ARTICLE IN PRESS

Available online at www.sciencedirect.com

ScienceDirect

Phytomedicine ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Phytomedicine

www.elsevier.de/phymed

Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus

Kwanghee Kim[a], Hyunyul Kim[a], Jeunghak Kwon[a], Sungwon Lee[a], Hyunseok Kong[a], Sun-A Im[b], Young-Hee Lee[b], Young-Ran Lee[b], Sun-Tack Oh[b], Tae Hyung Jo[c], Young In Park[d], Chong-Kil Lee[b], Kyungjae Kim[a,*]

[a]*Department of Pharmacy, SahmYook University, Seoul, South Korea*
[b]*College of Pharmacy, Chungbuk National University, Cheongju, South Korea*
[c]*Univera Inc., Seoul, South Korea*
[d]*School of Life Sciences and Biotechnology, Korea University, Seoul, South Korea*

Abstract

The effects of processed *Aloe vera* gel (PAG) on the course of established diet-induced non-insulin-dependent diabetes mellitus (NIDDM) were studied in C57BL/6J mice. NIDDM was induced in C57BL/6J mice by feeding them a high-fat diet. Mice exhibiting diet-induced obesity (DIO) with blood glucose levels above 180 mg/dl were selected to examine the antidiabetic effects of PAG. Oral administration of PAG for 8 weeks reduced circulating blood glucose concentrations to a normal level in these DIO mice. In addition, the administration of PAG significantly decreased plasma insulin. The antidiabetic effects of PAG were also confirmed by intraperitoneal glucose tolerance testing. PAG appeared to lower blood glucose levels by decreasing insulin resistance. The administration of PAG also lowered triacylglyceride levels in liver and plasma. Histological examinations of periepididymal fat pad showed that PAG reduced the average size of adipocytes. These results demonstrate that the oral administration of PAG prevents the progression of NIDDM-related symptoms in high-fat diet-fed mice, and suggest that PAG could be useful for treating NIDDM.

Keywords: *Aloe vera* gel; Antidiabetic activity; Type 2 diabetes; Diet-induced obesity; Insulin sensitivity; Adipocyte

Introduction

NIDDM is the most common form of the disease, and accounts for more than 90% of diabetes patients. Current understanding of disease progression in NIDDM is that insulin resistance in peripheral tissues leads to compensatory hyperinsulinemia, followed by β-cell failure, which leads initially to prandial and later to overt fasting hyperglycemia (Defronzo et al. 1992). The number of people diagnosed with NIDDM is increasing at an alarming rate in western societies; prompted by a dramatic increase in the incidence of obesity and sedentary lifestyles. According to recent estimates, approximately 220 million people worldwide will be affected by the disease by 2010 (King et al. 1998; Zimmet et al. 2001). NIDDM is a progressive disease with associated complications of retinopathy, nephropathy, neuropathy, and atherosclerosis (Marcovecchio et al. 2005). In order to minimize the development of

*Corresponding author. Tel.: +82 2 3399 1601; fax: +82 2 3399 1617.
E-mail address: kimkj@syu.ac.kr (K. Kim).

0944-7113/$ - see front matter © 2009 Elsevier GmbH. All rights reserved.
doi:10.1016/j.phymed.2009.02.014

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

such complications, the maintenance of near-normal blood glucose levels is the therapeutic goal in NIDDM patients.

During the past 20 years, reports have shown that *Aloe* preparations have beneficial therapeutic effects on diabetes. The hypoglycemic effect of *Aloe* species was first demonstrated in 1985 by Agarwal. During this previous study, a prescribed diet containing the leaves of *Aloe vera* was administered to 3167 diabetic patients twice daily for 5 years, and was found to markedly decrease blood sugar and serum total cholesterol and triglyceride levels (Agarwal 1985). Since then the antidiabetic effects of *Aloe* preparations have been demonstrated in diabetic patients (Ghannam et al. 1986; Ajabnoor 1990; Bunyapraphatsara et al. 1996; Yongchaiyudha et al. 1996), and in alloxan or streptozotocin-induced diabetic animal models (Beppu et al. 1993; Rajasekaran et al. 2004, 2005, 2006; Beppu et al. 2006).

Animal models of diabetes differ significantly and no single model can be taken to represent the essential features of human NIDDM. It is well-known that alloxan and streptozotocin produce diabetes by selectively destroying pancreatic β-cells, and thus cause insulin-dependent (type I) diabetes (Rakieten et al. 1963; Wilson et al. 1984). Experimental animal models of NIDDM can be constructed with these drugs by manipulating the dosages and timings of administrations to destroy only a portion of β-cells (Portha et al. 1989; Beppu et al. 1993; Serradas et al. 1991). However, these animal models conceptually deviate from the pattern of NIDDM in humans, in whom the disease is often preceded by obesity. Moreover, commonly used genetic models, such as, ob/ob and db/db mice, also deviate from human NIDDM, because they contain mutations in the leptin structural gene (ob) or in the leptin receptor gene (db), which are rare in human NIDDM (Coleman 1978; Surwit et al. 1984; Kuhn et al. 1987).

In the present study, we examined the antidiabetic effects of PAG in DIO mice, which have been shown to closely resemble human NIDDM in terms of metabolic abnormalities, such as hyperglycemia, obesity and insulin resistance (Wencel et al. 1995; Surwit et al. 1988; Mills et al. 1993). Our results demonstrate that the oral administration of PAG improves blood glucose and lipid homeostasis in these mice.

Materials and methods

Processed *Aloe vera* gel (PAG)

The PAG used in the present study was prepared from the gel of *Aloe vera* (*Aloe vera* (L.) *Burm. f. syn. A. barbadensis Mill*). The basic processing methodology used to prepare crude PAG, which involves incubation of *Aloe vera* gel with cellulase, termination of the reaction by heating, and then passage through a charcoal column to remove anthraquinones and other colored substances, is the same as that used for the preparation of crude modified *Aloe* polysaccharides (MAP) (Qiu et al. 2000). To enrich polysaccharides while decreasing monosaccharide content, crude PAG preparation was sieved with an ultrafiltration cell (Amicon) inserted with a 5000 Da-molecular weight cut-off membrane until the total volume inside the ultrafiltration cell reaches to one half. The total polysaccharide content of the PAG was $23.85 \pm 0.35\%$ (based on the dry weight of the residual fraction inside a dialysis sac (weight cut-off, 3500 Da) after extensive dialysis against distilled water), which is significantly higher than that contained in crude MAP (12–15%). Monosaccharide composition of the PAG was analyzed by high performance anion exchange chromatography using a CarboPac PA1 column (Dionex) after hydrolysis with 2 M trifluoroacetic acid at 100 °C for 4 h, according to the methods described previously (Qiu et al. 2000). The average molar ratio of mannose, galactose and glucose of the PAG was 12:0.3:1, which is comparable to that of native *Aloe vera* gel (mannose:galactose: glucose = 11:0.2:1). The major monosaccharide composing the polysaccharides that were purified from the PAG using DEAE-Sephacel column (Amersham Pharmacia Biotech) was mannose (approximately 93%). The PAG was dissolved in phosphate buffered saline (PBS) just before administration.

Animals and the experimental protocol

Male C57BL/6NCrjBgi mice were purchased from the Charles River Laboratory of Animal Science (Orient Co., Seoul, Korea) at 4 weeks old and fed a normal diet for 1 week. Animals were housed in individual cages with free access to water and food in temperature-controlled animal facility under a 12 h light–dark cycle at 22 ± 2 °C and $55 \pm 5\%$ humidity. Mice were either fed a high-fat diet (OpenSource diets #D12492; Research Diets Inc., New Brunswick, NJ) to induce obesity, or a regular diet (OpenSource diets #D12450B; Research Diets Inc.). The nutritional contents of the high-fat diet were similar to those of the regular diet except for a low carbohydrate content and a high level of fat. At 26 weeks of age, the mice exhibiting blood glucose levels of >180 mg/dl were selected as NIDDM animals and were divided into five groups of 18 animals per group. One group was administrated with PBS only and served as diabetic controls; three groups received daily 25, 50, or 100 mg/kg of PAG, respectively, and the fifth group were administered pioglitazone (PGZ, 2.5 mg/kg,

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

Lilly, USA), an antidiabetic drug currently in clinical use. Mice were weighed and blood samples were collected weekly by tail bleeding into heparin-coated tubes after a 4 h fast. At the end of the experimental period, mice were sacrificed and blood samples were taken from the inferior vena cava to determine plasma insulin and lipid levels. After collecting blood, liver, thymus, pancreas, kidney, lung, heart, and spleen were removed, rinsed with physiological saline solution, and immediately stored at −70 °C. White adipose tissues were immediately removed from periepididymal and perirenal fat for morphological examinations. Mice were treated in accordance with the guidelines issued by Sahmyook University for the care and use of laboratory animals.

Blood glucose and plasma insulin

Blood glucose concentrations were measured using a glucometer (Optimum, Medisence), and plasma insulin concentrations using commercial insulin ELISA kits (Shibayagi Co., Japan).

Indexes of insulin resistance (IRI)

IRI values were calculated using the relation between fasting blood glucose and plasma insulin levels, as defined by the equation: IRI = insulin (μU/ml) × glucose (mM)/22.5.

Intraperitoneal glucose tolerance testing (IPGTT)

After an overnight fast, mice were injected intraperitoneally with glucose at 1.5 g/kg of body weight, and blood glucose levels were determined in tail blood samples taken at 0 min (prior to glucose administration) and at 30, 60, and 120 min after glucose administration.

Plasma and hepatic lipid levels

Plasma triglyceride and total cholesterol levels were determined using a blood chemistry analyzer (Express Plus, Bayer, USA). To determine triglyceride levels in liver, 50 mg of liver tissue from each mouse was homogenized in 1 ml of PBS and centrifuged for 10 min at 4 °C at 3000 rpm. Supernatants were then collected and triglyceride and cholesterol contents were measured.

Histological examinations

Periepididymal fat wedges from representative mice in each group were fixed overnight in 10% neutral buffered formalin, embedded in paraffin, cut into thin section (4 μm), and mounted on slide glasses. Hematoxylin and eosin staining was performed in the normal manner to examine general morphology. Micrographs were taken at × 100 (BX41, Olympus, Tokyo).

Statistical analysis

Data were assessed using SPSS program (version 15.0, SPSS Inc., Chicago, IL, USA). P values of <0.05 between mean values were considered statistically significant.

Results

Effects of PAG on fasting glucose levels

To examine the effects of PAG on the progression of NIDDM-related symptoms, the NIDDM state was first induced in C57BL/6 mice by feeding them a high-fat diet for 21 weeks. All of the mice on this diet developed a DIO phenotype and had markedly higher levels of circulating blood glucose than mice on a regular diet. DIO mice exhibiting fasting blood glucose levels of above 180 mg/dl were selected, grouped randomly into experimental groups, and then orally administrated different doses of PAG for 8 weeks with continued free access to the high-fat diet. The mean fasting blood glucose level of DIO mice before PAG administration was 199.7 ± 21.7 mg/dl, while that of regular diet-fed mice was 131.5 ± 13.4 mg/dl. The fasting blood glucose levels increased gradually in untreated DIO mice over the 8-week treatment period, and reached 266.5 ± 0.7 mg/dl. However, when PAG was administrated orally, the fasting blood glucose levels decreased significantly and dose-dependently (Fig. 1). The antihyperglycemic effects PAG were apparent from treatment week 2, and continued throughout the experimental periods. The mean fasting blood glucose level of DIO mice that were treated with 100 mg/kg PAG for 8 weeks was 127.7 ± 11.4 mg/dl, which was not significantly different from that of regular diet-fed mice. The plasma glucose lowering activity of PAG at 100 mg/kg was almost comparable to that of PGZ, which was administrated to DIO mice at 2.5 mg/kg daily. No differences in food-intake or body weights were observed over the treatment period in PAG-treated and untreated DIO mice (data not shown).

Effects of PAG on glucose tolerance

At the near end of the 8-week experimental period (3 days before sacrifice), glucose tolerance was examined using the IPGTT method. Briefly, overnight-fasted mice were injected intraperitoneally with glucose at 1.5 g/kg of body weight, and blood glucose levels were measured

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

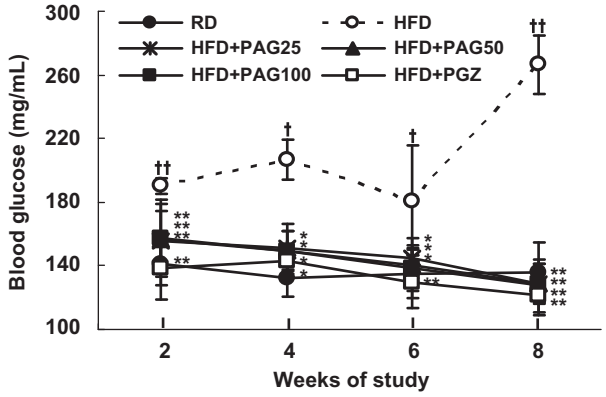

Fig. 1. Effects of PAG on fasting blood glucose levels. Male C57BL/6N mice were either fed a high-fat diet (HFD) to induce DIO phenotype, or a regular diet (RD) for 21 weeks. DIO mice with fasting blood glucose levels >180 mg/dl were selected, and allocated randomly into five groups of 18 animals per group. Animals were administrated either PBS, PAG (25, 50, and 100 mg/kg, respectively), or PGZ (2.5 mg/kg) orally for 8 weeks with free access to the high-fat diet. Mice fed regular diet served as normal controls. Blood samples were collected from tails weekly after a 4 h fast, and blood glucose concentrations were measured using a glucometer. Results are means ± SEM. $^{+}p<0.05$, $^{++}p<0.01$ compared with RD-fed mice. $*p<0.05$, $**p<0.01$ compared with untreated DIO mice.

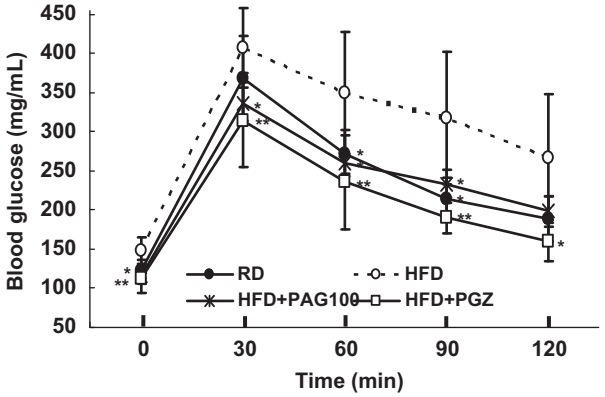

Fig. 2. Effects of PAG on glucose tolerance. Three days before sacrifice, mice were fasted overnight, and then injected intraperitoneally with glucose (1.5 g/kg body weight). Blood glucose levels were determined using tail blood samples at the indicated times postinjection. Results are means ± SEM ($n = 18$). $*p<0.05$, $**p<0.01$ compared with untreated DIO mice.

before and after this glucose administration. As shown in Fig. 2, DIO mice treated with 100 mg/kg PAG showed a remarkable improvement in overall glucose response as compared with untreated DIO mice, and the plasma glucose lowering effects of PAG were observed during the first hour after glucose loading.

Effects of PAG on plasma insulin levels and IRI

The plasma insulin levels measured after the various treatments are presented in Fig. 3. The plasma insulin levels of untreated DIO mice were significantly (4.2-fold) higher than those of regular diet-fed mice. Treatment of DIO mice with PAG for 8 weeks significantly reduced plasma insulin levels. Using the plasma glucose and insulin levels obtained, homeostatic model assessment values for insulin resistance were calculated (Table 1). The mean IRI value of the untreated DIO group was 8.2–fold that of the regular diet-fed group. The IRI values of the DIO group treated with 25, 50, and 100 mg/kg PAG were 31.4%, 32.1%, and 31.1%, respectively, of that of the untreated DIO group (Table 1).

Effects of PAG on the liver and plasma lipid profiles

Liver and plasma triglyceride and cholesterol levels for each group at the end of the 8-week experimental period are shown in Table 2. Triglyceride levels in the

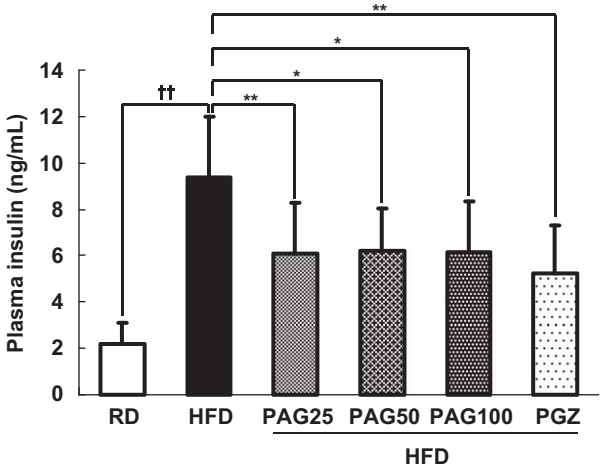

Fig. 3. Effects of PAG on plasma insulin levels. At the end of the 8-week experimental period, blood samples were taken from the inferior vena cava, and plasma insulin concentration was measured using commercial insulin ELISA kits. Results are means ± SEM ($n = 18$). $^{++}p<0.01$ compared with RD-fed mice. $*p<0.05$, $**p<0.01$ compared with untreated DIO mice.

liver and plasma were significantly higher in untreated DIO mice than those of regular diet-fed mice (178.2 ± 47.1 vs. 52.0 ± 26.0 mg/dl, 128.9 ± 27.0 vs. 83.7 ± 11.5 mg/dl, respectively). After 8 weeks of PAG treatment, triglyceride levels in the liver and plasma decreased significantly and dose-dependently. Triglyceride levels in the liver and plasma in the DIO group treated with 100 mg/kg PAG were 51.0% and 72.7%, respectively, of that of the untreated DIO group (Table 2). The effect of PAG on the total cholesterol levels in the liver and plasma, however, was not statistically significant.

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

Effects of PAG on fat mass and periepididymal fat pad morphology

The mean body weight of animals in untreated DIO group was approximately 29.7% higher than in the regular diet-fed group, and the untreated DIO group had showed a 1.3-fold increase in periepididymal fat pad mass versus regular diet-fed mice (data not shown). Histological analysis of periepididymal fat pads further confirmed this result and indicated that increases in the adipocyte size of periepididymal fat pads in untreated DIO mice resulted mainly from an accumulation of lipids (Fig. 4). On the other hand, the average size of adipocytes in periepididymal fat pads of mice treated with 25, 50, and 100 mg/kg PAG was decreased by 1.8%, 2.8%, and 30%, respectively (Fig. 4).

Discussion

It has been well established that C57BL/6J mice fed a high-fat diet develop diet-induced obesity (DIO) and hyperglycemia and that they reasonably model NIDDM in man (Wencel et al. 1995; Surwit et al. 1988; Mills et al. 1993). As occurs in man, this mouse model has a genetic basis, it is associated with obesity, which can be induced by a high-fat diet, and exhibits many of the symptoms of NIDDM. In the present study, we investigated the effects of PAG on the progression of NIDDM in C57BL/6J mice fed a high-fat diet. PAG was administrated orally to DIO mice that had already developed moderate NIDDM (blood glucose: 180–220 mg/dl). In particular, our results demonstrate that the administration of PAG to these mice prevented the development of NIDDM-related symptoms.

The administration of PAG to DIO mice reduced fasting blood glucose concentration to a normal level despite continued access to a high-fat diet. The anti-hyperglycemic effects PAG were apparent from treatment week 2, and then continued throughout the 8-week treatment period. The current understanding of disease progression in NIDDM is that insulin resistance in peripheral tissues leads to compensatory hyperinsulinemia followed by β-cell failure (DeFronzo et al. 1992). In the present study, it was found that PAG significantly reduced plasma insulin concentrations in a fasted state. These results show that PAG increases insulin sensitivity by decreasing blood glucose and insulin levels. Improved blood glucose homeostasis was also observed by intraperitoneal glucose tolerance testing in PAG-treated DIO mice.

A high-fat intake and increased levels of free fatty acids in the circulation might lead to insulin resistance (Manco et al. 2004a, 2004b). Oral administration of PAG reduced plasma lipid levels and hepatic triacylglyceride concentrations in DIO mice. Thus, we are tempted to speculate that reductions in plasma lipid levels and in hepatic triacylglyceride concentrations by PAG ameliorated insulin resistance. Although the data were not shon in this paper, we examined the expressions of adipogenic genes in adipose tissue by semiquantitative RT-PCR to determine whether PAG reduces lipogenesis. It was found that PAG suppressed the expressions of the adipogenic genes SREBP-1a, FAS, and GPAT, suggesting that PAG might improve insulin resistance by reducing the toxic effects of lipids in liver.

Table 1. Index of insulin resistance (IRI).

Group	Blood glucose (mM)	Insulin (μU/ml)	IRI
RD	7.6±0.7	92.4±37.7	31.2±1.1
HFD	14.8±0.1†	390.6±68.5†	257.0±0.1†
HFD+PAG25	7.1±0.7**	254.6±90.4**	80.7±2.9**
HFD+PAG50	7.2±0.7**	259.1±74.8*	82.6±2.3*
HFD+PAG100	7.1±0.6**	256.8±91.5*	80.0±2.6*
HFD+PGZ	6.8±0.7**	218.2±86.8**	65.6±2.6**

IRI values were calculated using: IRI = insulin (μU/ml) × glucose (mM)/22.5. $^{+}p<0.05$ compared with RD-fed mice. $*p<0.05$, $**p<0.01$ compared with untreated DIO mice.

Table 2. Effects of PAG on the liver (A) and plasma (B) triacylglyceride and cholesterol contents.

Group	Hepatic		Plasmic	
	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	Total cholesterol (mg/dl)
RD	52.0±26.0	133.5±6.4	83.7±11.5	230.9±39.2
HFD	178.2±47.1††	220.5±0.7†	128.9±27.0††	237.9±61.7
HFD+PAG25	105.1±44.5**	202.3±50.7	121.7±29.0*	261.4±51.5
HFD+PAG50	96.3±38.2**	235.2±30.7	98.1±19.8**	249.7±37.9
HFD+PAG100	90.9±27.0**	244.2±30.7	93.7±17.8**	288.2±46.8
HFD+PGZ	154.8±24.9	195.8±30.1	62.1±13.8**	279.5±68.7

Hepatic triglyceride concentrations were measured in blood taken from the inferior vena cava at the end of the experimental period. Results are means±SEM ($n=18$). $^{+}p<0.05$, $^{++}p<0.01$ compared with RD-fed mice. $*p<0.05$, $**p<0.01$ compared with untreated DIO mice.

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

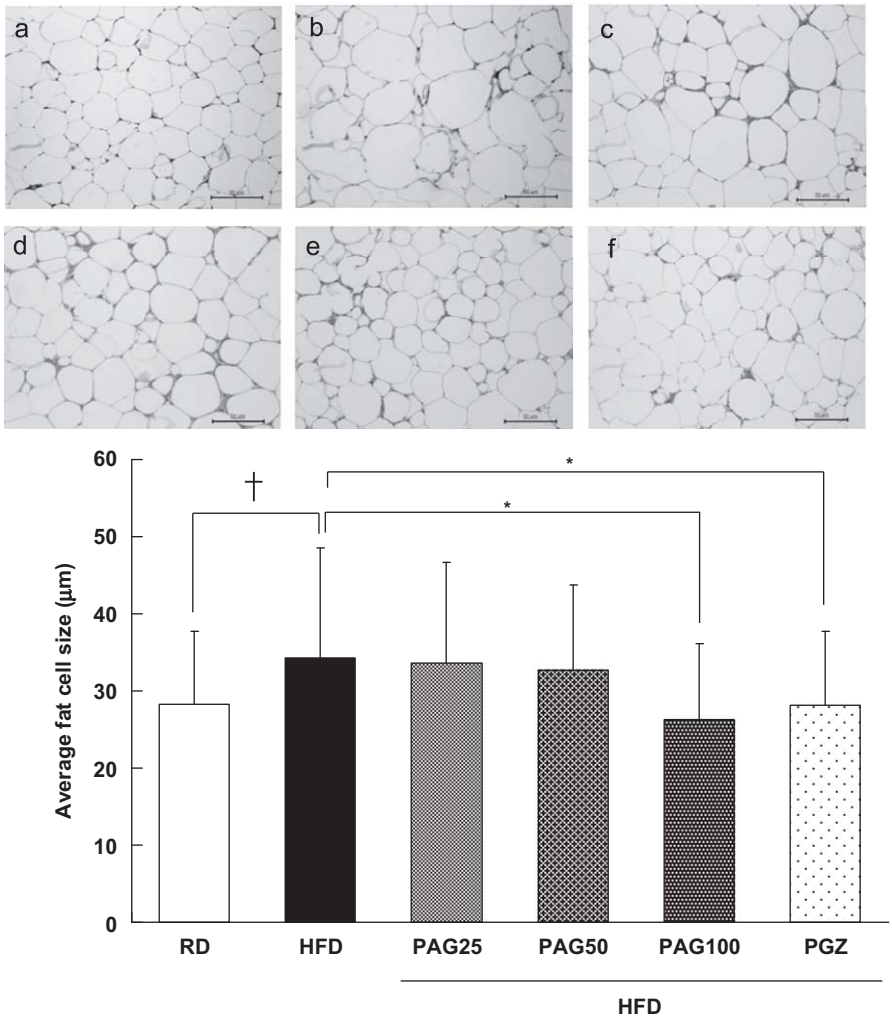

Fig. 4. Morphology of epididymal fat pads. (A) At the end of the experimental period, epididymal fat pads were isolated from representative mice of each group, sectioned, and then stained with hematoxylin and eosin. Photomicrographs are of tissues isolated from RD-fed mice (a), untreated DIO mice (b), PAG 25 mg/kg (c), PAG 50 mg/kg (d), and PAG 100 mg/kg treated DIO mice (e), or 2.5 mg/kg PGZ treated DIO mice (f). Photomicrographs were taken at a magnification of $\times 100$. (B) The average size of the adipocytes was calculated from the results of (A).

It has been previously reported that *Aloe* components have beneficial effects on diabetes in man (Agarwal 1985; Ghannam et al. 1986; Ajabnoor 1990; Bunyapraphatsara et al. 1996; Yongchaiyudha et al. 1996) and in animals made diabetic with streptozotocin or alloxan (Ghannam et al. 1986; Ajabnoor 1990; Beppu et al. 1993; Rajasekaran et al. 2004, 2005, 2006; Beppu et al. 2006). Moreover, the hypoglycemic polysaccharides, arboran A and arboran B, isolated from *Aloe arborescens* (Hikino et al. 1986), a 'bitter principle' isolated from the exudates of *Aloe vera* (Ajabnoor 1990), the dried sap of *Aloe vera* (Ghannam et al. 1986), two different antidiabetic components of apparent molecular weight >3500 Da isolated from the leaf pulp and the leaf skin of *Aloe arborescens* (Beppu et al. 1993), and phytosterols isolated from the gel of *Aloe vera* (Tanaka et al. 2006) have been shown to have antidiabetic activity. On the other hand, negative results have also been reported. For example, oral *Aloe vera* gel was reported to increase plasma glucose levels in alloxan-induced diabetic rats (Koo 1994), although clinical studies showed that the chronic administration of *Aloe vera* gel reduced fasting blood glucose and hemoglobin A1c (HbA1c) levels (Bunyapraphatsara et al. 1996; Yongchaiyudha et al. 1996). These controversial reports on the hypoglycemic activity of *Aloe* preparations are probably due to the parts of the plant used, and the different animal models used.

The present report is the first to find that *Aloe vera* component(s) exerts antidiabetic activity in a mouse

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

model of diabetes that is widely recognized to closely resemble human NIDDM. However, the active component(s) responsible for its antidiabetic activity have not been identified. Further studies on this topic are necessary.

Acknowledgements

This work was supported by 2006 Industry-University-Institute R&D Consortium from Small and Medium Business Administration (SMBA), and in part by the Research Center for Bioresource and Health Grant from ITEP and MOCIE, Korea.

References

Agarwal, O.P., 1985. Prevention of atheromatous heart disease. Angiology 36, 485–492.

Ajabnoor, M.A., 1990. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. J. Ethnopharmacol. 28, 215–220.

Beppu, H., Nagamura, Y., Fujita, K., 1993. Hypoglycaemic and antidiabetic effects in mice of *Aloe arborescens* Miller var. *natalensis* Berger. Phytother. Res. 7, S37–S42.

Beppu, H., Shimpo, K., Chihara, T., Kaneko, T., Tamai, I., Yamaji, S., Ozaki, S., Kuzuya, H., Sonoda, S., 2006. Antidiabetic effects of dietary administration of Aloe arborescens Miller components on multiple low-dose streptozotocin-induced diabetes in mice: investigation on hypoglycemic action and systemic absorption dynamics of aloe components. J. Ethnopharmacol. 103, 468–477.

Bunyapraphatsara, N., Yongchaiyudha, S., Rungpitarangsi, V., Chokechaijaroenporn, O., 1996. Antidiabetic activity of *Aloe vera* L. juice. II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. Phytomedicine 3, 245–248.

Coleman, D.L., 1978. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 14, 141–148.

DeFronzo, R.A., Bonadonna, R.C., Ferrannini, E., 1992. Pathogenesis of NIDDM. A balanced overview. Diabetes Care 15, 318–368.

Ghannam, N., Kingston, M., Al-Meshaal, I.A., Tariq, M., Parman, N.S., Woodhouse, N., 1986. The antidiabetic activity of aloes: preliminary clinical and experimental observations. Horm. Res. 24, 288–294.

Hikino, H., Takahashi, M., Murakami, M., Konno, C., Mirin, Y., 1986. Isolation and hypoglycemic activity of Arborans A and B, glycans of *Aloe arborescens* var. *natalensis* leaves. Int. J. Crude Drug Res. 24, 183–186.

King, H., Aubert, R.E., Herman, W.H., 1998. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21, 1414–1431.

Koo, M.W.L., 1994. *Aloe vera*: antiulcer and antidiabetic effects. Phytother. Res. 8, 461–464.

Kuhn, C.M., Cochrane, C., Feinglos, M.N., Surwit, R.S., 1987. Exaggerated peripheral responses to catecholamines contributes to stress-induced hyperglycemia in the ob/ob mouse. Pharmacol. Biochem. Behav. 26, 491–495.

Manco, M., Bertuzzi, A., Salinari, S., Scarfone, A., Calvani, M., Greco, A.V., Mingrone, G., 2004a. The ingestion of saturated fatty acid triacylglycerols acutely affects insulin secretion and insulin sensitivity in human subjects. Br. J. Nutr. 92, 895–903.

Manco, M., Calvani, M., Mingrone, G., 2004b. Effects of dietary fatty acids on insulin sensitivity and secretion. Diabetes Obes. Metab. 6, 402–413.

Marcovecchio, M., Mohn, A., Chiarelli, F., 2005. Type 2 diabetes mellitus in children and adolescents. J. Endocrinol. Invest. 28, 853–863.

Mills, E., Kuhn, C.M., Feinglos, M.N., Surwit, R., 1993. Hypertension in CB57BL/6J mouse model of non-insulin-dependent diabetes mellitus. Am. J. Physiol. 264, R73–R78.

Portha, B., Blondel, O., Serradas, P., McEvoy, R., Giroix, M.H., Kergoat, M., Bailbe, D., 1989. The rat models of non-insulin dependent diabetes induced by neonatal streptozotocin. Diabetes Metab. 15, 61–75.

Qiu, Z., Jones, K., Wylie, M., Jia, Q., Orndorff, S., 2000. Modified Aloe barbadensis polysaccharide with immunoregulatory activity. Planta Med. 66, 152–156.

Rajasekaran, S., Sivagnanam, K., Ravi, K., Subramanian, S., 2004. Hypoglycemic effect of Aloe vera gel on streptozotocin-induced diabetes in experimental rats. J. Med. Food 7, 61–66.

Rajasekaran, S., Sivagnanam, K., Subramanian, S., 2005. Modulatory effects of Aloe vera leaf gel extract on oxidative stress in rats treated with streptozotocin. J. Pharm. Pharmacol. 57, 241–246.

Rajasekaran, S., Ravi, K., Sivagnanam, K., Subramanian, S., 2006. Beneficial effects of aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes. Clin. Exp. Pharmacol. Physiol. 33, 232–237.

Rakieten, N., Rakieten, M.L., Nadkarni, M.R., 1963. Studies on the diabetogenic action of streptozotocin (NSC-37917). Cancer Chemother. Rep. 29, 91–98.

Serradas, P., Bailbe, D., Blondel, O., Portha, B., 1991. Abnormal B-cell function in rats with non-insulin-dependent diabetes induced by neonatal streptozotocin: effect of in vivo insulin, phlorizin, or vanadate treatments. Pancreas 6, 54–62.

Surwit, R.S., Feinglos, M.N., Livingston, E.G., Kuhn, C.M., McCubbin, J.A., 1984. Behavioral manipulation of the diabetic phenotype in ob/ob mice. Diabetes 33, 616–618.

Surwit, R.S., Kuhn, C.M., Cochrane, C., McCubbin, J.A., Feinglos, M.N., 1988. Diet-induced type II diabetes in C57BL/6J mice. Diabetes 37, 1163–1167.

Tanaka, M., Misawa, E., Ito, Y., Habara, N., Nomaguchi, K., Yamada, M., Toida, T., Hayasawa, H., Takase, M., Inagaki, M., Higuchi, R., 2006. Identification of five phytosterols from Aloe vera gel as anti-diabetic compounds. Biol. Pharm. Bull. 29, 1418–1422.

Wencel, H.E., Smothers, C., Opara, E.C., Kuhn, C.M., Feinglos, M.N., Surwit, R.S., 1995. Impaired second phase

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014

insulin response of diabetes-prone C57BL/6J mouse islets. Physiol. Behav. 57, 1215–1220.

Wilson, G.L., Patton, N.J., McCord, J.M., Mullins, D.W., Mossman, B.T., 1984. Mechanisms of streptozotocin- and alloxan-induced damage in rat B cells. Diabetologia 27, 587–591.

Yongchaiyudha, S., Rungpitarangsi, V., Bunyapraphatsara, N., Chokechaijaroenporn, O., 1996. Antidiabetic activity of *Aloe vera* L. juice. I. Clinical trial in new cases of diabetes mellitus. Phytomedicine 3, 241–243.

Zimmet, P., Alberti, K.G., Shaw, J., 2001. Global and societal implications of the diabetes epidemic. Nature 414, 782–787.

Please cite this article as: Kim, K., et al., Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine (2009), doi:10.1016/j.phymed.2009.02.014