Food Sci. Biotechnol. Vol. 15, No. 3, pp. 413 ~ 417 (2006)

Food Science and Biotechnology

The Hypoglycemic Effect of *Saururus chinensis* Baill in Animal Models of Diabetes Mellitus

Hee-Jeong Joo, Ming-Jung Kang, Tae-Jin Seo, Hyun-A Kim, Sung-Ja Yoo, Soo-Kyung Lee, Hwa-Jae Lim[1], Boo-Hyeong Byun[2], and Jung-In Kim*

Biohealth Product Research Center, School of Food and Life Science, Institute for Food Sciences, Inje University, Gimhae, Gyeongnam 621-749, Korea

[1]Department of Food and Nutrition, Dong-eui University, Busan 614-714, Korea

[2]Department of Oriental Medicine, Daegu Haany University, Daegu 706-060, Korea

Abstract The purpose of this study was to investigate the hypoglycemic effect of *Saururus chinensis* Baill *in vitro* and *in vivo*. Methanol extract of *S. chinensis* Baill inhibited yeast α-glucosidase activity by 49.8%, which was twice as strong as that of acarbose at a concentration of 0.5 mg/mL *in vitro*. The effect of *S. chinensis* Baill methanol extract on the postprandial increase in blood glucose levels was studied in streptozotocin-induced diabetic rats using a carbohydrate load test. Oral administration of *S. chinensis* Baill extract (500 mg/kg) significantly decreased incremental blood glucose levels at 60 and 90 min ($p<0.05$) after oral ingestion of starch (1 g/kg). The area under the glucose response curve of the *S. chinensis* Baill group was significantly decreased compared to that of the control group ($p<0.05$). The effect of prolonged feeding of *S. chinensis* Baill was studied in an animal model of type 2 diabetes. Three-week-old db/db mice were fed an AIN-93G diet or a diet containing 0.5% *S. chinensis* Baill extract for 7 weeks after 1 week of adaptation. Plasma glucose, insulin, and blood glycated hemoglobin levels of the mice fed *S. chinensis* Baill extract were significantly lower than those of the control group ($p<0.05$). Therefore, we conclude that *S. chinensis* Baill is effective in controlling hyperglycemia in animal models of diabetes mellitus.

Keywords: *Saururus chinensis* Baill, hypoglycemic effect, alpha-glucosidase, db/db mouse, diabetes mellitus

Introduction

The prevalence of diabetes mellitus is increasing in the general population, and it has been predicted that globally, the number of people with diabetes will rise from about 150 million in 2000 to 300 million by 2025 (1). Keeping blood glucose levels as close to normal and preventing diabetic complications are the major goals in the treatment of diabetes mellitus (2, 3). Intensive glycemic control is essential for risk reduction of diabetes-related complications, which are the major causes of premature death among patients with diabetes.

Agents with α-glucosidase inhibitory activity delay the digestion of dietary carbohydrates and thereby reduce an increase in postprandial glucose levels. α-Glucosidase inhibitors such as acarbose (4), voglibose (5), and miglitol (6) are used as oral hypoglycemic agents. However, because the chronic use of these agents can result in side effects such as flatulence, abdominal cramping, vomiting, and diarrhea, their use may be limited (7). Therefore, numerous studies have evaluated natural products with α-glucosidase inhibitory activity, including plant materials, as alternative hypoglycemic agents for diabetes to be used in addition to conventional treatments (8-10).

Saururus chinensis Baill is a perennial herbaceous plant that has been used for the treatment of edema, jaundice, gonorrhea, and inflammation in Korean folk medicine (11). It has been reported that *S. chinensis* Baill has a strong antioxidative effect (12) and flavonol glycosides showing free radical-scavenging activities against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and superoxide have been isolated (13). Since oxidative stress generated by free radical species plays a major role in the progression of diabetes (14), *S. chinensis* Baill may be beneficial for the prevention and treatment of diabetes via its antioxidative effects. However, the effects of *S. chinensis* Baill on the symptoms of diabetes have not been previously studied.

Since intensive glycemic control is one of the major goals in the treatment of diabetes, and essential to reducing the risk of diabetic complications (2, 3), it would be worthwhile to study the effect of *S. chinensis* Baill on glycemic control in diabetes. Thus we investigated the effect of prolonged feeding of *S. chinensis* Baill extract on glycemic control in an animal model of diabetes to evaluate its possible use as a hypoglycemic agent. The α-glucosidase inhibitory activity of *S. chinensis* Baill, *in vitro* and *in vivo*, was also determined to elucidate the underlying mechanism of glycemic control.

Materials and Methods

Reagents We purchased a glucose assay kit from Yeongdong Co. (Seoul, Korea), an insulin assay kit from Linco Co. (St. Charles, MO, USA), and glycated hemoglobin (HbA_{1C}) assay kit from BioSystems (Barcelona, Spain). 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,

*Corresponding author: Tel: 82-55-320-3236; Fax: 82-55-321-0691
E-mail: fdsnkiji@inje.ac.kr
Received February 22, 2006; accepted May 8, 2006

Korea). Yeast α-glucosidase, *p*-nitropheny-α-D-glucopyranoside, streptozotocin, alphacel, choline bitartrate, and all other chemical reagents used in this study were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Preparation of the methanol extract *S. chinensis* Baill was obtained from a local market in Busan, Korea. Leaves of *S. chinensis* Baill were freeze-dried, powdered, and extracted with ten volumes of methanol for 12 hr three times at room temperature. The solvent was removed by rotary evaporation at 40°C. The dry extract was dissolved in dimethylsulfoxide (DMSO) at a concentration of 5 mg/mL for use as a test material *in vitro*.

Enzyme inhibition assay Yeast α-glucosidase inhibitory activity was measured by the method described by Watanabe *et al.* (9) using a microplate reader (model 550; Bio-Rad, Hercules, CA, USA). Yeast α-glucosidase (0.7 U) was dissolved in 100 mM phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin, 0.2 g/L NaN_3 and 5 mM *p*-nitrophenyl-α-D-glucopyranoside. The substrate was dissolved in the same solution. The final concentration of the *S. chinensis* Baill extract and acarbose, a positive control, was 0.5 mg/mL. Each measurement was performed in triplicate.

Measurement of postprandial blood glucose in streptozotocin-induced diabetic rats Male Sprague-Dawley rats weighing between 230 and 260 g were purchased from Orient Co. (Seoul, Korea). All rats were fed a commercial chow *ad libitum* for 1 week after arrival. The animals were rendered diabetic by intraperitoneal injection of streptozotocin (STZ; 65 mg/kg) in citrate buffer at pH 4.5. Blood samples were taken from the tail tip after 1 week, and the blood glucose concentration was measured using a glucometer (Glucotrend, Roche Diagnostics, UK). Animals were considered diabetic if the fasting blood glucose levels exceeded 200 mg/dL. The animals were maintained under standard laboratory conditions of 24±5°C and 55±5% relative humidity with a regular 12-hr light:12-hr dark cycle. The rats (n=16) were randomly divided into two groups. After an overnight fast, the animals were given soluble starch (1 g/kg) alone or starch mixed with methanol extract of *S. chinensis* Baill (500 mg/kg) by gastric intubation. Blood samples were collected from the tail tip after 30, 60, 90, 120, 180, and 240 min. Feed was withheld during the test. Blood samples were collected and centrifuged at 2,000×g for 15 min. Plasma glucose was measured using a commercial glucose assay kit. Plasma glucose levels were expressed as increments from the baseline. Incremental areas under the response curves (AUC) were calculated using the trapezoidal rule with fasting levels as the baseline.

Measurement of hypoglycemic effect in db/db mice Three-week-old male db/db (+/+) C57BL/KsL mice (n=14) were purchased from the Korea Research Institute of Bioscience and Biotechnology (Daejeon, Korea). After 1 week of adaptation during which the animals had free access to commercial chow, they were randomly divided into a control and a *S. chinensis* Baill treatment group. The diets for the animals were based on the AIN-93G diet, which contained 39.8% cornstarch, 20% casein, 13.2% dextrinized cornstarch, 10% sucrose, 7% soybean oil, 5% Alphacel, 3.5% mineral mixture, 1% vitamin mixture, 0.3% L-cystine, 0.25% choline bitartrate, and 0.0014% *tert*-butyl hydroquinone. The mice in the control group were fed a standard AIN-93G diet, whereas the treatment group was fed the same diet supplemented with 0.5% (w/w, final conc.) of *S. chinensis* Baill methanol extract *ad libitum* for 7 weeks. The mice were maintained under standard laboratory conditions of 24±5 °C and 55±5% relative humidity with a regular 12-hr light:12-hr dark cycle. At the end of the experimental period, the mice were sacrificed by heart puncture after an overnight fast. Blood HbA_{1C} levels were measured by the chromatographic method using a commercial assay kit. Plasma glucose and insulin were measured by glucose-oxidase method and by radioimmunoassay, respectively. The experiments were performed according to the guidelines of animal experimentation approved by the Animal Resource Center at Inje University, Korea.

Statistical analysis All data are 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 and Discussion

Inhibition of α-glucosidase activity *in vitro* The inhibitory activity of the methanol extract of *S. chinensis* Baill toward yeast α-glucosidase is shown in Table 1. The methanol extract of *S. chinensis* Baill inhibited yeast α-glucosidase activity by 49.8% at a concentration of 0.5 mg/mL *in vitro*. Acarbose, an α-glucosidase inhibitor used as an oral hypoglycemic agent, inhibited the enzyme activity by 25.2%. Inhibition of α-glucosidase, the enzyme that digests dietary carbohydrates, leads to a delayed and reduced rise in postprandial blood glucose levels (4). Thus, oral administration of specific α-glucosidase inhibitors could effectively manage diabetes by improving postprandial hyperglycemia. At present, α-glucosidase inhibitors are the most common oral agents used to control postprandial hyperglycemia (15). However, synthetic α-glucosidase inhibitors have side effects such as flatulence and abdominal bloating, which may limit their potential as the preferred medication (16). Therefore, much attention has focused on the importance of natural (plant) substances that show potent inhibitory activity against α-glucosidase and have fewer side effects (17-19). *Rhus chinensis* (17), *Commelina communis* (18), *Scutellaria baicalensis*, *Rheum officinale*, and *Paeonia suffruticosa* (19) have shown

Table 1. Inhibitory activities of *S. chinensis* Baill against yeast α-glucosidase

Sample	α-Glucosidase inhibitory activity (%)
S. chinensis Baill	49.8
Acarbose	25.2

potent inhibitory activity against α-glucosidase *in vitro*. In our study, the α-glucosidase inhibitory activity of *S. chinensis* Baill extract was two times stronger than that of acarbose *in vitro*.

Inhibition of α-glucosidase activity in STZ-induced diabetic rats To investigate the inhibitory effect of the *S. chinensis* Baill extract on α-glucosidase *in vivo*, we used STZ-induced diabetic rats. Plasma glucose response to a single oral dose of starch (1 g/kg) alone or starch with *S. chinensis* Baill extract (500 mg/kg) is shown in Fig. 1. Incremental plasma glucose levels of rats that consumed starch alone reached a peak (88.0±8.0 mg/dL) at 90 min. Consumption of *S. chinensis* Baill extract significantly decreased incremental plasma glucose levels at 60 and 90 min ($p<0.05$). The AUC for glucose response was significantly lower in the *S. chinensis* Baill group (8,898± 838 mg·min/dL) than in the control group (12,348±1,110 mg·min/dL, $p<0.05$; Table 2).

These data demonstrate that *S. chinensis* Baill exerts α-glucosidase inhibitory activity *in vivo* to decrease postprandial glucose levels. Inoue *et al.* (20) reported that an α-glucosidase inhibitor that flattens the peak postprandial blood glucose levels leads to a reduction in the AUC of the blood glucose response curve. In our study, *S. chinensis* Baill extract decreased both the AUC and incremental blood glucose at the peak time point. Postprandial glucose is a major contributor to the glycosylation of hemoglobin and other proteins (21). HbA_{1C} measurements are highly associated with a higher risk of cardiovascular disease and coronary heart disease mortality (22). Postprandial hyperglycemia is strongly correlated with risks for the micro- and macrovascular complications of diabetes (22). One of the main benefits of

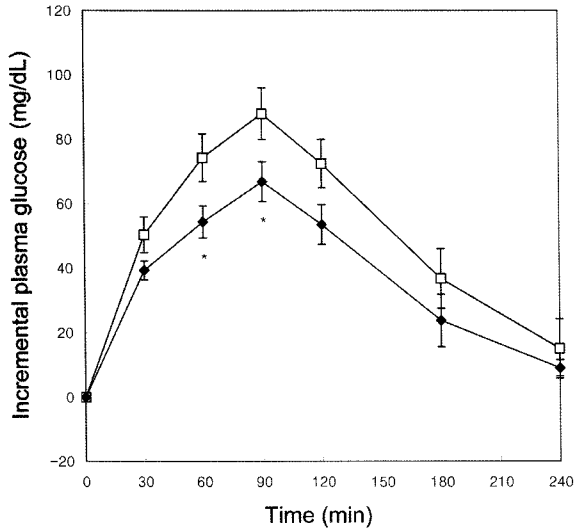

Fig. 1. Increase in blood glucose after administration of *S. chinensis* Baill extract in STZ-induced diabetic rats. Control group (□), Starch (1 g/kg) was administered orally to rats after an overnight fast. *S. chinensis* Baill group; (◆), starch (1 g/kg) plus methanol extract of *S. chinensis* Baill (500 mg/kg) was administered orally to rats after an overnight fast. Values represent mean±SE. *Significantly different at $p<0.05$.

Table 2. Area under the glucose response curve of STZ-induced diabetic rats

Group	AUC (mg·min/dL)
Control group	12,348 ± 1,110
S. chinensis Baill group	8,898 ± 838[1)]

Values represent mean ± SE (n = 8).
[1)]Significantly different at $p<0.05$.

α-glucosidase inhibitors, including acarbose, is to control postprandial hyperglycemia, which could alleviate micro- and macrovascular complications (23). Thus, *S. chinensis* Baill was found to be beneficial in reducing risks for cardiovascular complications by controlling postprandial hyperglycemia in diabetic rats.

Hypoglycemic effect of prolonged feeding of *S. chinensis* Baill extract to db/db mice The food intake, body weight, and food efficiency values of the *S. chinensis* Baill group did not significantly differ from the control group (Table 3). Prolonged feeding of a diet containing 5 % *Lonicera japonica* flowers with α-glucosidase inhibitory activity to eight-week-old rats significantly decreased body weight gain, suggesting that α-glucosidase inhibitors may exert an anti-obesity effect (24). In our study, however, *S. chinensis* Baill did not show any significant influence on body weight of db/db mice, an animal model of type 2 diabetes and obesity. *Touchi* extract containing α-glucosidase inhibitory action does not exert significant effects on the body weight of KKY mice, another animal model of type 2 diabetes (25), and the long-term consumption of acarbose does not influence the body weight of diabetic patients (26).

Plasma glucose (398±17 mg/dL) and insulin (4.2±0.3 ng/mL) were significantly reduced in the *S. chinensis* Baill group compared to the control group (461±15 and 4.8±0.2 ng/mL, respectively, $p<0.01$ and $p<0.05$; Fig. 2). Consumption of *S. chinensis* Baill significantly decreased blood HbA_{1C} (6.4±0.2%) compared to the control group (7.1±0.2%, $p<0.05$).

Maintaining blood glucose levels as close to normal is of major importance in treating diabetes mellitus and preventing diabetic complications (2, 3). 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 retinopathy, nephropathy, and neuropathy (3). Type 2 diabetes mellitus, which constitutes 85-95% of diabetes cases, results from insulin resistance. Consumption of *S. chinensis* Baill for 7 weeks was effective in reducing

Table 3. Body weight, food intake, and feed efficiency ratio in db/db mice fed control and *S. chinensis* Baill diets

Group	Body weight (g)	Food intake (g/d)	Feed efficiency ratio (%)[1)]
Control group	44.2 ± 1.0	4.4 ± 0.1	0.203 ± 0.011
S. chinensis Baill group	43.9 ± 1.1	4.2 ± 0.2	0.208 ± 0.013

[1)]Food efficiency ratio (%) = [Body weight gain (g) / food intake (g)] × 100. Values represent mean ± SE.

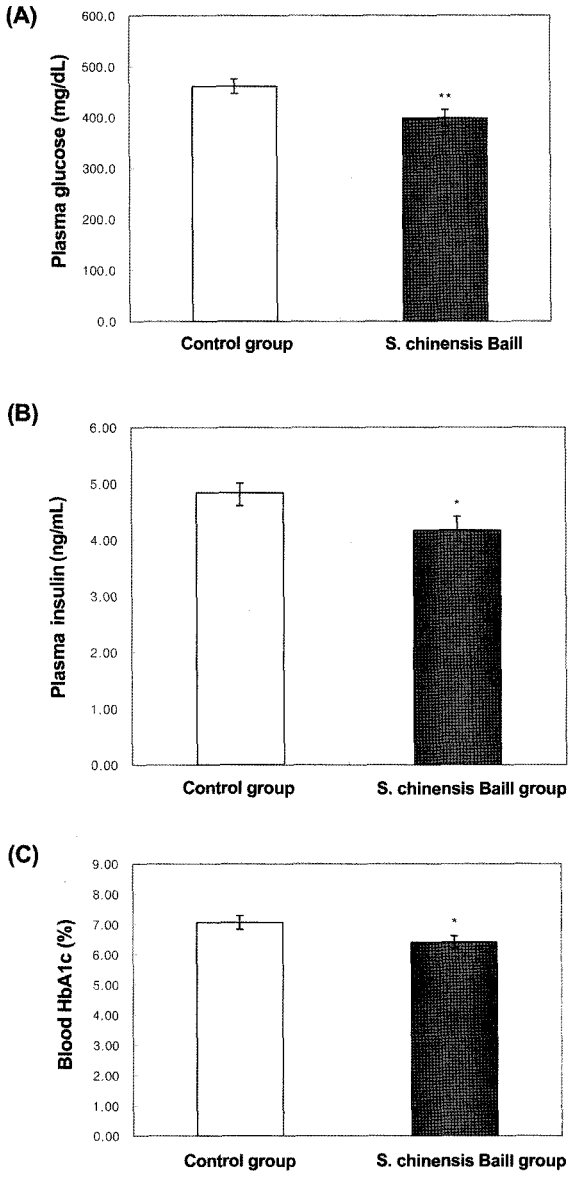

Fig. 2. Hypoglycemic effect of *S. chinensis* Baill extract in db/db mice. A. Fasting plasma glucose; B. Plasma insulin; C. Blood glycated hemoglobin (HbA_{1c}). Values represent mean±SE. *Significantly different at $p<0.05$, **Significantly different at $p<0.01$.

plasma glucose and insulin levels in mice. It was also reported that chronic feeding of *touchi* extract containing α-glucosidase inhibitory action reduced both fasting glucose and insulin levels in KKY mice (25). Several clinical trials confirm that acarbose monotherapy lowers fasting blood glucose significantly in patients with type 2 diabetes and the mechanism for this effect is secondary to the lowering of postprandial hyperglycaemia (26-31). Lebovitz (32) suggested that reduced glucose toxicity due to decreased postprandial glucose elevation by an α-glucosidase inhibitor such as acarbose results in an improvement of overall glycemic control. 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 (33, 34). It is possible that *S. chinensis* Baill could reduce glucose toxicity through decreasing postprandial blood glucose elevation and increasing GLP-1 via α-glucosidase inhibition, thus resulting in reduced fasting blood glucose levels.

The consumption of *S. chinensis* Baill also significantly reduced blood glycated hemoglobin. Numerous studies have demonstrated that acarbose significantly lowers HbA_{1c} (35-37). HbA_{1c} is a marker that represents chronic blood glucose control and reflects both fasting plasma glucose and postprandial glucose levels. A reduction in HbA_{1c} levels is associated with decreased complications of diabetes such as cardiovascular complications, neuropathy, and retinopathy (3, 38, 39).

In conclusion, *S. chinensis* Baill was effective in controlling fasting and postrandial hyperglycemia by the inhibition of α-glucosidase activity in an animal model of diabetes. Thus, *S. chinensis* Baill may be useful for the improvement of overall glycemic control, and the reduction of risk for diabetic complications. Further studies to isolate the active components are currently in progress.

Acknowledgments

This study was supported by a grant from the Ministry of Commerce, Industry, and Energy (MOCIE) and the Korea Institute of Industrial Technology Evaluation & Planning (ITEP) through the Biohealth Products Research Center (BPRC) of Inje University.

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025 Prevalence, numerical estimates and projections. Diabetes Care 21: 1414-1431 (1998)
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl. J. Med. 329: 977-986 (1993)
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 352: 837-853 (1998)
4. Stand E, Baumgartl HJ, Füchtenbusch M, Stemplinger J. Effect of acarbose on additional insulin therapy in type 2 diabetic patients with late failure of sulphonylurea therapy. Diabetes Obes. Metab. 1: 215-220 (1999)
5. Saito N, Sakai H, Sekihara H, Yajima Y. Effect of an α-glucosidase inhibitor (voglibose), in combination with sulphonylureas, on glycaemic control in type 2 diabetes subjects. J. Int. Med. Res. 26: 219-232 (1998)
6. Sels JP, Huijberts MS, Wolffenbuttel BH. Miglitol, a new alpha-glucosidase inhibitor. Expert Opin. Pharmaco. 1: 149-156 (1999)
7. Hanefeld M. The Role of acarbose in the treatment of non-insulin-dependent diabetes mellitus. J. Diabetes Complicat. 12: 228-237 (1998)
8. Matsui T, Yoshimoto C, Osajima K, Oki T, Osajima Y, Oki T, Osajima Y. *In vitro* survey of α-glucosidase inhibitory food components. Biosci. Biotechnol. Biochem. 60: 2019-2022 (1996)
9. Watanabe J, Kawabata J, Kurihara H, Niki R. Isolation and identification of α-glucosidase inhibitors from Tochu-cha (*Encommia ulmoides*). Biosci. Biotechnol. Biochem. 61: 177-178 (1997)
10. Fujita H, Yamagami T, Ohshima K. Fermented soybean-derived touchi extract with anti-glycaemic effect via α-glucosidase inhibitory action in rats and humans. J. Nutr. 131: 1211-1213 (2001)

11. Chung BS, Shin MG. Dictionary of Korean Folk Medicine. Young Lim Sa, Seoul, Korea. p. 813 (1990)
12. Lee WS, Baek Y-I, Kim J-R, Cho K-H, Sok D-E, Jeong T-S. Antioxidant activities of a new lignan and a neolignan from *Saururus chinensis*. Bioorg. Med. Chem. Lett. 14: 5623-5628 (2004)
13. Choi CW, Kim SC, Hwang SS, Choi BK, Ahn HJ, Lee MY, Park SH, Kim SK. Antioxidant activity and free radical scavenging capacity between Korean medicinal plants and flavonoids by assay-guided comparison. Plant Sci. 163: 1161-1168 (2002)
14. Kaneto H, Nakatani Y, Kawamori D, Miyatsuka T, Matsuoka TA, Matsuhisa M, Yamasaki Y. Role of oxidative stress, endoplasmic reticulum stress, and c-Jun N-terminal kinase in pancreatic β-cell dysfunction and insulin resistance. Int. J. Biochem. Cell Biol. 37: 1595-1608 (2005)
15. Mooradian AD, Thurman JE. Drug therapy of postprandial hyperglycemia. Drugs 57: 19-29 (1999)
16. Bressler R, Johnson D. New pharmacological approaches to therapy of NIDDM. Diabetes Care 15: 792-805 (1992)
17. Shim YJ, Doo HK, Ahn SY, Kim YS, Seong JK, Park IS, Min BH. Inhibitory effect of aqueous extract from the gall of *Rhus chinensis* on alpha-glucosidase activity and postprandial blood glucose. J. Ethnopharmacol. 85: 283-287 (2003)
18. Youn JY, Park HY, Cho KH. Anti-hyperglycemic activity of *Commelina communis* L.: inhibition of α-glucosidase. Diabetes Res. Clin. Pr. 66S: S149-155 (2004)
19. Nishioka T, Kawabata J, Aoyama Y. Baicalein, an alpha-glucosidase inhibitor from *Scutellaria baicalensis*. J. Nat. Prod. 61: 1413-1415 (1998)
20. Inoue I, Takahashi K, Noji S, Awata T, Negishi K, Katayama S. Acarbose controls postprandial hyper-proinsulinemia in non-insulin-dependent diabetes mellitus. Diabetes Res. Clin. Pr. 36: 143-151 (1997)
21. Soonthornpun S, Rattarasarn C, Leelawattana R, Setasuban W. Postprandial plasma glucose: a good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. Diabetes Res. Clin. Pr. 46: 23-27 (1999)
22. Campbell RK, White JR, Nomura D. The clinical importance of postprandial hyperglycemia. Diabetes Educator 27: 624-637 (2001)
23. Baron AD. Postprandial hyperglycaemia and α-glucosidase inhibitors. Diabetes Res. Clin. Pr. 40: S51-55 (1998)
24. Kwon CS, Son KH, Kim JS. Effect of *Lonicera japonica* flower on body weight gain and glucose tolerance in rodents. Food Sci. Biotechnol. 13: 768-771 (2004)
25. Fujita H, Yamagami T. Fermented soybean-derived touchi-extract with anti-diabetic effect via alpha-glucosidase inhibitory action in a long-term administration study with KKAy mice. Life Sci. 70: 219-227 (2001)
26. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44) Diabetes Care 22: 960-964 (1999)
27. Balflour JA, McTavish D. Acarbose. An update of its pharmacology and therapeutic use in diabetes mellitus. Drugs 46: 1025-54 (1993)
28. Coniff RF, Shapiro JA, Robbins D, Kleinfield R, Seaton TB, Beisswenger P, McGill JB. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. Diabetes Care 18: 817-824 (1995)
29. Seifarth C, Bergmann Y, Bergmann J, Holst JJ, Schmiegel W, Nauck M. Prolonged and enhanced secretion of glucagon like peptide-1 (7-36 amide) after oral sucrose due to alpha glucosidase inhibition (acarbose) in type 2 diabetic patients. Diabetic Med. 15: 485-91 (1998)
31. Meneilly GS, Ryan EA, Radziuk J. Effect of acarbose on insulin sensitivity in elderly patients with diabetes. Diabetes Care 23: 1162-1167 (2000)
32. Lebovitz HE. α-Glucosidase inhibitors as agents in the treatment of diabetes. Diabetes Rev. 6:132–145 (1998)
33. Qualmann C, Nauck MA, Holst JJ, Orskov C, Creutzfeldt W. Glucagon-like peptide 1 (7-36 amide) secretion in response to luminal sucrose from the upper and lower gut. A study using alpha-glucosidase inhibition (acarbose). Scand. J. Gastroenterol. 30: 892-896 (1995)
34. Seifarth C, Bergmann J, Holst JJ, Ritzel R, Schmiegel W, Nauck MA. Prolonged and enhanced secretion of glucagon-like peptide 1 (7-36 amide) after oral sucrose due to alpha-glucosidase inhibition (acarbose) in type 2 diabetic patients. Diabetic Med. 15: 485-491 (1998)
35. Mertes G. Efficacy and safety of acarbose in the treatment of type 2 diabetes: data from a 2-year surveillance study. Diabetes Res. Clin. Pr. 40: 63-70 (1998)
36. Mertes G. Safety and efficacy of acarbose in the treatment of type 2 diabetes: data from a 5-year surveillance study Diabetes Res. Clin. Pr. 52: 193-204 (2001)
37. Hanefeld M. The role of acarbose in the treatment of non-insulin-dependent diabetes mellitus. J. Diabetes Complicat. 12: 228-237 (1998)
38. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). Brit. Med. J. 322: 1-6 (2001)
39. Coutinho M, Gerstein H, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. Diabetes Care 22: 233-240 (1999)