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Hypoglycemic and hypolipidemic effects of *Saururus chinensis* Baill in streptozotocin-induced diabetic rats*

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Abstract

Saururus chinensis Baill was reported to inhibit α-glucosidase *in vitro* and flatten postprandial increase in blood glucose in streptozotocin (STZ)-induced diabetic rats. We studied the effect of chronic consumption of *S. chinensis* Baill on blood glucose and lipid profile in STZ-induced diabetic male rats fed high fat diet. Male rats weighing 100-120 g were fed 30% fat diet with and without 10% freeze-dried leaves of *S. chinensis* Baill for 7 weeks after 1 week of adaptation. The rats were rendered diabetic by intravenous injection of STZ (60 mg/kg) after 6-week feeding of the assigned diets. At 1 week after the injection, the rats were sacrificed after an overnight fast. Plasma glucose (380.2 ± 14.4 mg/dL), total cholesterol (93.9 ± 7.9 mg/dL) and triglyceride levels (123.6 ± 7.5 mg/dL) of the *S. chinensis* Baill group were significantly lower than those of the control group (418.1 ± 12.0 mg/dL, 119.9 ± 9.4 mg/dL, 152.0 ± 10.3 mg/dL, respectively, $p<0.05$). Chronic consumption of *S. chinesis* Baill significantly decreased maltase activity of the small intestinal mucosa (120.1 ± 8.7 U/g protein) compared with the control group (96.8 ± 7.0 U/g protein, $p<0.05$). These results suggest that *S. chinensis* Baill have hypoglycemic and hypolipidemic effects by inhibiting α-glucosidase activity in the animal model of diabetes mellitus.

Key Words: *Saururus chinensis* Baill, glucose, cholesterol, triglyceride, streptozotocin

Introduction

The prevalence of diabetes mellitus among Koreans is increasing due to an aging population, increased urbanization and more sedentary lifestyles (King *et al.*, 1998). Diabetes mellitus results from defects in insulin secretion, insulin action, or both. Abnormalities of carbohydrate, lipid, and protein metabolism are common in diabetic patients. Cardiovascular disease (CVD) is a major complication and the leading cause of premature death among patients with diabetes (Centers for Disease Control and Prevention, 1999).

Evidence from prospective randomized clinical trials suggests that achieving near-normal glycemic control in patients with diabetes mellitus is associated with sustained decreased rates of diabetes-related cardiovascular complications (The Diabetes Control and Complications Trial (DCCT) Research Group, 1993; United Kingdom Prospective Diabetes Study (UKPDS), 1998). It was also reported that aggressive therapeutic treatment of diabetic dyslipidemia reduced the risk of CVD in diabetic patients (American Diabetes Association, 2003).

α-Glucosidase is an enzyme involved in the carbohydrate digestive process and hence α-glucosidase inhibitors could minimize increases in postprandial glucose levels. α-Glucosidase inhibitors such as acarbose (Stand *et al.*, 1999), voglibose (Saito *et al.*, 1998), and miglitol (Sels *et al.*, 1999) are used as oral hypoglycemic agents. It was reported that chronic consumption of acarbose could exert hypoglycemic and hypolipidemic effect in the patients with diabetes mellitus (Mughal *et al.*, 2000; Toeller, 1994). However, chronic use of these agents could result in side effects such as flatulence, abdominal cramping, vomiting and diarrhea so that their use may be limited (Hanefeld, 1998). Therefore, numerous studies have been carried out to isolate α-glucosidase inhibitors from natural products without side effects (Fujita *et al.*, 2001; Matsui *et al.*, 1996; Watanabe *et al.*, 1997). In the previous study, methanol extract of *S. chinensis* Baill leaves inhibited yeast α-glucosidase activity *in vitro* and significantly decreased postprandial increase in plasma glucose in STZ-induced diabetic rats (Joo *et al.*, 2006). However, hypo-

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glycemic and hypolipidemic effects of dietary *S. chinensis* Baill were not elucidated. Thus, the primary aim of this study was to determine the effect of the chronic consumption of *S. chinensis* Baill leaves on blood glucose and lipid profile and intestinal maltase activity in STZ-induced diabetic rats fed high fat diet to evaluate its possible use as an antidiabetic agent.

Materials and Methods

Reagents

Assay kits for glucose, cholesterol, HDL-cholesterol, and triglyceride were purchased from Asan Co (Seoul, Korea). Cornstarch was acquired from Daesang Co. (Seoul, Korea). Casein, L-cystine, mineral mixture, and vitamin mixture were purchased from ICN Pharmaceuticals Inc. (Costa Mesa, CA, USA) and *tert*-butyl hydroquinone from Fluka Co. (Milwaukee, WI, USA). Sucrose and soybean oil were obtained from Cheiljedang Co. (Seoul, Korea) and beef tallow from Lotte Samkang Co. (Seoul, Korea). STZ and other reagent grade chemicals were purchased from Sigma Chemical Co (St. Louis, MO, USA).

Animals and experimental design

Leaves of *S. chinensis* Baill was obtained from a local market in Busan, Korea and freeze-dried. Proximate analyses of *S. chinensis* Baill leaves were performed according to standard AOAC methods (AOAC, 1995).

Male Sprague-Dawley rats weighing between 100 and 120 g were purchased from Bio Genomics, Inc. (Seoul, Korea). The rats were housed individually in stainless steel wire-bottomed cages and located in a room where temperature (23-27℃), humidity (50-60%), and lighting cycle (0600-1800 hr light and 1800-0600 hr dark) were controlled. Body weight and food intake were measured three times a week. The rats (n=16) were fed a commercial chow diet (Samyang Co., Seoul, Korea) *ad libitum* for 7 days of adaptation period. The animals were randomly divided into two groups. Control group was fed 30% fat diet and experimental group 30% high fat diet containing 10% freeze-dried *S. chinesis* Baill *ad libitum* for 7 weeks (Table 1). The contents of protein, fat, and dietary fiber of the two diets were the same, respectively. After 6-week feeding of the assigned diet, the rats were rendered diabetic by intravenous injection of STZ (60 mg/kg) in citrate buffer, pH 4.5 into tail vein. At one week after the injection, the animals were sacrificed by heart puncture after an overnight fast. The small intestine samples were collected for further assay. The experiments were performed according to the guidelines of animal experimentation approved by the Animal Resource Center at Inje University, Korea.

Table 1. Diet composition

Ingredient	Basal diet	*S. chinensis* Baill diet (g/kg)
Corn starch[1)]	90*	90
Casein[2)]	255	246
Dextrinized cornstarch[3)]	132	132
Sucrose[4)]	100	100
Alpha-cellulose[5)]	60	5
Mineral mixture[6)]	44	44
Vitamin mixture[7)]	12.4	12.4
L-Cystine[2)]	3.8	3.8
Choline bitratrate[5)]	2.8	2.8
Tert-Butyl hydroquinone[8)]	0.014	0.014
Soybean oil[4)]	70	68
Beef tallow[9)]	230	230
S. chinensis Baill leaves[10)]	-	100

[1)] Daesang Co., Korea
[2)] ICN Pharmaceuticals Inc., USA
[3)] Dyets, Inc., USA
[4)] Cheiljedang Co., Korea
[5)] Sigma Co., USA
[6)] AIN-93G Mineral mix,, ICN Pharmaceuticals, USA
[7)] AIN-93G Vitamin mix,, ICN Pharmaceuticals, USA
[8)] Fluka Co., USA
[9)] Lotte Samkang Co., Korea
[10)] Freeze-dried and milled

Biochemical analyses

Blood samples were centrifuged at 3000 × g for 15 min and plasma was removed and frozen at -70℃ for further analysis. Plasma glucose, triglyceride, total cholesterol, and HDL-cholesterol were measured by enzymatic methods using commercial assay kits. To measure maltase activity, the small intestine was excised to remove duodenum. A 10 cm-segment was taken from the proximal part of the remaining small intestine. The segment was cut longitudinally, washed in 9 g/L of NaCl on ice, and then blotted on cheesecloth. The mucosa was scraped off with a microscopic slide glass and weighed. The mucosa was homogenized in four volumes cold distilled water. The homogenates were centrifuged at 12,000 × g for 30 min. The supernatants were stored at -70℃ for further analysis. Maltase activity was determined according to the method of Dahlqvist (Dahlqvist, 1984). Briefly, 100 μL of the supernatant was mixed with 100 μL of 0.056 M maltose in 0.1 M maleate buffer (pH 6.0) and incubated at 37℃ for 60 min. After 0.8 mL of distilled water added, the reaction mixture was incubated at 100℃ for 2 min and cooled in tap water. Five hundred μL of the reaction mixture was mixed with 3 mL of Tris-glucose oxidase reagent (Sigma Chemical Co, USA), incubated at 37℃ for 60 min, and absorbance was read at 420 nm. Maltase activity was determined by measuring the amount of glucose released from maltose. Protein concentration was determined by the method of Lowry *et al.* using bovine serum albumin as standard (Lowry *et al.*, 1951). The enzyme activity was expressed as specific activity (mmoles of maltose hydrolyzed/min/g protein).

Statistical analysis

All values were expressed as mean ± standard error (SE). All statistical analyses were performed using SAS (version 8.02). Differences between groups were assessed by Student's *t*-test and significance was defined as $p<0.05$.

Results

The proximate composition of freeze-dried leaves of *S. chinensis* Baill is shown in Table 2. The contents of fat, protein, ash, and dietary fiber were 2.1%, 8.8%, 9.7%, and 54.7%, respectively.

Body weight and food intake of the rats are shown in Table 3. Chronic consumption of *S. chinensis* Baill at the level of 10% of high fat diet did not significantly influence body weight, food intake and feed efficiency ratio in STZ-induced diabetic rats. The effect of *S. chinesis* Baill on plasma glucose and lipid profile are shown in Table 4. The fasting plasma glucose level was significantly lower in the *S. chinesis* Baill group (380.2 ± 14.4 mg/dL) than in the control group (418.1 ± 12.0 mg/dl, $p<0.05$, Table 4). Consumption of *S. chinesis* Baill significantly decreased plasma triglyceride (123.6 ± 7.5 mg/dL) and total cholesterol levels (93.9 ± 7.9 mg/dL) compared with the control group (152.0 ± 10.3 mg/dL and 119.9 ± 9.4 mg/dL, respectively, $p<0.05$). However, the plasma HDL-cholesterol level of *S. chinesis* Baill group (51.7 ± 6.6 mg/dL) was not significantly different from the control group (47.3 ± 4.2 mg/dL). The effect of chronic consumption of *S. chinesis* Baill on maltase activity of the small intestinal mucosa is shown in Table 5. Maltase activity of *S. chinesis* Baill group (120.1 ± 8.7 U/g protein) was significantly lower than that of the control group (96.8 ± 7.0 U/g protein, $p<0.05$).

Table 2. Proximate composition of freeze-dried leaves of S. chinensis Baill

Component	Moisture	Crude fat	Crude protein	Crude ash	Dietary fiber
%	7.0	2.1	8.8	9.7	54.7

Measurement was done in triplicate.

Table 3. Body weight, food intake, and feed efficiency ratio of the animals

	Control group	*S. chinensis* Baill group
Initial body weight (g)	97.1 ± 3.0	96.6 ± 3.3
Body weight at the time of injection of STZ (g)	412.4 ± 13.2	414 ± 9.1
Final body weight (g)	402.3 ± 13.5	398.4 ± 15.4
Body weight gain (g/d)	7.3 ± 0.3	7.4 ± 0.2
Food intake (g/d)	19.1 ± 0.3	19.8 ± 0.5
Feed efficiency ratio (%)*	38.5 ± 1.4	37.3 ± 0.7

Values represent mean ± SE (n=8).
*Feed efficiency ratio (%) = (body weight gain(g)/food intake(g)) × 100

Table 4. Plasma glucose and lipid profile of the animals

	Control group	*S. chinensis* Baill group
Glucose (mg/dL)	418.1 ± 12.0	380.2 ± 14.4*
Triglyceride (mg/dL)	152.0 ± 10.3	123.6 ± 7.5*
Total cholesterol (mg/dL)	119.9 ± 9.4	93.9 ± 7.9*
HDL-cholesterol (mg/dL)	47.3 ± 4.2	51.7 ± 6.6

* $p<0.05$
Measurement was done in triplicate.

Table 5. Maltase activity of the small intestinal mucosa of the animals

	Control group	*S. chinensis* Baill group
Specific activity (U/g protein)	120.1 ± 8.7	96.8 ± 7.0*

* $p<0.05$
Measurement was done in triplicate.
Specific activity was defined as mmoles of maltose hydrolyzed/min/g protein.

Discussion

At present, α-glucosidase inhibitors have been the most common oral agents in improving postprandial hyperglycemia since they were introduced in the early 1990s. However, it is well documented that synthetic α-glucosidase inhibitors have undesirable side effects, such as flatulence, diarrhea, and abdominal cramping (Hanefeld, 1998). Therefore, screening of α- glucosidase inhibitors with fewer side effects from natural plants is increasing. *S. chinensis* Baill is a perennial herbaceous plant used for the treatment of edema, jaundice, gonorrhea, antipyretic, diuretic, and inflammation in Korean folk medicine (Chung & Shin, 1990). It was reported that *S. chinensis* Baill leaves have α-glucosidase inhibitory activity *in vitro* and *in vivo* (Joo *et al.*, 2006). Chronic consumption of α-glucosidase inhibitors was reported to improve metabolism of carbohydrate and fat (Balflour & McTavish, 1993; Zavaroni & Reaven, 1981). In this study, we investigated the effect of chronic consumption of *S. chinensis* Baill leaves on hyperglycemia and dyslipidemia in STZ-induced diabetic rats fed high fat diet.

The food intake, body weight, and feed efficiency values of the *S. chinensis* Baill group did not significantly differ from the control group (Table 3). Chronic feeding of *Lonicera japonica* flowers with α-glucosidase inhibitory activity to rats significantly decreased body weight gain, suggesting that α-glucosidase inhibitors may exert an anti-obesity effect (Kwon *et al.*, 2004). In our study, however, *S. chinensis* Baill did not show any significant influence on body weight of rats fed 30% fat diet. Long-term consumption of acarbose did not influence the body weight in diabetic patients (Holman *et al.*, 1999). Plasma glucose was significantly reduced in the *S. chinensis* Baill group compared to the control group (Table 4). Several clinical trials confirmed that chronic consumption of acarbose lowers fasting blood glucose significantly in diabetic patients (Balflour & McTavish, 1993; Coniff *et al.*, 1995; Holman *et al.*, 1999).

It was suggested that reduced glucose toxicity through decreasing postprandial glucose elevations results in an improvement

of overall glycemic control (Lebovitz, 1998). It has also been suggested that acarbose induces a prolonged increase in the intestinal hormone glucagon-like peptide-1 (GLP-1) which can potentiate the reduction of fasting blood glucose levels (Qualmann *et al.*, 1995; Seifarth *et al.*, 1998). It is possible that *S. chinensis* Baill could reduce glucose toxicity by decreasing postprandial blood glucose elevations and increasing GLP-1 via α-glucosidase inhibitory action, resulting in reduced fasting blood glucose levels. Consumption of *S. chinensis* Baill for 7 weeks was effective in reducing plasma triglyceride and total cholesterol and tended to increase HDL-cholesterol (Table 4). It was reported that long-term consumption of acarbose reduced blood cholesterol and triglycerides levels in animal model of diabetes (Azuma *et al.*, 2006; Yamashita *et al.*, 1984). Chronic consumption of touchi with α-glucosidase inhibitory activity decreased blood triglyceride and total cholesterol in animal model of diabetes (Fujita *et al.*, 2001) and blood triglyceride in diabetic patients (Fujita *et al.*, 2003). Chronic consumption of mulberry juice and cake powder with α-glucosidase inhibitory activity reduced blood triglyceride and total cholesterol and increased HDL-cholesterol in STZ-induced diabetic rats (Kwon *et al.*, 2007). It was suggested that acarbose improves blood lipid profile by increasing insulin sensitivity (Azuma *et al.*, 2006). Zavaroni & Reaven suggested that chronic α-glucosidase inhibitor lowers VLDL-triglyceride secretion resulting in improvement of hypertriglyceridemia and hypercholesterolemia (Zavaroni & Reaven, 1981).

In this study, the consumption of *S. chinensis* Baill for 7 weeks significantly decreased maltase activity of small intestine compared with the control group (Table 5). Feeding of acarbose at the level of 100 mg/100 g chow to alloxan-induced CBA mice for 7 days significantly decreased small intestinal maltase activity (22.64 U/g protein) compared with diabetic control group (55.83 U/g protein, Juretic *et al.*, 2003). It was reported that injection of STZ almost doubled maltase activity of middle small intestine of rats over 120 U/g protein compared with normal control group (Yoo *et al.*, 2002). Chronic consumption of mulberry juice powder with α-glucosidase inhibitory activity at the level of 0.5%, 1%, and 2% of AIN-76 diet significantly decreased maltase activities of proximal, middle, and distal small intestine in STZ-induced diabetic rats (Kwon *et al.*, 2007). Reduced in maltase activity of small intestine by *S. chinensis* Baill could partially impair digestion of dietary carbohydrates and contribute to the control of hyperglycemia.

Achieving near-normal glycemic control and lowering plasma lipid levels lead to a decrease in the risk of micro- and macrovascular complications of diabetes (DCCT Research Group, 1993; UKPDS, 1998). Our data demonstrated that *S. chinensis* Baill leaves efficiently improved hyperglycemia, hypertriglyceridemia and hypercholesterolemia in STZ-induced diabetic rats fed high fat diet. Thus *S. chinensis* Baill could be effective in controlling risks for cardiovascular complications.

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