



Original Article

Suppressive effect of *Sasa veitchii* extract on obesity induced by a high-fat diet through modulation of adipose differentiation in mice

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ABSTRACT — Obesity is a major health problem worldwide that is associated with the increased risk of type 2 diabetes and other chronic diseases. *Sasa veitchii*, which belongs to the *Gramineae* family, has various properties including anti-obesity properties. However, detailed mechanism of anti-obesity was not reported. This study aimed to investigate the therapeutic effect of *Sasa veitchii* leaf extract (SE) on obesity characteristics induced by a high-fat diet (HFD) such as hyperglycemia, insulin resistance, and inflammatory response. Four-week-old male ddY mice were freely fed a HFD or a normal diet (control) for 12 weeks. During the experimental 12-week period, treatment with saline or SE, 0.2 mL twice per day by oral gavage, was conducted, and body weight was measured weekly. At the end of the experiment, the mice were euthanized after a 16-hr fasting period, and their plasma was collected. Liver and epididymal adipose tissue samples were collected and weighed. Moreover, after 10 weeks of feeding, oral glucose tolerance test was performed. Treatment with SE significantly decreased body weight, adipose tissue weight, plasma glucose, insulin, leptin, and pro-inflammatory cytokines compared with HFD groups, and markedly reduced the impairment of glucose tolerance in obese mice. Furthermore, HFD-induced adipocyte hypertrophy was improved by treatment with SE. Moreover, adipocyte differentiation marker such as proliferator-activated receptor γ was activated by SE treatment. Our findings demonstrate that SE may reduce obesity-induced glucose and insulin tolerance, presumably by the induction of the proliferator-activated receptor γ .

Key words: Obesity, Adipocyte, Inflammation, *Sasa veitchii*

INTRODUCTION

Obesity is one of the most important risk factors for the development of lifestyle-related diseases such as type 2 diabetes, cardiovascular diseases, atherosclerosis, lipid abnormalities, and hypertension (Aronne and Isoldi, 2007). Obesity is usually viewed as being the result of increases in the number and size of adipocytes (Gregoire *et al.*, 1998). However, recent studies have

indicated that obesity is related to low-grade inflammatory conditions, suggesting that inflammation is a potential mechanism by which obesity leads to insulin resistance (Fernandez-Real and Ricart, 2003). White adipose tissue (WAT) is not only a fuel store but also a complex endocrine organ that secretes various adipokines. Physiological adipocytes of normal sizes, which are observed in lean individual fat pads, secrete adipokines such as adiponectin to enhance insulin sensitivity (Kadowaki *et al.*, 2006),

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while pathologically enlarged adipocytes in the obese adipose tissues secrete other adipokines such as tumor necrosis factor α (TNF α) and monocyte chemoattractant protein 1, which worsens insulin sensitivity (Suganami *et al.*, 2005). The balance in the secretion of these adipokines with reciprocal functions determines the pathophysiological state in insulin resistance and inflammation (Nishimura *et al.*, 2009). Therefore, to reduce insulin resistance, it is important to decrease the production of proinflammatory mediators derived from the obese adipose tissues such as TNF α and monocyte chemoattractant protein 1.

Bamboo leaves are a common perennial plant consisting of several species of the genus *Sasa*. It is widely distributed in Asian countries, and its roots and leaves have been used in food and medicine. Indeed, these leaves have been extensively used in folk medicine as an antifebrile and antihypertensive medication for centuries. *Sasa veitchii*, which belongs to the *Gramineae* family, has recently been found to contain a large number of bioactive molecules such as polyphenol and flavones (Zhang *et al.*, 2008; Zulkafli *et al.*, 2014). This plant has long been found to be useful in this region of the world; for example, in Japan, its leaves are used to wrap sushi sheets to protect against bacterial spoilage.

Studies have demonstrated that *S. veitchii* extract (SE) has various properties, including antitumor, antiallergic, and antiviral (Seki *et al.*, 2010; Hayashi *et al.*, 2014; Usuda *et al.*, 2016). Other studies have reported on SE's anti-inflammatory and anti-obesity properties (Yang *et al.*, 2010; Van Hoyweghen *et al.*, 2014). In addition, our previous study indicated SE reduced obesity-induced insulin resistance and hepatic steatosis in mice (Yoshioka *et al.*, 2017). However, it remains unclear whether SE can attenuate an obesity-induced increase in WAT since our previous study focused on the liver. Moreover, it is unclear whether the treatment period alters the anti-obesity effect, because our previous investigation involving SE treatment consisted of only one protocol and a relatively shorter period of 4 weeks than the total experimental time in this study of 12 weeks.

In order to understand these questions, we examined whether the HFD-induced obesity responses, especially in adipocytes, are altered by treatment with SE for the entire experimental period.

MATERIALS AND METHODS

Preparation of SE

SE is kindly provided from Sunchlon Co. Ltd., (Nagano, Japan). This SE is sold as non-prescription drugs in Japan. The 1 mL dose of SE is equivalent to 2.82 g of *S. veitchii*

leaves, as previously described (Yoshioka *et al.*, 2016). In addition, the components of the SE have been previously reported (Usuda *et al.*, 2016).

Animal treatment

Male 3-week-old ddY mice were purchased from Japan SLC (Shizuoka, Japan). Mice were housed under standard conditions of controlled temperature (24°C \pm 1°C), humidity (55% \pm 5%), and light (12-hr:12-hr light/dark cycles) and provided with food and water *ad libitum*. Animals were acclimatized to laboratory conditions for 1-week, and 4-week-old mice were used in the experiments. All experiments were approved by the Institutional Animal Care and Experiment Committee of Kinjo Gakuin University (No. 128).

Experimental protocol

Mice were fed a HFD (HFD-60 [Oriental Yeast Co., Tokyo, Japan]; 5.06 kcal/g; 23% protein [casein, L-cysteine], 25.3% carbohydrate [corn, maltodextrin, sucrose], 35.0% fat [lard, soybean oil], and other) or normal diet (CE-2 [CLEA Japan, Inc., Tokyo, Japan]; 3.59 kcal/g; 24.9% protein [soybean waste, whitefish meal, yeast], 51.0% carbohydrate [wheat flour, corn, Milo], 4.6% fat [cereal germ, soybean oil], and other) for a total of 12-weeks. The mice were divided into vehicle groups (CE-2; control and HFD) that received saline and treatment groups that were given SE (Sunchlon Co. Ltd.) (HFD + SE). The treatment duration with saline or SE, 0.2 mL twice per day by oral gavage, lasted 12-weeks.

Body weight were measured every week throughout the study. Following the experiment, the mice from each group were fasted for 16-hr, euthanized using pentobarbital, and bled for plasma samples, which were stored at -80°C pending assays. Liver and epididymal adipose weights were determined. Separate adipocyte samples were snap frozen in liquid nitrogen and subsequently stored at -80°C or fixed in 15% neutral buffered formalin (pH 7.4).

Plasma biochemical analysis

Plasma glucose and total cholesterol (T-CHO) levels were determined enzymatically, using commercially available assay kits (glucose CII-test and cholesterol E-test, respectively; Wako Pure Chemicals, Osaka, Japan) according to the manufacturer's instructions. Plasma insulin (Morinaga Co., Tokyo, Japan), leptin (R&D systems, Minneapolis, MN, USA), tumor necrosis factor (TNF)- α and interleukin-6 (IL-6; eBioscience, San Diego, CA, USA) were determined using commercially available enzyme-linked immunosorbent assay kits,

according to the manufacturers' instructions. The calibration curves were prepared using standard solutions.

Histopathological findings

A portion of epididymal adipose tissue from each animal was fixed in formalin solution, dehydrated, and embedded in paraffin; 10- μ m-thick sections were obtained from the paraffin-embedded blocks. These sections were dewaxed in xylene and rehydrated in a graded ethanol series. After rehydration, sections were stained with Mayer's hematoxylin solution (Nacalai Tesque, Kyoto, Japan). After rinsing in running tap water, the sections were stained with 0.1% eosin solution (Wako Pure Chemical) containing acetic acid. Finally, sections were dehydrated, cleared, and mounted with cover glass, and histopathological features were examined using a light microscope.

Oral glucose tolerance test (OGTT)

After 10-weeks of feeding with HFD or CE-2, the mice were fasted for 16-hr; thereafter, a basal blood sample (0-min) was collected from the tail vein. Blood samples were drawn 15-min, 30-min, 60-min, 90-min, and 120-min after oral administration of glucose (2 g/kg). Blood samples were centrifuged (3,000 g for 10 min at 4°C), and plasma samples were stored at -80°C until analysis. Plasma glucose levels were measured as described above, and the area under the curve (AUC) for blood glucose was calculated.

Western blot analysis

Adipose sections (0.1-g) were homogenized with 500 μ L ice-cold phosphate-buffered saline containing protease inhibitor and centrifuged (18,000 g for 20 min at 4°C). The resulting supernatant for each sample was collected, and the protein level determined using the BCA protein assay kit (Nacalai Tesque). Protein samples (20 μ g) were subjected to sodium dodecyl sulfate-polyacrylamide electrophoresis on a 10% gel and transferred to a polyvinylidene difluoride membrane. Rabbit anti-peroxisome proliferator-activated receptor γ (PPAR γ) monoclonal antibody and rabbit anti-CCAAT enhancer-binding protein (C/EBP) α monoclonal antibody were used as primary antibodies (1:1,000 dilution) for immunoblotting. A peroxidase-conjugated anti-rabbit immunoglobulin G (IgG; Cell Signaling Technology, Beverly, MA, USA) was used as secondary antibody (1:3,000 dilution). Mouse anti- β -actin monoclonal antibody (MBL, Aichi, Japan) was used as primary antibody (1:2,000 dilution) for immunoblotting. A peroxidase-conjugated anti-mouse IgG was used as secondary antibody (1:5,000 dilution;

MBL). The immunoreactive bands were visualized with the ECL system (BioRad, Hercules, CA, USA).

Statistical analysis

Multiple comparisons were made by one-way analysis of variance (ANOVA) with posthoc Tukey-Kramer's test or two-way repeated-measures ANOVA. All statistical analyses were performed using SPSS Statistics for Windows software (version 19.0; IBM Corp., Armonk, NY, USA). Values of $P < 0.05$ were considered statistically significant.

RESULTS

Prevention of adipocyte hypertrophy by SE treatment

Mice were fed an HFD or CE-2 with or without SE treatment for 12-weeks. At 3-week, body weight was greater in the HFD group than in the control group (Fig. 1A). Finally, more than a 40% body weight gain ratio compared with the control group was observed in the HFD group. For the HFD + SE group, although no significant body weight change was observed in the first 4-weeks in comparison with the HFD group, a significant body weight decrease was observed at the end of the experimental period (i.e., only 11.2% body weight gain ratio compared with the control group). In addition, to test whether organ weight is decreased by treatment with SE against HFD-induced body weight gain, we measured the weight of liver and epididymal adipose samples. The weight of the liver samples did not differ significantly between HFD and HFD + SE groups (Fig. 1B). In contrast, the weight of epididymal adipose tissue from HFD mice was significantly decreased by the SE treatment (Fig. 1C). These data indicate that SE prevents the increase of WAT mass in HFD-fed mice.

Decreased levels of plasma biochemical parameters by SE treatment

Further, to test whether SE reduces obesity-induced hyperglycemia, we measured fasting plasma glucose levels (Fig. 2A), insulin levels (Fig. 2B), plasma leptin levels (Fig. 2C) and plasma T-CHO levels (Fig. 2D). The mice in the HFD group showed increased plasma concentrations of glucose compared with the mice in the control groups. Treatment with SE for 12-weeks significantly decreased HFD-induced hyperglycemia. Moreover, the same result was observed regarding the plasma insulin and leptin levels. In contrast, T-CHO levels were not changed by the SE treatment. These results indicate that the SE treatment decreases the plasma levels of glucose,

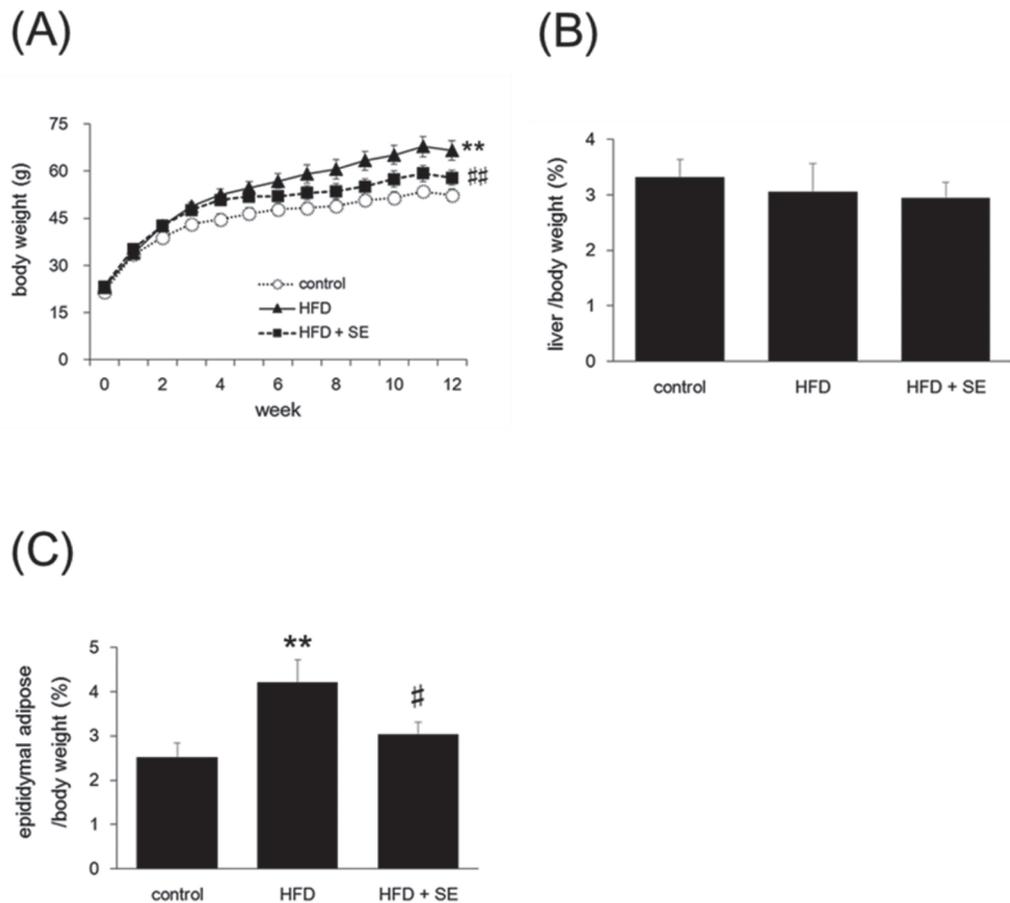


Fig. 1. Effect of *Sasa veitchii* leaf extract on body, liver, and epididymal adipose weight. Mice were fed a high-fat diet (HFD) or a normal diet for 12-weeks. At all periods of the experiment, treatment with *S. veitchii* leaf extract (SE) or saline was conducted. Panel (A), (B), and (C) indicate body weight, liver weight ratio, and epididymal adipose weight ratio, respectively. The other data are plotted as the mean \pm standard deviation (SD) and are representative of 6-10 mice per group. ** $p < 0.01$ versus control group, and # $p < 0.05$ and ## $p < 0.01$ versus HFD group.

insulin, and leptin, suggesting that SE improves glucose metabolism.

We focused on the anti-inflammatory effect of SE and the production of obesity-related factors such as TNF α and IL-6. Plasma TNF α (Fig. 2E) and IL-6 (Fig. 2F) levels of the SE-treated mice were significantly decreased by SE treatment. The data indicate that SE-treated mice have decreased adipokines, suggesting that SE has an anti-inflammatory effect in the adipose tissues.

Improvement of glucose tolerance by SE treatment

To further analyze the effect of SE, we performed OGTT 10-weeks after SE administration. After oral administration of 2 g/kg glucose, the plasma glucose levels were significantly higher at all time points in the HFD

group than in the control group (Fig. 3A). In contrast, glucose levels were significantly lower in the HFD + SE group than in the HFD groups. The AUC was also lower in the HFD + SE group than in the HFD group (Fig. 3B). These results indicate that SE improves glucose intolerance in HFD-induced obese mice.

Decreased adipose sizes by SE treatment

In parallel with the measurement of plasma biochemical parameters, we conducted histopathological studies. Histological analysis showed that the enlarged adipose tissues were observed in HFD-induced obese mice (Fig. 4B), while these tissues in SE-treated mice were much smaller than those in the HFD group (Fig. 4C). The data indicate SE promotes the differentiation of adipocytes.

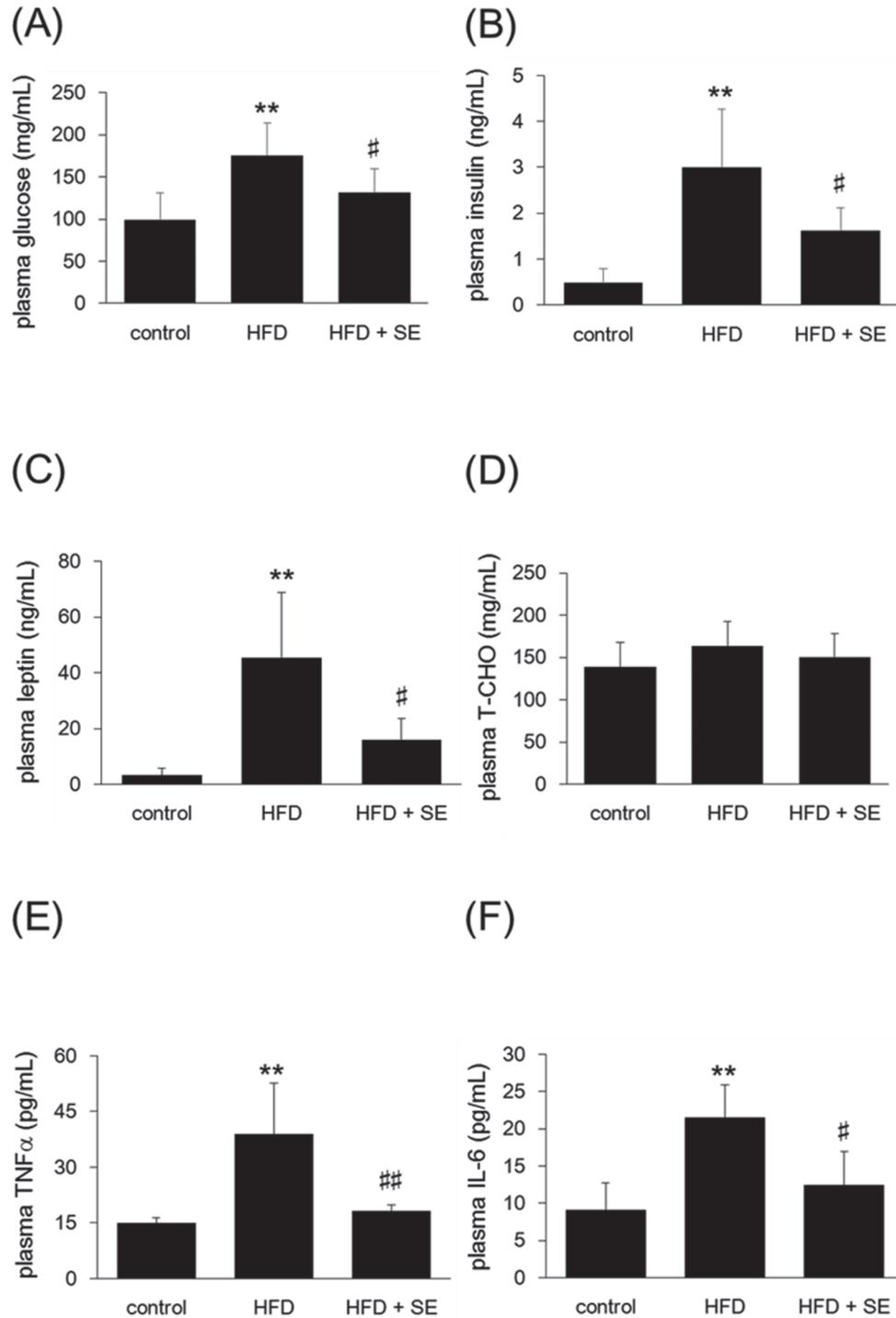
Sasa veitchii extract modulate adipose differentiation in mice

Fig. 2. Effect of *Sasa veitchii* leaf extract on plasma biochemical parameters. Mice were fed a high-fat diet (HFD) or a normal diet for 12-weeks. At all periods of the experiment, treatment with *S. veitchii* leaf extract (SE) or saline was conducted. Following the experiment, the mice from each group were fasted for 16-hr and euthanized and bled for plasma. Panel (A), (B), (C), (D), (E), and (F) indicate plasma glucose, insulin, leptin, total cholesterol (T-CHO), tumor necrosis factor α (TNF α), and interleukin-6 (IL-6), respectively. Data are plotted as the mean \pm standard deviation (SD) and are representative of 6-10 mice per group. ** $p < 0.01$ versus control group, and # $p < 0.05$, and ## $p < 0.01$ versus HFD group.

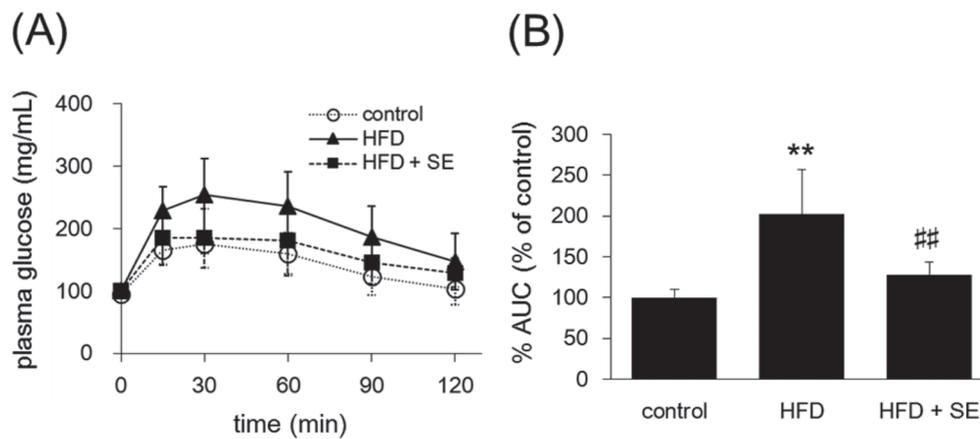


Fig. 3. Effect of *Sasa veitchii* leaf extract on glucose tolerance. Mice were fed a high-fat diet (HFD) or a normal diet for 12-weeks. At all periods of the experiment, treatment with *S. veitchii* leaf extract (SE) or saline was conducted. Oral glucose tolerance testing (OGTT) was conducted for 10-weeks. Before OGTT, the mice were fasted for 16-hr. Panel (A) and (B) indicate plasma glucose levels during an OGTT and the area under the curve (AUC) for plasma glucose, respectively. Data are plotted as the mean \pm standard deviation (SD) and are representative of 6-10 mice per group. ** $p < 0.01$ versus control group, and ## $p < 0.01$ versus HFD group.

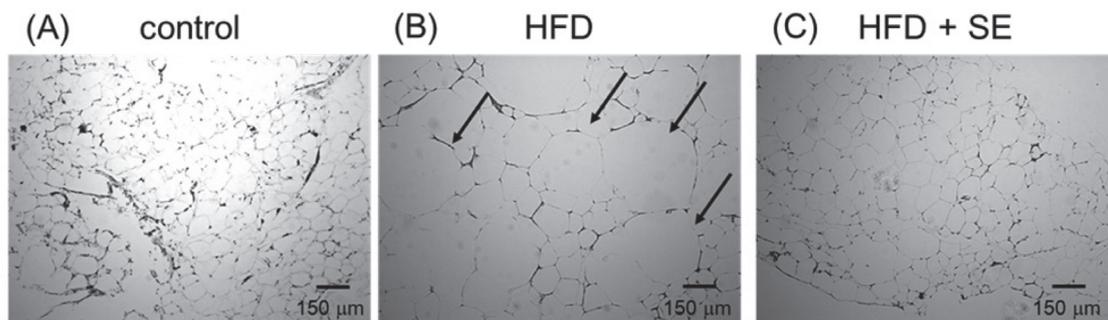


Fig. 4. Effect of *Sasa veitchii* leaf extract on adipocyte size in white adipose tissue, as assessed by hematoxylin and eosin staining. Mice were fed a high-fat diet (HFD) or a normal diet for 12-weeks. At all periods of the experiment, treatment with *S. veitchii* leaf extract (SE) or saline was conducted. Following the experiment, the mice from each group were euthanized and adipose tissues were harvested at necropsy. Adipocyte specimens were fixed and processed by standard methods, and sections were stained with hematoxylin and eosin (H&E). Panel (A), (B), and (C) indicate control, HFD, and HFD + SE, respectively. Black arrows and bar indicate an enlarged adipocyte and 150- μ m, respectively.

Modulated adipose differentiation by SE treatment

Finally, to elucidate effects of SE on the functions of adipocytes, we observed expression levels of adipocyte differentiation markers by western blotting (Fig. 5). The expression levels of PPAR γ and C/EBP α increased by SE treatment in the adipose tissues, respectively. These findings indicate that SE activates adipose differentiation in mice.

DISCUSSION

In the present study, we investigated the effect of SE on obesity and analyzed the underlying mechanism using mice with HFD-induced obesity. We found that SE significantly reduced body weight as well as adipose tissue and plasma glucose, insulin, leptin levels. Furthermore, SE increased glucose intolerance compared with the HFD-induced obese mouse. These results suggest SE ameliorates adiposity, hyperglycemia, and insulin resistance in obese mice. In addition, the duration of SE administration

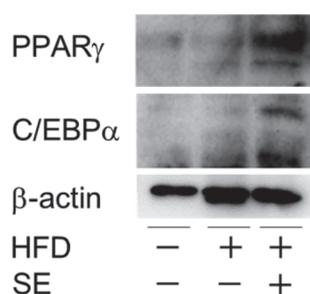
Sasa veitchii extract modulate adipose differentiation in mice

Fig. 5. Effect of *Sasa veitchii* leaf extract on the expression levels of lipid-metabolism-related proteins in white adipose tissue. Mice were fed a high-fat diet (HFD) or a normal diet for 12-weeks. At all periods of the experiment, treatment with *S. veitchii* leaf extract (SE) or saline was conducted. Following the experiment, the mice from each group were euthanized, and the protein was prepared from the white adipose tissue (WAT) and used to measure protein levels by western blotting. As an internal control, we measured β -actin.

in our previous study was only 4-weeks, whereas it was 12-weeks in the present investigation, which proved to be more effective regarding its impact on obesity. These findings indicate that a long phase administration of SE may be more effective in the prevention of obesity.

Adipose tissues play an important role in the maintenance of energy homeostasis and release leptins, adipokines, and adiponectin that are active intracellular mediators (Fasshauer and Paschke, 2003). In addition, plasma leptin concentrations are positively correlated with adiposity in humans and rodents (Maffei *et al.*, 1995). Our study indicated plasma leptin levels were lower in the HFD + SE group than in the HFD group. Moreover, adipose tissues were much smaller in the SE-treated mice, including the HFD + SE group, than in the HFD group. These data suggest that SE treatment reduced lipid accumulation in the adipose tissues.

It is well known that disordered adipokine secretion can cause obesity-induced inflammation, which links obesity to the pathogenesis of insulin-resistant type 2 diabetes (Fernandez-Real and Ricart, 2003). Adiponectin-deficient mice exhibit glucose and insulin resistance, whereas the overexpression of adiponectin in adipose tissue improves insulin intolerance in mice (Nawrocki *et al.*, 2006; Combs *et al.*, 2004). In contrast, inflammatory cytokines such as TNF α and IL-6 impair insulin signaling. TNF and TNF-receptor knockout mice enhanced insulin sensitivity (Uysal *et al.*, 1997). In our study, SE decreased plasma TNF α and IL-6 levels, respectively. These data suggest SE may help to correct the adipokine expression profiles. In particular, PPAR γ plays a crit-

ical role in adipokine regulation (Chinetti *et al.*, 2000), including adiponectin. PPAR γ agonists such as thiazolidinediones have been reported to suppress the production of proinflammatory cytokines including TNF α and IL-6 (Fagerberg *et al.*, 2005). In addition, pioglitazone, which is widely used in the treatment of insulin resistance and type 2 diabetes, elicit anti-inflammatory effects by depressing levels of these cytokines by activating PPAR γ (Kang *et al.*, 2009). As shown in the present study, SE treatment showed PPAR γ activation. Based on this result, SE may correct adipokine release by targeting PPAR γ , thereby improving insulin sensitivity.

Most studies, including ours, utilize an extract obtained from the *S. veitchii* leaves, which have many components. Its pharmacological active substance has not been characterized. Although we hypothesized it was a PPAR γ agonist in the SE, another candidate bioactive molecule is chlorophyll, because it is also present in abundance (250 mg/mL). Moreover, chlorophyll has documented anti-inflammatory activity (Subramoniam *et al.*, 2012). In addition, many new flavonoids or polyphenols have also been discovered in *S. veitchii* (Zhang *et al.*, 2008; Zulkafli *et al.*, 2014), many of which have anti-inflammatory properties. These compounds are also well known for being strong antioxidants that help prevent pathological processes such as obesity and diabetes processes (Hsu *et al.*, 2007). Moreover, our previous study indicated SE showed antioxidant property in the liver (Yoshioka *et al.*, 2016). Hence, these compounds may mediate the anti-obesity effect of SE partially making them candidate bioactive molecules. Further analysis of *Sasa* components will lead to the identification of the active substance(s) in *S. veitchii*. Further investigation is needed to elucidate this question in future studies, which are currently in progress.

In conclusion, we found that the oral administration of SE reduces adipose weight, plasma glucose levels, plasma insulin levels, plasma leptin levels, and glucose resistance in HFD-induced obese mice. These effects were accompanied by changes in the regulation of the adipocytokine gene expression and the activation of the PPAR γ . Our findings suggest that SE is a useful tool for improving not only obesity-induced inflammation but also obesity-related metabolic disorders.

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Conflict of interest--- The authors declare that there is no conflict of interest.

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