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The effects of Jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress in subjects with prediabetes or newly diagnosed type 2 diabetes

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The effects of Jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress in subjects with prediabetes or newly diagnosed type 2 diabetes

A Master's Thesis
Submitted to the Department of Science for Aging
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for the degree of Master in Science for Aging.

Cho Rong Seo

June 2015

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감사의 글

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그리고 논문 쓰는데 조언해주신 현영언니, 무엇이든 열심히 하시는 샘언니, 친구지만 배울 점이 많은 미향이, PBMC 실험 할 때 부터 하나하나 알려주신 영주언니, 밝은 에너지가 넘치는 아영언니, 성실한 하나, 첨단에서 나와 LDL particle size 실험하면서 정든 혜진이, NK Cell 실험하며 함께 고생 많이 한 윤욱오빠, 많이 친해지지 못해 아쉬운 민정이, 착한 후배인 민선이, 지수, 난희와 1학기 후배들 많은 도움 주셔서 깊은 감사의 인사를 드립니다.

오송에서 서울로 매일 통학하느라 힘들었는데 제가 택한 길이며 꿈이 있었기 때문에 포기할 수 없었습니다. 이제 끝이라 생각하니 시원섭섭하고 또 다른 시작을 앞두고 설레는 마음입니다.

많은 도움 주신 분들에게 부끄럼 없는 제가 되도록 더욱 열심히 살며 보답하도록 하겠습니다. 감사합니다.

2015년 6월

서 초 롱

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ABSTRACT

The effects of Jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress in subjects with prediabetes or newly diagnosed type 2 diabetes

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Objective: The objective was to evaluate the effect of jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress.

Methods: A randomized, double-blinded, placebo-controlled study was conducted on 60 subjects with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or newly diagnosed type 2 diabetes (T2DM). The subjects were randomly assigned to either a group ingesting 40 g jerusalem

artichoke and fermented soybean powder mixture supplementation daily or a placebo group for 12-week. We assessed fasting and postprandial levels of glucose, free fatty acid (FFA), homeostasis model assessment-insulin resistance (HOMA-IR), and oxidative stress markers.

Results: The jerusalem artichoke and fermented soybean powder mixture supplementation reduced fasting glucose (p=0.001) and FFA (p=0.008), glucose level at 60 min (p=0.004), and glucose (p=0.007) and FFA (p=0.044) areas under the response curve (AUC), and HOMA-IR (p=0.032). The jerusalem artichoke and fermented soybean powder mixture supplementation also decreased urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) (p=0.028). In addition, ∆ glucose at 120 min (r=0.472, p=0.027) and ∆ glucose AUC (r=0.572, p=0.005) correlated positively with ∆ plasma malondialdehyde (MDA) in the test group.

Conclusion: The consumption of jerusalem artichoke and fermented soybean powder mixture supplementation for 12 weeks reduced fasting and postprandial glucose and oxidative stress in subjects with IFG, IGT or newly diagnosed T2DM.

KEY WORDS: jerusalem artichoke; fermented soybean; prediabetes;

newly diagnosed type 2 diabetes; glucose; oxidative stress

1. INTRODUCTION

Diabetes is common chronic metabolic disease worldwide that results from the reduced function of organs, such as lack of insulin or insulin resistance [1]. According to the World Health Organization (WHO), 347 million people worldwide had diabetes in 2013 and diabetes will be the 7th cause of death by 2030 [2]. In 2010, the prevalence of diabetes worldwide was 6.4 % and will increase to 7.7 % by 2030 [3]. According to the '2013 Korean National Health and Nutrition Examination Survey', the incidence of diabetes increased 2 % since 2012 [4]. IFG, IGT or both are at high risk of progressing to T2DM that are risk for cardiovascular disease [5,6]. The progression of IFG or IGT to T2DM can be delayed or prevented by lifestyle change and pharmacological interventions [7]. According to the American Diabetes Association, medical nutrition therapy is an effective therapy in the management of diabetes [8].

Jerusalem artichoke is a root vegetable that the main component is fructans (fructose molecules connected by β-2,1 bonds), which are inulin and fructooligosaccharides [9]. Inulin and fructooligosaccharides have been reported to stimulate immune system, reduce the synthesis of triglycerides and fatty acids in the liver, and decrease the blood glucose levels [10]. Fermented soybean has been reported the antidiabetic effects in diabetic

animals and humans [11-13]. The previous study reported that combination of jerusalem artichoke and fermented soybean had complementary antidiabetic effects through potentiation of insulinotropic action and reduction of insulin resistance in diabetes rat [14]. Therefore, we hypothesized that this might be extrapolated to the human and the aim of this study was to investigate the effect of jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress.

2. BACKGROUND

2.1. Diabetes Mellitus diagnosis

The diagnosis of diabetes mellitus is based on plasma glucose criteria, both the Hemoglobin A1c (HbA1c) test and the fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT) (Table 1) [15].

Table 1. Criteria for the diagnosis diabetes

HbA1c ≥ 6.5 % *
OR
FPG ≥ 126 mg/dL (7.0 mmol/L) *
OR
2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT *
OR
In a patient with classic symptom of hyperglycemic or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

* In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing [15].

Normal blood glucose levels is defined when postprandial blood glucose concentration is under the 140 mg/dl or fasting blood glucose concentration is 70-100 mg/dl [15].

Both IGT and IFG are not diabetes mellitus correctly, but they are considered as 'prediabetes'. So they mean blood glucose levels are higher than nomal and, a high potential of progress to diabetes (Table 2) [16]. Impaired glucose regulation is related to a high rate of cardiovascular disease (CVD) and CVD motality [17-18].

Table 2. Categories of increased risk for diabetes (prediabetes)

IGT	2-h plasma glucose in the 75 g OGTT 14 mg/dL (7.8 mmol/L) to 199 mg/dL(11.0 mmol/L)
	OR
IFG	FPG ≥100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)
	OR
HbA1c ≥ 6.5 %	5.7 – 6.4 % *

* For all there tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range [15].

2.2. *Helianthus tuberosus L.*

2.2.1. The characteristics of *Helianthus tuberosus L.*

Helianthus tuberosus L., also known as 'Jerusalem artichoke', is a perennial plant that originated in North America, but grows throughout Korea due to suitable climatic conditions.

The main component of *Helianthus tuberosus L.* is inulin, a fructose polymer (fructose molecules connected by β-2,1 bonds) [19] that accounts for 75 % of the *Helianthus tuberosus L.* dry weight [20]. *Helianthus tuberosus L* is a perennial grass 1~3 m tall, with an irregularly shaped rhizome. Its straight stem branches at the top, with short and tough hair or bristles.

2.2.2. The effects of *Helianthus tuberosus L.*

Inulin is a dietary fiber common to a number of tuberous plants such as chicory, yacon, and dahlia in addition to *Helianthus tuberosus L*. It has been reported to relieve constipation, prevent intestinal diseases, and reduce serum cholesterol, serum lipid, and blood sugar levels [21]. Therefore, there is growing need to scientifically examine the functionality of *Helianthus tuberosus L.* using standardized inulin content to test its effects on blood sugar in appropriate human subjects. Based on previous clinical studies, the Ministry of Food and Drug Safety (MFDS) has approved inulin for ‘blood cholesterol improvement,’ ‘inhibition of blood sugar increase after meals,’ and ‘contribution to active bowel movement’ [22].

2.3. Fermented soybean paste

2.3.1. Characteristics of fermented soybean paste

Fermented soybean paste is a traditional fermented food that is ubiquitous in Korea's dietary culture. It offers great nutritional value and is a valuable protein source in the standard grain-rich Korean diet. Along with other types of pastes, fermented soybean paste has been an important protein source for Koreans, who have traditionally had a relatively low protein intake. It is a highly nutritious food that is higher in protein and fat than bean or chili pastes [23].

Because *Bacillus* species are responsible for the fermentation, enzymes and various bioactive substances are found in fermented soybean paste that are not present in soybeans. Bacteria such as *B. Subtilis* or *B. licheniformis* weaken the activity of intestinal saprogenic bacteria, have antibacterial effects on pathogens, and even adsorb and excrete toxins [24].

In addition, bioactive substances produced during the fermentation process have been reported to be effective in chronic degenerative diseases, increasing awareness of fermented soybean paste [25].

2.3.2. The effects of fermented soybean paste

Soybeans have long been known to have positive effects on diabetes in Korea, and several studies proved its effectiveness in decreasing blood sugar levels and blood lipid concentrations [26-28].

Kwon *et al.* [29] reported suppression of the increase in post-meal blood sugar levels when diabetic animal models were provided short-term diets containing soybean or fermented soybean paste. This is likely because soybean or fermented soybean paste inhibits the activity of carbohydrate digestive enzyme (α-glucosidase) in the small intestine, and soluble dietary fiber from soybean or fermented soybean paste slows the movement of food in the digestive tract.

Pinitol, a sugar alcohol of soybeans, is converted to chiro-inositol, which complements the insulin signal transduction system in tissues and lowers blood sugar, thereby exerting an anti-diabetic effect [30].

Other studies reported that supplementing mice with soybean powder or fermented soybean paste resulted in decreased blood sugar levels, as well as reduced glycosylated hemoglobin and serum lipid concentrations. Supplementing fermented soybean paste in particular, rather than soybean powder, reportedly had a superior effect on blood sugar control and improved lipid metabolism [31].

Soybean intake suppresses obesity and improves insulin resistance, and may therefore contribute to diabetes prevention and treatment [32-33].

2.4. The beneficial effects of combined Jerusalem artichoke powder and fermented soybean paste

Thus, a combination of *Helianthus tuberosus L.* powder and fermented soybean paste may have a synergetic effect on blood sugar control and blood control mechanisms due to increased insulin secretion and decreased insulin resistance induced by fermented soybean paste and *Helianthus tuberosus L*, respectively. A previous study reported that a 5 % combination of *Helianthus tuberosus L.* powder and fermented soybean paste [34] added to the diet of sprague-dawley (SD) rats significantly decreased blood sugar levels, increased insulin secretion, and decreased insulin resistance based on results of OGTT.

Therefore, this study aimed to inulin, the major component of *Helianthus tuberosus L*., based on nonclinical studies, and to verify its effects on blood sugar control in humans with the expectation of synergetic effects on blood sugar control with added fermented soybean paste, in order to develop a functional food with high value.

3. SUBJECTS AND METHODS

3.1. Study subjects

Participants were included in age between 20 and 70 year old and recruited from the outpatient clinics at Ilsan hospital (Gyeonggi-do, Korea) and advertisements in local newspaper. After the glucose screening test, subjects with IFG (100 mg/dL ≤ IFG ≤ 125 mg/dL) or IGT (140 mg/dL ≤ IGT ≤ 199 mg/dL 2-h OGTT) or newly diagnosed T2DM (fasting glucose ≥ 126 mg, blood glucose ≥ 200 mg/dL 2-h OGTT) were enrolled in the study.

Exclusion criteria that all selected patients met were:

- Having insulin injections or taking glucose-lowering medications
- Having an evidence or alcoholism
- Pregnant of in breast feeding
- Having chronic gastrointestinal disorders
- Patients with serious kidney problems
- Patients with serious liver problems
- Other patients who were considered unsuitable for this study by the researchers

60 study subjects with IFG or IGT were enrolled and they gave written consent forms for the study, which protocol was approved by the Institutional Review Board of Yonsei University.

3.2. Study design and test product

This study was a randomized, double-blind, placebo-controlled intervention trial, lasting a total of 12 weeks. The study subjects were assigned randomly to either test group (n=30) or placebo group (n=30) and study design is presented below (Figure 1).

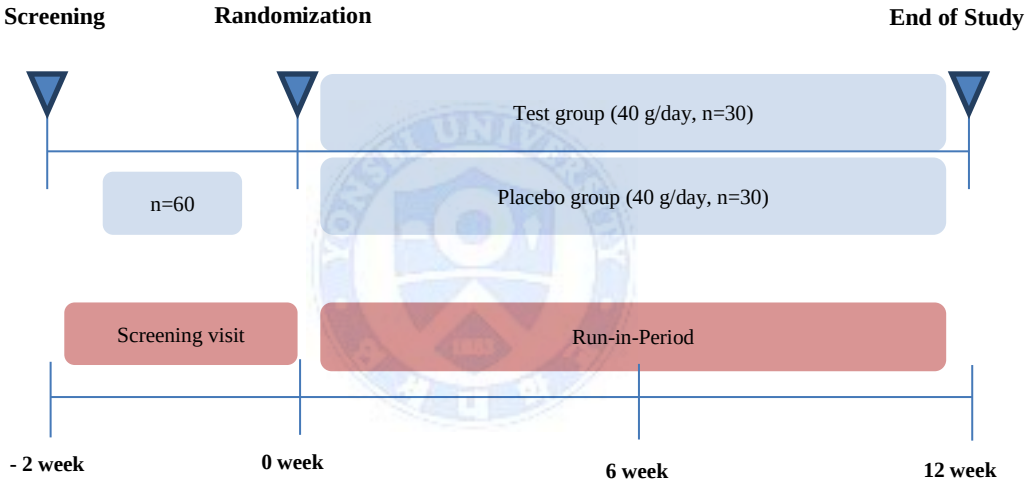


Figure 1. Study design

Participants were randomly assigned to the test group or the placebo group. 8 people gave up the middle among the study participant total 60 peoples due to the personal private. The compliance of the test product 5 people was dropped because of 80 % less than over the study period. The

test group (n=22) consumed a combination of *Helianthus tuberosus L.* powder and fermented soybean paste before each meal (3 times/day for 12 weeks). And the placebo group (n=25) consumed powdered rice flour before each meal (3 times/day for 12 weeks). The products were provided by Midari Farm (Yeongwol, Kangwon-Do, Korea). Composition of test product and placebo product is shown in Table 3.

Table 3. Composition of test product and placebo product

Test product		
	Component	Content (%)
Main component	A combination of *Helianthus tuberosus L.* powder and fermented soybean paste	97.27
Excipien	Cornstarch	2.65
	Caramel Color	0.07
	L-mentol	0.01
total		100
Placebo product		
	Component	Content (%)
Excipien	Rice flour	84.71
	Cornstarch	2.32
	Caramel Color	0.003
	L-mentol	0.01
	Water	12.96
total		100

Participants met with the investigational team at four different time points : screening (Week 2), randomization and treatment baseline (Week 0), treatment midpoint (Week 6), and treatment endpoint (Week 12). Daily intake were measured 24-hour recall method and physical activity at week 0, week 6, and week 12 of the treatment period. Compliance with study restrictions and products consumption was monitored via daily document by participants on individualized study calendars and end-study count of returned products.

3.3. Materials and methods

3.3.1 Dietary food intake and total energy expenditure

Usual food intake assessed using a 24-hour recall method and a semiquantitative food frequency quency questionnaire (FFQ) [35].

Total nutrient intake was examined and calculated based on the 3-day dietary records using the Computer Aided Nutritional Analysis Program (CAN-pro 3.0, Korean Nutrition Society, Seoul, Korea).

Total energy expenditure (TEE, kcal/day) was calculated based on basal metabolic rate (BMR), the activity patterns of participants, 24-hour physical activity [36], and the food specific dynamic action. The BMR for each subject was calculated with the Harris-Benedict equation [37].

3.3.2. Anthropometric parameters, blood pressure, and blood and urine collection

Height and weight were measured in the morning and Body Mass Index (BMI) was by the standard formula (kg/m^2). Waist and hip circumferences were measured using a flexible measuring tape and used to calculate the waist to hip ratio (WHR). Blood pressure (BP) was measured in the left arm with an automatic BP monitor (EASY X 800, Jawon Medical,

Republic of Korea). After a 12-hour fast period, venous blood specimens were collected in ethylenediaminetetraacetate (EDTA) treated tubes and plain tubes that were centrifuged to produce plasma and serum. Urine was collected in polyethylene bottles containing 1 % butylated hydroxytoluene. The collected samples were stored at -70 ℃ until analysis.

3.3.3. Serum lipid profiles

TG and Total serum cholesterol (T-chol) were measured using available kits on Hitachi model 7600 autoanalyzer (Hitachi Ltd., Tokyo, Japan). High density lipoprotein cholesterol (HDL-C) in the supernatant was measured by an enzymatic method. Low density lipoprotein cholesterol (LDL-C) was indirectly estimated for subjects using the Friedewald Formula with serum TG levels<400 mg/dL (4.52 mol/L) [Friedewald formula ; LDL-chol = T-chol – {HDL-chol – (TG × 0.2)}].

3.3.4. Blood glucose level, related biomarkers, and free fatty acids (FFA)

Serum glucose was measured using a hexokinase method with a Hitachi 7600 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). Serum insulin was measured by an immunoradiometric assay kit from DIA source ImmunoAssays S.A. (Louvain, Belgium). IR was calculated by the HOMA using the following equation: HOMA-IR=[Fasting insulin (μIU/mL) × Fasting glucose (mmol/L)] / 22.5. Serum C-peptide was measured by an immunoradiometric (IRMA) assay with a C-peptide IRMA kit (Immunotech, Czech). HbA1c was measured by an Immunoturbidimetric analyzer with a turbidimeter. FFA were measured by an enzymatic assay using the acylCoA synthetase-acylCoA oxidase (ACS-ACOD) method with a Hitachi 7600 Autoanalyzer (Hitachi Ltd., Tokyo, Japan).

3.3.5. Urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) and plasma malondialdehyde (MDA)

Urinary 8-epi-PGF_{2a} was measured by a urinary isoprostane ELISA kit (Oxford Biomedical Research Inc., Rochester Hills, MI). Urinary creatinine levels were determined using an alkaline picrate (Jaffe) reaction. Plasma MDA was measured using thiobarbituric acid-reactive substances (TBARS) by a TBARS Assay Kit (ZeptoMetrix Co., Buffalo, NY).

3.3.6. Statistical analysis

Statistical analysis was performed with SPSS version 21.0 (IBM/SPSS Corp. Chicago, IL, USA). A paired t-test with the Wilcoxon signed rank test was evaluated to compare the effect within each group both before and after intervention. An independent t-test with the Mann-Whitney U-test was evaluated to compare net change between the test and placebo groups. The logarithmic transformation was performed on skewed variables. The results were expressed as mean ± SE and a *p*-value < 0.05 was considered statistically significant.

4. RESULTS

4.1. The clinical and biochemical characteristics at baseline

The clinical and biochemical characteristics of the placebo and test groups were showed in Table 4. There was no significant difference between the groups in baseline characteristics (*i.e*. age, sex distribution, height, weight, BMI, WHR, BP, serum lipid profiles, HbA1c, glucose, insulin, HOMA-IR, C-peptide, FFA, or MDA). Urinary 8-epi-$PGF_{2\alpha}$ was significantly different between two groups at baseline (p=0.032). Estimated total calorie intake (TCI), TEE, BMR, % carbohydrate intake, % protein intake, and % fat intake did not significantly differ between groups (data not shown).

Table 4. Clinical and biochemical characteristics of placebo and test groups at baseline

	Total (n=47)		*P*
	Placebo group (n=25)	**Test group (n=22)**	
Age (year)	56.0±1.28	54.4±1.31	0.390
Male/Female n, (%)	10 (40.0) / 15 (60.0)	4 (18.2) / 18 (81.8)	0.102
Height (cm)	161.6±1.24	158.9±1.38	0.154
Weight (kg)	64.3±1.72	60.4±2.35	0.188
BMI (kg/m^2)	24.6±0.50	23.8±0.63	0.336
WHR	0.90±0.01	0.88±0.01	0.387
Systolic BP (mmHg)	128.5±2.69	127.4±3.17	0.801
Diastolic BP (mmHg)	79.5±1.72	82.2±1.83	0.291
Total-chol (mg/dL)[f]	193.7±5.29	201.6±6.03	0.320
HDL-chol (mg/dL)[f]	51.6±1.91	58.0±2.77	0.076
LDL-chol (mg/dL)[f]	119.9±4.90	120.9±6.38	0.993
TG (mg/dL)[f]	110.9±10.1	114.0±13.1	0.976
HbA1c (%)[f]	5.96±0.07	5.99±0.14	0.909

Table 4. ***(continued)***

	Total (n=47)		*P*
	Placebo group (n=25)	**Test group (n=22)**	
Glucose (mg/dL)[ƒ]	107.6±1.48	107.2±1.68	0.839
Insulin (μIU/dL)[ƒ]	9.92±0.55	10.1±0.84	0.969
HOMA-IR	2.66±0.17	2.71±0.25	0.937
C-peptide (μEq/L)[ƒ]	2.16±0.12	2.21±0.16	0.977
Free fatty acid (μEq/L)[ƒ]	572.4±42.0	663.2±50.5	0.132
8-epi-$PGF_{2\alpha}$ (pg/mg creatinine)[ƒ]	1699.4±141.0	2427.7±284.6	0.032
Malondialdehyde (nmol/mL)[ƒ]	8.68±0.35	8.33±0.27	0.685

Mean ± SE. [ƒ]Tested by logarithmic transformation, *P*-values derived from independent *t*-test with the Mann-Whitney U-test.
HOMA-IR: {fasting insulin (μIU/mL) × fasting glucose (mmol/L)}/22.5, 8-epi-PGF2α: urinary 8-epi-prostaglandin $F_{2\alpha}$.

4.2. The effects of a 12-week consumption of jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose level

Except for blood glucose level, HOMA-IR, FFA, and urinary 8-epi-$PGF_{2\alpha}$, there were no significant mean changes in any of the tested clinical and biochemical characteristics between the placebo and test groups (data not shown). After 12 weeks of treatment, the test group showed a significant decrease in serum level of blood glucose at 0 min (p=0.001), 60 min (p=0.004), and glucose AUC (p=0.007) (Table 5). The change in serum level of blood glucose at 60 min (p=0.013), 120 min (p=0.021), and glucose AUC (p=0.012) in test group was significantly different from the placebo group.

Table 5. Blood glucose level and glucose related biomarkers of study participants

	Total (n=47)							
	Placebo group (n=25)		Test group (n=22)		P^a	P^b	P^c	P^d
	Baseline	Follow-up	Baseline	Follow-up				
Glucose 0 min (mg/dL) $^{\phi}$	107.6±1.48	101.3±1.73**	107.2±1.68	97.7±2.63***	0.839	0.193		
Change	-6.28±1.78		-9.45±1.90				0.230	0.210
Glucose 30 min (mg/dL) $^{\phi}$	189.2±6.36	185.6±6.56	189.7±9.73	186.8±8.17	0.849	0.956		
Change	-3.56±4.84		-2.91±8.86				0.947	0.963
Glucose 60 min (mg/dL) $^{\phi}$	192.3±9.88	195.8±9.51	205.2±11.8	181.3±12.0**	0.402	0.243		
Change	3.56±7.28		-23.9±7.74				**0.013**	**0.021**
Glucose 120 min (mg/dL) $^{\phi}$	153.4±8.71	166.5±11.5	167.7±11.2	154.0±11.8	0.367	0.463		
Change	13.1±8.22		-13.7±7.51				**0.021**	**0.031**
Glucose AUC (mg/dL×h) $^{\phi}$	342.4±13.1	348.3±14.5	359.4±17.3	330.8±16.3**	0.470	0.378		
Change	5.86±9.05		-28.6±9.45				**0.012**	**0.017**
Free fatty acid 0 min (μEq/L) $^{\phi}$	572.4±42.0	647.6±43.6	663.2±50.5	563.7±26.2*	0.132	0.175		
Change	75.2±45.9		-99.5±41.6				**0.008**	**0.027**

Table 5. ***(continued)***

	Total (n=47)							
	Placebo group (n=25)		Test group (n=22)		P^a	P^b	P^c	P^d
	Baseline	Follow-up	Baseline	Follow-up				
Free fatty acid 30 min (μEq/L) $^{\phi}$	304.6±23.5	350.2±30.3	334.8±41.4	327.1±32.6	0.986	0.652		
Change	45.6±23.6		-7.77±38.8				0.234	0.163
Free fatty acid 60 min (μEq/L) $^{\phi}$	251.2±27.5	281.8±30.6	251.6±33.3	254.5±40.3	0.935	0.268		
Change	30.6±20.8		2.86±27.7				0.421	0.400
Free fatty acid 120 min(μEq/L) $^{\phi}$	92.4±4.40	84.5±5.48	104.2±13.9	88.1±9.80	0.961	0.794		
Change	-7.92±5.18		-16.1±13.2				0.569	0.429
Free fatty acid AUC (μEq/L×h) $^{\phi}$	530.0±29.2	590.6±30.4	574.0±39.2	539.3±34.5	0.401	0.237		
Change	60.6±33.5		-34.7±30.8				**0.044**	0.066

Mean ± SE. $^{\phi}$tested by logarithmic transformation, P^a-values derived from independent t-test in baseline with the Mann-Whitney U-test. P^b-values derived from independent t-test in follow-up with the Mann-Whitney U-test. P^c-values derived from independent t-test with the Mann-Whitney U-test in Changed value. P^d-values adjusting for baseline. *P <0.05, **P <0.01, ***P <0.001 derived from paired t-test with the Wilcoxon signed rank test. AUC: area under the curve.

4.3. The effects of a 12-week consumption of jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose related biomarkers

The 12 weeks intervention with jerusalem artichoke and fermented soybean powder mixture supplementation resulted a significant reduction in HOMA-IR (p=0.032) (Figure 2). Serum FFA level at 0 min in the test group showed a significant decrease after 12-week intervention (p=0.034) (Table 5). The change in serum level of FFA at 0 min (p=0.008), and FFA AUC (p=0.044) in test group was significantly different from the placebo group.

HOMA-IR

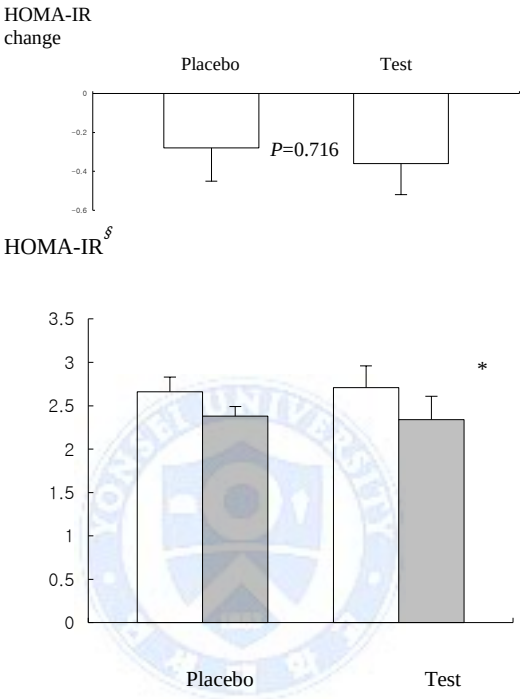


Figure 2. HOMA-IR at initial visit (□) and at 12-week follow-up (■) and mean changes according to treatment

Mean ± SE. §Tested by logarithmic transformation. P-values determined using an independent t-test with the Mann-Whitney U-test. *P<0.05 compared with baseline values in each group as determined by paired t-test with the Wilcoxon signed rank test.

4.4. The effects of a 12-week consumption of jerusalem artichoke and fermented soybean powder mixture supplementation on oxidative stress markers

After 12 weeks of treatment, the test group showed a significant decrease in urinary 8-epi-$PGF_{2\alpha}$ (p=0.028) and the placebo group showed a significant increase in urinary 8-epi-$PGF_{2\alpha}$ (p=0.040) (Figure 3). The change in urinary 8-epi-$PGF_{2\alpha}$ in test group was significantly different from the placebo group (p=0.003). In the test group, Δ glucose 120 min was positively correlated with Δ MDA (r=0.472, p=0.027), and Δ glucose AUC was positively correlated with Δ MDA (r=0.572, p =0.005) (Figure 4).

Urinary 8-epi-PGF$_{2\alpha}$

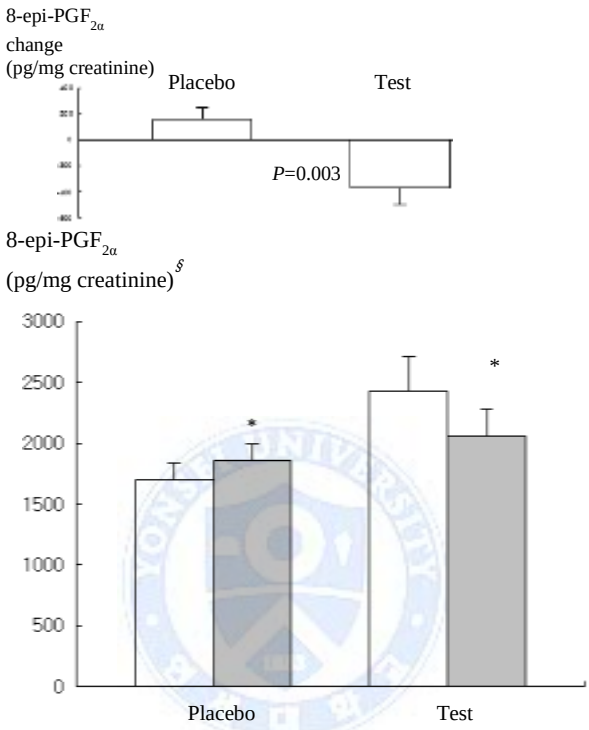


Figure 3. Urinary 8-epi-PGF2α levels at initial visit (□) and at 12-week follow-up (■) and mean changes according to treatment.

Mean ± SE. §Tested by logarithmic transformation. *P*-values determined using an independent t-test with the Mann-Whitney U-test. *$P<0.05$ compared with baseline values in each group as determined by paired t-test with the Wilcoxon signed rank test.

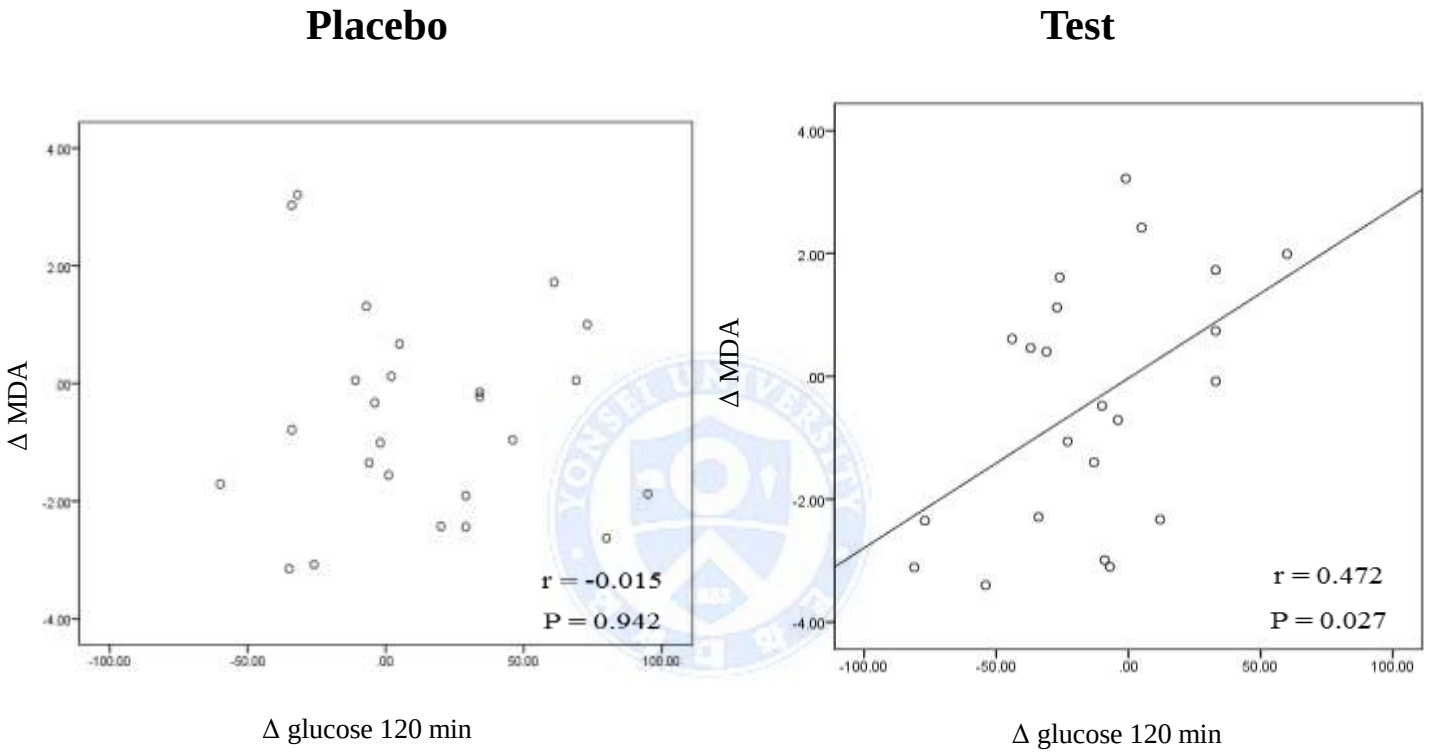
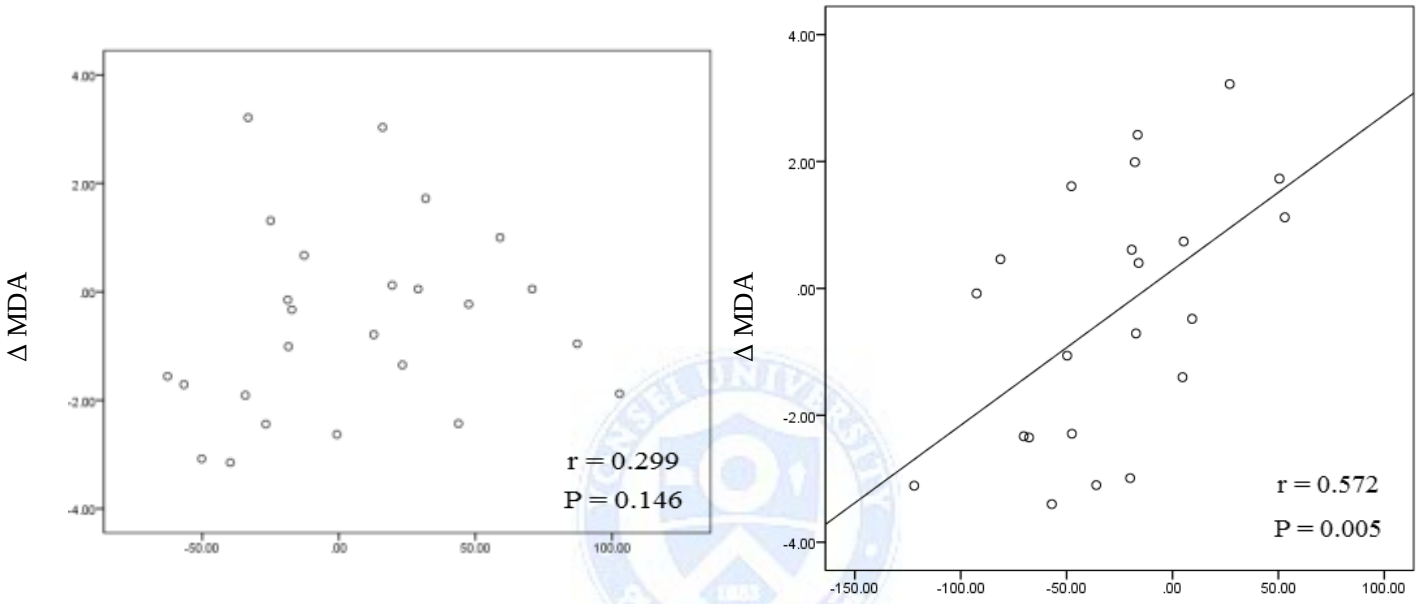


Figure 4. Correlation between changes (difference from baseline) in blood glucose level and plasma MDA in the placebo and test groups.



r : Spearman's correlation coefficients.

Figure 4. ***(continued)***

5. DISCUSSION

The antidiabetic effects of jerusalem artichoke and fermented soybean have raised interest in recent years. The antidiabetic mechanisms of jerusalem artichoke and fermented soybean might be different. Therefore, we hypothesized that the combination of the jerusalem artichoke and fermented soybean might have a synergy. This randomized, double-blind, placebo-controlled study evaluated the effect of jerusalem artichoke and fermented soybean powder mixture supplementation on glucose control in subjects with IFG, IGT, or newly T2DM. The 12 weeks intervention with jerusalem artichoke and fermented soybean powder mixture supplementation resulted in an improvement in blood glucose and glucose related biomarkers as well as a reduction in oxidative stress.

Main component of jerusalem artichoke is fructans, which were inulin and fructooligosaccharides that were not absorbed in the intestines [38]. Therefore, consumption of jerusalem artichoke did not affect insulin levels and the present study showed that jerusalem artichoke and fermented soybean powder mixture supplementation had not effect on insulin levels. The previous study showed that fructooligosaccharides supplementation reduced the fasting plasma glucose levels after 2 weeks in T2DM [39]. Other clinical trial demonstrated antidiabetic effect of inulin-enriched pasta

in human, which reduced fasting glucose levels, HbA1c and HOMA-IR [40]. The *in vivo* studies reported that jerusalem artichoke supplementation improved IR and decreased the OGTT [41] and plasma glucose level decreased with increasing level of supplemented jerusalem artichoke [42]. Inulin and fructooligosaccharides might affect glucose levels by changing the secretion of glucagon-like peptide-1 (GLP-1), which increased insulin secretion, delayed gastric emptying, promoted β-cell proliferation, and reduced β-cell apoptosis [43-47]. The mechanisms of hypoglycemic effect by jerusalem artichoke remains largely obscure.

In clinical trial, fermented soybean product consumption decreased fasting blood glucose and HbA1c after 3 months in borderline and mild T2DM subjects [48]. The previous studies showed that long-term consumption of fermented soybean attenuated IR and improved glucose homeostasis in type 2 diabetic animal model [11,49]. The biologically active components of fermented soybean were isoflavonoids and small peptides that are associated with insulin resistance and glycemic control [50,51]. The potential mechanisms could be explained the antidiabetic effect of fermented soybean. According to the previous study, isoflavonoids might have antidiabetic effect through estrogen-like action. Estrogen might reduce insulin resistance through inhibition of intestinal glucose uptake and

prevention of glucose-induced lipid peroxidation by decreasing sodium-dependent glucose transporter [52]. In addition, estrogen might be associated with the stimulation of liver fatty acid metabolism and suppression of hepatic glucose production [53]. FFA was known to cause insulin resistance by inhibiting insulin-stimulated glucose uptake. High level of plasma FFA was associated with to increase diacylglycerol and to activate protein kinase C, which leading to increased tyrosine phosphorylation of the insulin receptor substrate-1 and resulting in increased insulin-stimulated glucose transport activity and IR [54,55]. The present study showed that jerusalem artichoke and fermented soybean powder mixture supplementation decreased FFA and IR that might be explained by isoflavonoids of fermented soybean.

T2DM was associated with oxidative stress and lipid peroxidation was the main marker of oxidative stress that played the major role in the pathogenesis of T2DM [56]. 8-epi-$PGF_{2\alpha}$ was secondary end products of peroxidation that could impair β-cell function and lead to apoptosis [57]. Improved metabolic control reduced 8-epi-$PGF_{2\alpha}$ by 32 % in T2DM patients [58] and the clinical trial reported that 8-epi-$PGF_{2\alpha}$ was threefold higher in T2DM patients than in healthy individuals [59]. Therefore, level of 8-epi-$PGF_{2\alpha}$ presented the diabetic state.

In present study, we observed that 8-epi-$PGF_{2\alpha}$ significantly decreased in the test group. Jerusalem artichoke and fermented soybean powder mixture supplementation had an effect on reduction of oxidative stress in subjects with IFG, IGT, or newly diagnosed T2DM. MDA was a primary biomarker of free radical mediated lipid damage and oxidative stress that was elevated in T2DM patients [60-62]. The previous finding could explain the positive correlation between changes in glucose with changes in MDA in the test group of this study that presented lipid peroxidation was related to glycemic control and affected by jerusalem artichoke and fermented soybean powder mixture supplementation. The result of present study was concluded that inulin of jerusalem artichoke and isoflavonoids of fermented soybean might affect complementary glucose control and jerusalem artichoke and fermented soybean powder mixture supplementation was able to improve the already existing oxidative stress in subjects with IFG, IGT, or newly diagnosed T2DM.

There are several limitations in our study design. First, we specifically focused on Korean subjects with IFG, IGT, or newly diagnosed T2DM. Therefore, our data cannot be generalized to other ethnic groups or severe T2DM patients. Second, because of the small sample size, the results should be interpreted with caution. Despite these limitations,

jerusalem artichoke and fermented soybean powder mixture supplementation for 12 weeks showed antidiabetic and antioxidant effects in IFG, IGT, or newly diagnosed T2DM subjects.

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국문 요약

당뇨 전 단계 또는 초기 제 2형 당뇨병 환자의 혈당 및 산화스트레스에 대한 돼지감자 청국장 분말 섭취의 효과

당뇨병은 만성대사성 질환으로 전 세계적으로 유병률이 증가하고 있으며, 당뇨 전 단계인 공복혈당장애와 내당능장애는 당뇨병뿐만 아니라 심혈관계 질환을 유발할 수 있는 위험인자로 대두되고 있다. 당뇨와 심혈관계 질환을 예방하고 삶의 질을 높이기 위해서는 효과적인 혈당의 조절이 중요하다고 할 수 있다.

돼지감자 (*Helianthus tuberosus L.*)는 국화과 해바라기속의 다년생 식물로 주 성분은 Fructose 중합체 (Fructose 분자들이 β-2,1 결합으로 연결)인 Inulin이며 식품의약품안전처는 현재까지 수행된 인체적용시험 중심으로 Inulin의 '혈중 콜레스테롤 개선', '식후 혈당상승 억제', '배변활동 원활에 도움을 줄 수 있음'의 기능성을 인정하고 있다.

청국장은 예로부터 우리나라의 식생활에서 빠질 수 없는 대두를

발효한 전통발효식품으로 단백질 섭취량이 비교적 적은 한국인에게 장류와 함께 단백질의 중요한 공급원이었다. 콩의 섭취가 비만을 억제하고, 인슐린 저항성을 개선시켜 당뇨병의 예방 및 치료에 도움을 주는 것으로 여러 연구에서 콩의 혈당 및 혈중 지질농도 저하효과가 입증되었다.

따라서, 본 연구에서는 규명된 작용기전을 통해 돼지감자와 청국장의 시너지 효과를 기대하며 사람을 대상으로 혈당조절 기능성을 검증함으로서 고부가가치의 건강기능식품을 개발하는 것을 목표로 연구를 진행시키고자 하였다.

본 연구에서는 무작위 배정, 이중맹검, 플라시보 대조 디자인의 인체적용시험을 통하여 공복혈당장애 및 내당능장애 및 초기당뇨를 가진 대상자에게서 돼지감자 청국장 분말의 섭취가 혈당조절과 산화스트레스에 미치는 영향을 평가하였다.

공복혈당장애, 내당능장애, 초기 당뇨병 환자 60명을 대상으로 돼지감자 청국장 분말 또는 플라시보를 12주간 섭취하도록 한 후, 혈당, 혈당반응면적, 인슐린, C-peptide, FFA, 8-epi-$PGF_{2\alpha}$, MDA 등을 측정하여 섭취 전후의 유의적 변화가 있는지 확인하고, 대조군과 실험군 간의 유의적 차이가 있는지 검정하였다.

그 결과 실험군은 혈청에서의 공복혈당 (p=0.001)과 유리지방산 (p=0.008)이 유의적으로 감소하였고, 혈청에서 분석한 60분째 혈당이 205.2±11.8 mg/dL에서 12주 후 181.3±12.0 mg/dL (p=0.004)로 크게 감소하였다.

혈당관련 바이오마커인 혈당반응면적 (p=0.007)과 인슐린저항성 (p=0.032), 0분에서 혈청의 유리지방산 (p=0.034) 또한 유의적으

로 감소하였다. 또한 산화스트레스 지표인 8-epi-PGF_2는 12주 후 실험군 (p=0.003)과는 다르게 대조군 (p=0.040)은 증가하였고, 실험군에서 혈당수치과 혈장 MDA에서 베이스라인과 다르게 상관관계를 보였다.

결론적으로 본 연구에서는 당뇨병 전 단계인 공복혈당장애와 내당능장애, 초기 당뇨병 대상자들에게 12주 간 식사 전 1일 3회 (40 g) 의 돼지감자 청국장 분말을 섭취시켰을 때 공복혈당 및 식후혈당과 산화스트레스 관련 지표가 개선되는 것을 볼 수 있었다.

앞으로의 연구에서 좀 더 정확한 결과를 얻기 위해서는 대상자 수를 더 확보하고 용량을 세분화한 후속 연구가 필요할 것으로 사료된다.

핵심 용어 : 당뇨 전 단계; 초기 제 2형 당뇨; 돼지감자; 청국장; 혈당; 산화스트레스