively. This indicates that Jerusalem Artichoke administration could be dangerous for patients with a the risk of hyperkalemia due to diabetic nephropathy [23].

Since functional foods were introduced in the late 1990s,

commercial development and use of functional foods have increased. Accordingly, interest about the safety and risk of functional foods is also increasing. The European Union focused on safety in the establishment of policies about functional foods, and indicated that safety was based on risk analysis [24]. Among these, misuses and overuse of ginseng which has been safely administered as a tonic and panacea in Asia for a long time and used as a functional food in Western countries, led to cardiovascular toxicity, renal toxicity, hepatotoxicity, hypertension, gynecomastia, affective disorder, allergy, QT prolongation and torsades de pointes [25].

Therefore, advertisements focusing on the effects reported by some studies on Jerusalem Artichoke, which has not been previously administered, without proper establishment of safety standards would lead to indiscreet use of Jerusalem Artichoke and consequently to dangerous conditions for patients. Thus, warning policies are needed.

For the mice of the Jerusalem Artichoke group that developed severe adverse effects, we were unable to obtain serum samples to identify inflammatory markers or to examine the conditions of the livers and spleens of dead mice. Finally, because electrolytes are excreted through kidneys, which would maintain homeostasis through normal renal function even if a large amount were administered, we did not measure electrolytes. However, measurement of electrolytes might be beneficial in this study.

In conclusion, this study verified that there is no glucose reducing effect of inulin and JAE, and inulin does not stimulate insulin secretion. Instead, severe adverse effects including death developed in 56% of mice in the Jerusalem Artichoke group. Therefore, we suggest that indiscreet administration of Jerusalem Artichoke endanger to patients and should be prohibited until its safety is established.

FUNDING

This study was performed with funding from the Honam branch of the Korean Diabetes Association.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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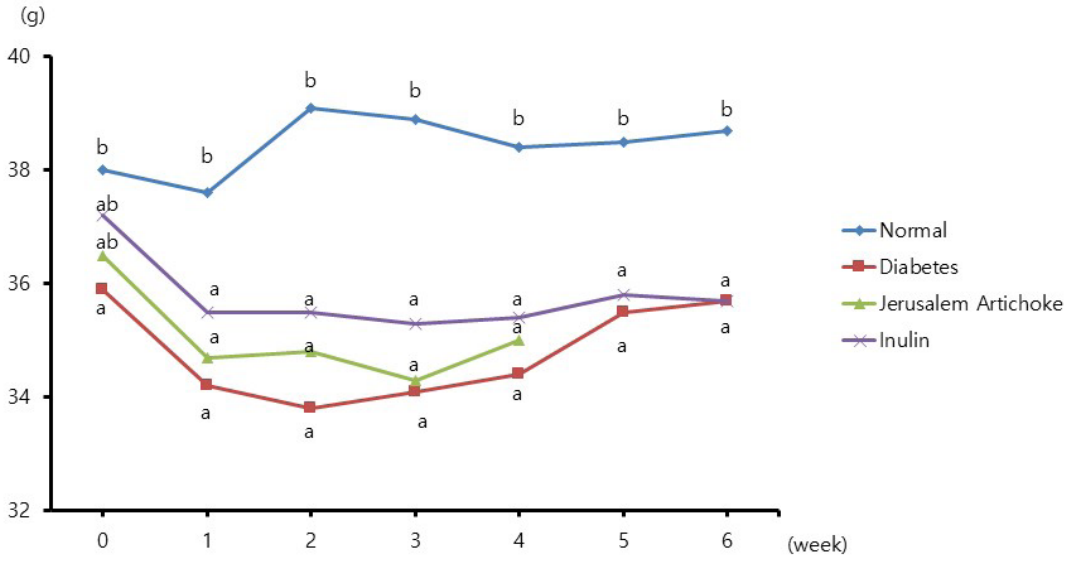
Supplements

Supplementary Table 1. The change of food intake in normal, diabetes, Jerusalem Artichoke, and inulin group

Week	Normal (g/wk)	Diabetes (g/wk)	Jerusalem Artichoke (g/wk)	Inulin (g/wk)
1	4.4 ± 0.3[a]	5.5 ± 1.0[b]	5.0 ± 0.7[ab]	5.6 ± 0.9[b]
2	6.0 ± 0.3[a]	7.5 ± 0.8[b]	6.6 ± 1.2[ab]	7.3 ± 0.9[b]
3	5.8 ± 0.3[a]	8.2 ± 1.1[b]	7.0 ± 1.7[ab]	7.6 ± 1.6[b]
4	5.6 ± 0.3[a]	8.8 ± 1.7[b]	6.8 ± 1.6[a]	8.3 ± 1.4[b]
5	5.9 ± 0.4[a]	8.5 ± 1.8[b]		8.1 ± 1.6[b]
6	5.8 ± 0.5[a]	8.0 ± 2.2[b]		8.2 ± 2.0[b]

Values are presented as mean ± standard deviation.
[a,b]Means in the same row not sharing a common superscript are significantly different among groups ($P < 0.05$).



Supplementary Fig. 1. Change of the body weight in normal, diabetes, Jerusalem Artichoke, and inulin group.
[a,b]Means not sharing a common letter are significantly different among groups ($P < 0.05$).

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