

Effect of Oral Administration of Jerusalem Artichoke Inulin on Reducing Blood Lipid and Glucose in STZ-Induced Diabetic Rats

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Abstract: This study was carried out to investigate the effect of inulin extracted from Jerusalem artichoke (*Helianthus tuberosus*) on decrease of blood lipids and blood glucose in STZ-induced diabetic rats. The oral administration of inulin decreased blood lipids and blood glucose, implying the utility of artichoke-extracted inulin as a bioactive material to prevent metabolic diseases related to blood lipids and blood glucose of humans. Twenty four white rats were completely randomly allocated into four treatment groups with six rat per group and inulin was orally administrated to them. The experimental treatment groups were divided into one Normal Control group (NC) and three diabetic groups. The diabetic groups consisted of DC (diabetic control group), DC 50 (diabetic control group+oral administration of inulin, 50 mg kg⁻¹ body weight) and DC 100 (diabetic control group+oral administration of inulin, 100 mg kg⁻¹ body weight). Concerning growth performance, in comparison with the DC group, daily weight gain in the inulin-administered rats increased and recovered to the normal level. The diet intake was significantly low in the inulin-administrated groups ($p < 0.05$) while statistically significant difference in the dietary efficiency between the DC and the inulin-administrated groups and between NC and the inulin-administrated groups was not found. Blood glucose was significantly lowered in the inulin-administrated groups ($p < 0.05$). Compared with DC, the decrease of blood glucose in the inulin-administrated groups was 60.73-63.4% in the 4th week and showed a tendency of gradual recovery. Triacylglycerides in the blood, total cholesterol, LDLC and atherogenic index were significantly decreased by 27.13-32.91, 22.42-23.31, 35.41-38.28 and 49.71-57.11%, respectively in the inulin-administrated groups compared to the DC group. Conversely, HDLC was significantly increased by 24.89-47.20% ($p < 0.05$). The weights of liver, kidney and heart but not the spleen were significantly heavy in the DC group, compared with the inulin-administrated groups ($p < 0.05$).

Key words: Inulin, Jerusalem artichoke, blood lipid, blood glucose, diabetic rats, national

INTRODUCTION

As the South Korean economy has grown and the national income has increased, the average diet has become more westernized and the incidence rate of type 2 Diabetes Mellitus (DM) has gradually increased (Ministry of Health and Welfare, 2009; Halton *et al.*, 2008). DM is a metabolic disease that has glucose excreted with urine and causes disorders of protein, lipid and electrolyte metabolism as glucose in the blood increases, resulted from disorders of carbohydrate metabolism in the body due to short of insulin secreted from β -cell of Langerhans inlets in the pancreas (Wolf *et al.*, 2005; Rayfield and Ishimura, 1987; Abrams *et al.*, 1982; Tisch and McDevitt, 1996). DM is classified as type 1 DM which is insulin dependent and which presently requires insulin injections and type 2 DM which is non-insulin dependent and is caused by increased insulin resistance in the affected peripheral tissues of muscles, liver and fat cells by living

habits such as obesity, lack of exercise, smoking, and alcohol consumption. DM typically causes disorders of lipid metabolism such as increased Triacylglyceride (TAG) in the blood, total cholesterol, Low Density Lipoprotein Cholesterol (LDLC) and atherogenic index and decreasing High Density Lipoprotein Cholesterol (HDLC) which result in serious complications (Treadway *et al.*, 2001; Steinberg *et al.*, 1996; Hayden and Reaven, 2000). DM may increase death rate due to complications such as cerebrovascular or cardiovascular diseases or hypertension caused by decreased activities of anti-oxidative enzymes and resulting increased oxidative stresses in the body (Jerums *et al.*, 2003; Giugliano *et al.*, 1996; Jang *et al.*, 1998; Chapman and Chapman, 1980).

Inulin is a non-degradable oligosaccharide polymer comprised of 30-35 fructose units that are linearly-arranged in a β -1, 2 linkage with an α -1, 2 linked D-glucose at the non-reducing end (Niness, 1999). The compound which is naturally present in plants wheat, onion, garlic,

banana and in bulbs of Compositae plants such as Jerusalem artichoke (*Helianthus tuberosus*), chicory, dahlia and dandelion (Lingyun *et al.*, 2007; Lopez-Molina *et al.*, 2005) has become a popular constituent of functional foods because of its' efficacy in decreasing blood lipids (Kelly, 2008).

Of the natural sources of inulin, Jerusalem artichoke has attracted much interest. The perennial plant belonging to Compositae, Complanulaceae, Dicotyledoneae, originated from North America. In South Korea where the climate is hospitable, it grows naturally nationwide. The plant whose contents are 14-19% inulin has emerged newly as a beneficial constituent of anti-diabetic prebiotics whose bioactivities include reduction of blood lipids, prevention of intestinal diseases, improvement of constipation and hypoglycemic activity (Gibson and Delzenne, 2008; Jackson *et al.*, 1999; Fiordaliso *et al.*, 1995; Bajpai and Bajpai, 1991). Despite these accomplishments, studies on the effects of Korean Jerusalem artichoke on decrease of blood lipids and blood glucose have been scant.

In this study, the effect on decrease of blood glucose and blood lipids was examined after inulin extracted from Korean Jerusalem artichoke was administrated orally to Streptozotocin (STZ) induced diabetic rats.

MATERIALS AND METHODS

Inulin with average Degree of Polymerization (DP) of 26 was extracted from Jerusalem artichoke purchased from South Korea Gangwon-do region by a previously described hot water and cooling extraction method (French, 1989). The extract was freeze-dried and pulverized for use as the testing material.

Twenty four white male Sprague Dawley rats (200 g) were obtained from orient bio (Seoul, Korea). The animal were adapted to their new environment with a diet of commercial chow for 1 week prior to the 4 weeks study. The 24 rats were randomly allocated into four treatment groups of six rats each. Each rat was housed in its own cage. The groups consisted of a Normal Control group (NC) and three diabetic groups: a Diabetic Control group (DC), oral administration of inulin group (50 mg kg⁻¹ body weight; DC 50) and oral administration of inulin group (100 mg kg⁻¹ body weight; DC 100). The experimental diets were made by palletizing the purified diets prepared on the basis of the AIN-76 diet (Bieri *et al.*, 1977). Formulation of the purified diets consisted of of 20% casein, 15% corn starch, 50% sugar, 5% α -cellulose, 5% corn oil, 3.5% mineral compound, 1% vitamin compound, 0.2% chlorine bitartrate and 0.3% DL-methionine. The energy and protein content in the diets was adjusted to be

the same. The feeding room for the experimental animals was maintained at a temperature of 20±2°C and relative humidity 60±5% and an alternating 12 h light/dark period. Considering the physiological characteristics of rats which are nocturnal, the lighting for daytime cycle (09:00-21:00) when many people came and went was darkened to minimize stress. In order to examine growth performance of the animals, researchers examined the dietary intake by measuring the feed ration and remaining diet once every 3 days, calculated weight gain by measuring weight every week and calculated Food Efficiency Ratio (FER) as the rate of the weight gain divided by the dietary intake. Weight was measured at a fixed time each week on empty stomach by withdrawing food and water 2 h prior to measurement. The specified dose of inulin per animal for each treatment group was dissolved in 1 mL of distilled hot water and was administrated daily orally using a gavage with diameter of 1 mm. The inulin was always provided at 11:00 for 4 weeks. For the negative control group, the same volume of distilled water was similarly administered. The animal experiment was carried out in accordance with the ethical and scientific standards provided in the European Union Standards for Laboratory Animal Handling License and was approved by the Institutional Animal Care and Use Committee (IACUC) of Kangwon National University, South Korea.

In order to induce type 2 DM there was used STZ (Sigma-Aldrich, St Louis, MO, USA) which specifically acts on the β -cells of the pancreas (Bruce *et al.*, 1988). STZ-mediated pancreatic β -cell damage inhibits insulin secretion which reduces glucose utilization and increases the biosynthesis of glucose due to abnormal glycometabolism; the eventual increase in blood glucose leads to DM (Kahn, 1985; Goldberg, 1981). Experimental animals were fasted for 12 h prior abstain from diets for 12 h prior to the administration of 1 mL of STZ [50 mg kg⁻¹ body weight, dissolved in 0.01 M citrae buffer (pH 4.5)] by peritoneal injection. Confirmation of DM was a blood glucose level >300 mg dL⁻¹ as measured an ACCU-CHEK Compact glucose meter (Roche Diagnostics GmbH, Penzberg, Germany) using blood collected from the tail vein after maintaining empty stomach for 12 h from the administration of STZ.

The sacrifice of experimental animals was made after completion of 4 weeks feeding. Rats were provided with only water in the 12 h preceding sacrifice for convenient anesthesia and dissection. Each rat was lightly anesthetized and an abdominal incision was made. Blood (2.0 mL) was collected from the abdominal aorta using a syringe and dispensed into a heparinized vacuum tube (Becton Dickinson, Franklin Lakes, NJ 07417, USA) to

prevent blood coagulation. The collected blood was immediately centrifuged at 3,000 rpm and 4°C for 20 min to obtain blood plasma. The separated blood plasma was quick-frozen in liquefied nitrogen gas (-196°C) and then stored in a freezer at -20°C until biochemical analyses. For the measurement of organ weights, the liver, kidney, heart and spleen were separated immediately on collecting the blood and their weights were measured after washing off blood with physiological saline solution and draining. Each liver was kept at -70°C until biochemical analysis was made.

Blood glucose was measured as described above. Blood total cholesterol, TAG and HDLC was measured with a commercial biochemical analysis kit (Asan Pharmaceutical, Seoul, Korea). LDLC was calculated using the formula of Friedewald *et al.* (1972): [Total cholesterol-(HLDC+TAG/5)]. The Atherogenic Index (AI) was calculated using the formula of Haglund *et al.* (1991): [(Total cholesterol-HDLC)/HLDC].

Statistical analysis: One-way Analysis of Variance (ANOVA) for all obtained data was carried out by using SPSS version 11.5 (SPSS, Chicago, IL, USA) and the statistically significant difference was tested at confidence level 95% by Duncan's multiple range test ($p < 0.05$).

RESULTS AND DISCUSSION

Weight gain, diet intake and food efficiency were examined following the oral administration of inulin extracted from Jerusalem artichoke to the STZ-induced diabetic rats. The results are shown in Table 1. Daily net weight gain was the highest in the NC group ($p < 0.05$) and there was tendency of more weight gain in rats receiving inulin compared with the DC group. The three DC groups were not statistically different. Diet intake was significantly lowered in the NC group and the inulin-administrated group ($p < 0.05$) compared with the DC group. No statistically significant difference was evident between the NC and DC 100 groups and between the DC 50 and DC 100 groups. Food efficiency was the highest in the NC group ($p < 0.05$) with no statistically significant difference evident between the DC, DC 50 and DC 100 groups and between the NC, DC 50 and DC 100 groups. The feeding behavior in the STZ-induced diabetic rats was typical of DM e.g., the diabetic rats took more feed but their weight decreased. As the result, the weight gain was higher than the DC group and their weight recovered to that of the NC group when inulin was administrated. Glycometabolism and lipid metabolism were controlled as the blood glucose (Table 2) and lipids (Table 3) were lowered due to administration of inulin.

Table 1: Effect of the oral dosing of Jerusalem artichoke inulin on net weight gain, feed intake and FER in STZ-induced diabetic rats

Groups ¹	Net weight gain (g day ⁻¹)	Feed intake (g day ⁻¹)	FER ²
NG	4.35±0.70 ^{3a}	13.30±0.33 ^c	0.32±0.02 ^a
DC	3.41±0.64 ^b	14.96±0.52 ^a	0.22±0.04 ^b
DI 50	4.05±0.68 ^{ab}	14.07±0.53 ^b	0.28±0.03 ^{ab}
DI 100	3.85±0.56 ^{ab}	13.57±0.61 ^{bc}	0.28±0.05 ^{ab}

NC: Non diabetic control group, DC: Diabetic Control group, DI 50: Diabetic group with inulin 50 mg kg⁻¹ body weight, DI 100: Diabetic group with inulin 100 mg kg⁻¹ body weight; ²FER: Feed Efficiency Ratio; ³values are mean±SD (n = 6); ^{a-c}Means with different superscripts in the same column are significantly different ($p < 0.05$)

Table 2: Effects of the oral dosing of Korean Jerusalem artichoke inulin on concentration of blood glucose in STZ-induced rats (mg dL⁻¹)

Weeks	Groups ¹			
	NC	DC	DI 50	DI 100
1	95.75±3.09 ^{2c}	321.7±30.27 ^a	273.7±18.46 ^b	251.4±30.50 ^b
2	93.80±4.48 ^c	337.5±36.45 ^a	208.8±38.78 ^b	197.2±28.50 ^b
3	96.33±0.41 ^c	328.8±41.78 ^a	180.4±40.47 ^b	168.3±31.69 ^b
4	94.90±0.27 ^c	313.5±40.15 ^a	123.1±37.25 ^b	114.5±22.77 ^b

¹The same as Table 1. ²Values are mean±standard deviation (n = 6). ^{a-c}Means with different superscripts in the same column are significantly different ($p < 0.05$)

Table 3: Effects of the oral dosing of Korean Jerusalem artichoke inulin on concentration of lipid profile of plasma in STZ-induced rats (mg dL⁻¹)

Items ²	Groups ¹			
	NC	DC	DI 50	DI 100
TAG	83.80±4.48 ^c	134.50±6.45 ^a	98.01±7.78 ^b	90.23±5.50 ^c
TC	72.33±3.41 ^c	108.80±3.75 ^a	84.40±2.47 ^b	83.43±5.69 ^c
HDLC	30.90±6.27 ^a	17.35±8.15 ^b	23.10±3.25 ^a	25.54±3.77 ^a
LDLC	24.67±0.28 ^c	64.55±0.33 ^a	41.69±0.38 ^b	39.84±0.29 ^c
AI	1.34±0.20 ^c	5.27±0.73 ^a	2.65±0.66 ^b	2.26±0.43 ^b

¹The same as Table 1. ²TAG: Triacylglyceride, TC: Total Cholesterol, HDLC: High Density Lipoprotein Cholesterol, LDLC: Low Density Lipoprotein Cholesterol, AI: Atherogenic Index (TC-HDLC)/HDLC; ³Values are mean±standard deviation (n = 6). ^{a-c}Means with different superscripts in the same column are significantly different ($p < 0.05$)

Induction of DM by STZ results in lowered cell utilization of glucose and metabolic characteristics like the starving condition appears, producing weight loss (Sexton, 1994). For the STZ-induced diabetic rat, weight loss is a typical index of DM and weight is reduced despite copious dietary intake because the glycogen content stored in the liver lowers and reaches a state of energy exhaustion when body protein is decomposed as a source of energy (Ghosh *et al.*, 1994; Preston *et al.*, 1991). The raised dietary intake of the STZ-induced diabetic as compared to the normal group, reflects an increase of neuropeptide Y (NPY) mRNA and decreased activity of the leptin receptor of the hypothalamus in the diabetic rats with insufficient insulin; consequentially, weight is reduced even if the dietary intake is more in diabetic rats (Lee *et al.*, 1994).

The change of blood glucose level when inulin extracted from Jerusalem artichoke was orally administrated to STZ-induced diabetic rats is shown in

Table 2. At the beginning of the experiment, the blood glucose level of the STZ-induced diabetic rabbits was $327.8 \pm 35.78 \text{ mg dL}^{-1}$ but it significantly lessened as the experimental days passed in the DC 50 and DC 100 groups of diabetic rats, comparing with the DC group ($p < 0.05$). The blood glucose decrease in the DC 50 and DC 100 rats was 14.92 and 21.85%, respectively, in week 1, 38.13 and 41.57%, respectively in week 2, 45.13 and 48.81%, respectively in week 3 and 60.73 and 63.47%, respectively in week 4. Comparing the blood glucose level of the DC 50 and DC 100 groups with NC revealed that the recovered values of 28.20 and 19.60 mg in the DC 50 and DC 100 groups, respectively were similar to the NC level.

Blood glucose in the STZ-induced diabetic rats administered inulin was significantly lowered comparing with DC and it could be considered that the continuous supply of inulin from the Jerusalem artichoke could normalize their blood glucose level. The result was similar to the reports using water-soluble extract from chicory lowered blood glucose in rats (Kim and Shin, 1996) and the fructan of inulin from Jerusalem artichoke dropped blood glucose in humans (Rumessen *et al.*, 1990).

The blood glucose results likely resulted from the increasing secretion of insulin by inulin-stimulated β -cells of the pancreas or by the consumption of glucose by the transfer of glucose remaining in the blood to the cells. STZ inhibits the secretion of insulin by damaging the β -cells of the pancreas and consequentially, utilization of glucose is reduced by the abnormal glycometabolism and hyperglycemia is caused by gluconeogenesis (Kahn, 1985). Inulin from Jerusalem artichoke is effective in improvement of constipation and prevention of intestinal diseases as well as hypoglycemic activity (Pyorala *et al.*, 1987; Fiordaliso *et al.*, 1995). As well, plant extracts can activate glucose metabolism and lower blood glucose level by increasing the secretion of insulin via the stimulation of pancreatic β -cells or insulin-like substance stimulated regeneration of pancreas cells (Shanmugasundaram *et al.*, 1990).

Data concerning the change of blood lipid are shown in Table 3. TAG in the blood, total cholesterol, LDLC and AI were significantly decreased while HDLC was significantly increased in the DC 50 and 100 groups, compared with the DC group ($p < 0.05$). For TAG, no significant difference between DC 50 and 100 and between DC 100 and NC was found. But for total cholesterol and AI, a statistically significant difference between the inulin-administrated groups and NC was evident. For HDLC, no significant difference between the inulin-administrated groups and NC was found but for LDLC, a statistical significant difference among the DC 50, DC 100 and NC groups was evident ($p < 0.05$). The decreased rate

of each blood lipid in DC 50 and 100 rats, compared with DC rats was 27.13 and 32.91%, respectively for TAG, 22.42 and 23.31%, respectively for total cholesterol, 35.41 and 38.28%, respectively for LDLC and 49.71 and 27.11%, respectively for AI while the increase rate of HDLC was 24.89 and 47.20%, respectively.

The fact that decrease of lipids in the blood was observed in rates who received inulin implies that inulin from the Jerusalem artichoke improves lipid metabolism. This is supported by the observations that the water soluble extract from chicory lowers blood lipid in a rat model and for humans and animals, TAG in the blood and total cholesterol (Kim and Shin, 1996) and the lowered LDLC in a person with high cholesterol in the blood who took chicory-derived inulin (Beylot, 2005; Causey *et al.*, 2000; Davidson and Maki, 1999).

The increase of TAG in STZ-induced diabetic rats is due to the abnormal glycometabolism caused by induction of diabetes. In other words, it can be considered that the metabolism of Very Low Density Lipoprotein (VLDL) and chylomicron are lowered because the generation of VLDL increases and the Lipoprotein Lipase (LPL) activity at the peripheral tissues is lowered due to lack of insulin (Siegel *et al.*, 1996). A study on the kinetics of trigacylglyceride reported that the triacylglyceride content in the blood is increased in diabetics because the conversion rate from fat to triacylglycerides in the blood is increased (Nikkila and Kekki, 1973). The increases in total cholesterol and LDLC in the STZ-induced diabetic rats likely reflected the free fatty acid-stimulated synthesis of cholesterol with the excess cholesterol being increasingly utilized as the utilization of carbohydrate as the source of energy was decreased. In addition, it was assumed that the generation of LDL is increased due to the increased of generation of glycated LDL and increased LDL synthesis in the liver as observed in DM as well as delayed removal of LDL because of decreased LPL receptors caused by insufficient insulin (Goldstein and Brown, 1977; Brownlee *et al.*, 1984). When DM occurs, the movement of cholesterol into the blood increases because the activity of Hydroxymethyl Glutaryl-CoA (HMG-CoA) reductase in the liver is decreased while the activity of HMG-CoA reductase in the alimentary tract is increased which increases the total cholesterol in the blood (O'Meara *et al.*, 1990). The result of a previous study that there was no difference of HDLC between STZ-induced diabetic rats and a normal control group (Durrington and Stephens, 1980) is contrary to the result of this study. It was reported that the generation of HDLC was inhibited in the diabetic rats because the decomposition of lipoprotein enriched in triacylglycerides was lowered by decreased of the activity of LPL

(Betteridge, 2001). The increase of LDLC in the blood increases the rate of death due to the cardiovascular diseases such as myocardial infarction and arteriosclerosis while HDLC is very beneficial by the prevention of such diseases (Jensen *et al.*, 1999; Glueck, 1979). LDL is the most important lipid carrier for accumulation of cholesterol in the artery which transports cholesterol ester from the liver to the blood and the peripheral tissues throughout the body while HDL is a lipoprotein that transports cholesterol from the artery to the liver. Consequently, the increase of HDLC in the blood removes cholesterol in the blood by eventually increasing the transport ability of cholesterol from the blood and tissues to the liver i.e., by reverse transport. Accordingly, LDLC has been dubbed bad cholesterol because it is harmful to the body when it is present in excess in the blood while HLDC is termed good cholesterol (Grundy, 1986). AI indicates the content of triacylglycerides relative to HLDC in the body; an AI exceeding 3.0 indicates a dangerous level of arteriosclerosis (Rosenfeld, 1989).

Data on organ weight when inulin extracted from Jerusalem artichoke was orally administrated to the STZ-induced diabetic rats are shown in Table 4. The weights of liver, kidney and heart (but not the spleen) were significantly increased in DC rats ($p < 0.05$). Liver weight was not significantly different between DC 50 and 100 groups and between DC 100 and NC groups but was statistically significantly increased in DC 50 rats compared with NC rats ($p < 0.05$). Concerning kidney weight, no significant difference was evident between DC 50 and 100 rats but a statistically significant difference was evident in DC 50 and 100 rats compared with NC rats ($p < 0.05$). Concerning heart weight, no significant difference was evident between the DC 100 and NC groups but a significant difference was evident in the DC 50 group compared with the DC 100 and NC groups ($p < 0.05$).

The increase liver weight in STZ-induced diabetic rats reflected liver hypertrophied due to abnormal glycometabolism, accumulated acetyl-CoA, increased fat synthesis and accumulation of fat in the liver due to STZ-mediated inhibition of insulin secretion (Grey *et al.*, 1975;

Rhee and Lee, 1991). When DM occurs, the free fatty acid produced by decomposition of body fat due to lack of insulin is transferred into the liver. Triacylglycerides are synthesized and accumulated in the liver and eventually it makes the weight of liver increased (Goldberg, 1981). It is known that the reason why the weight of kidney is increased is that when diabetes mellitus occurs, the size and volume of kidney are increased together with increase of glomerular filtration rate as the burden of kidney is getting bigger due to increase of urine excretion (Gallaher *et al.*, 1993; Mogensen and Andersen, 1973). In diabetic rats, the kidneys can become hypertrophic due to the metabolism of glucose to UDP-glucose or glycogen that accumulates in the medangial cells in the glomerulus (Steer *et al.*, 1985) or discharge of glucose and increase of RNA and DNA synthesis that promotes cell division of the kidney (Dai *et al.*, 1994).

CONCLUSION

On the basis of the results, it can be concluded that the oral administration of inulin from Jerusalem artichoke to STZ-induced diabetic rats reduces blood lipids and blood glucose and implies that this inulin source may be a bioactive material to prevent metabolic diseases related to blood lipids and blood glucose in humans.

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Table 4: Effect of the oral dosing of Korean Jerusalem artichoke inulin on relative organ weight in STZ-induced diabetic rats (g 100 g⁻¹ body weight)

Groups ⁽¹⁾	Liver	Kidney	Heart	Spleen
NG	3.62±0.18 ^{2c}	0.63±0.02 ^c	0.35±0.02 ^c	0.20±0.02
DC	4.49±0.15 ^a	0.97±0.04 ^a	0.58±0.03 ^a	0.23±0.02
DI 50	4.08±0.14 ^b	0.80±0.04 ^b	0.43±0.01 ^b	0.26±0.04
DI 100	3.87±0.25 ^{bc}	0.77±0.03 ^b	0.38±0.01 ^c	0.24±0.04

¹The same as Table 1. ²Values are mean±standard deviation (n = 6); ^{a-c}means with different superscripts in the same column are significantly different ($p < 0.05$)

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