

Anti-obesity activity of *Allium fistulosum* L. extract by down-regulation of the expression of lipogenic genes in high-fat diet-induced obese mice

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Abstract. This study investigated the anti-obesity activity and underlying mechanism of a 70% ethanol extract from *Allium fistulosum* L. (AFE) in high-fat diet-induced obese mice. AFE was orally administered to mice with the high-fat diet at a dose of 400 mg/kg/day for 6.5 weeks. AFE treatment significantly reduced body weight and white adipose tissue (subcutaneous, epididymal and retroperitoneal) weight as well as adipocyte size compared to high-fat diet-induced control mice. AFE also significantly decreased triglyceride, total cholesterol, low density lipoprotein-cholesterol and leptin concentrations in the serum of the mice, whereas it increased adiponectin levels. Furthermore, AFE suppressed the mRNA expression of transcription factors, such as sterol regulatory element binding protein-1c and peroxisome proliferator activated receptor γ , as well as fatty acid synthase in the subcutaneous adipose tissue. These results suggest that AFE inhibited the adipose size, fat accumulation and serum lipid concentrations by down-regulation of the expression of genes involved in lipogenesis in the adipose tissue of high-fat diet-induced obese mice.

Introduction

Obesity is a major public health problem in the developed world. It is associated with a variety of metabolic disorders, such as hyperlipidemia, fatty liver, type 2 diabetes mellitus, atherosclerosis, hypertension and certain types of cancer (1-3). Obesity is defined as excessive body fat (adiposity), which

is caused by an imbalance between food intake and energy expenditure (4). Many pharmacological approaches to the treatment of obesity have recently been investigated. However, these pharmacological drugs for the control of lipid uptake or appetite have been reported to have some side effects, such as constipation, insomnia, vomiting, headache, stomachache and heart attack (5,6). Therefore, alternative therapies, such as plant extracts and natural products, have been in demand for effective and safe anti-obesity drugs. Oriental herbal medicine has been reported to be useful for the treatment of obesity without adverse effects (7-9).

Obesity is characterized by enlarged fat mass that results from increased adipose cell size and number (10). Adipose cell size is determined by the amount of fat that accumulates in the cytoplasm of adipocytes, which is involved in various enzymes, such as fatty acid synthase (FAS), lipoprotein lipase (LPL) and adipocyte fatty acid-binding protein (aP2). The transcriptional expression of these lipid metabolizing enzymes has been reported to be regulated by three major transcription factors: peroxisome proliferator activated receptor (PPAR) γ , sterol regulatory element binding protein (SREBP)-1c and CCAAT/enhancer binding protein (C/EBP) α (11).

Allium fistulosum L. (Welsh onion) is a gregarious perennial herb that is widely cultivated in Asia, including Japan, China, Vietnam and Korea. *Allium fistulosum* is a member of the onion family, Alliaceae. In Korea, *Allium fistulosum* is a popular vegetable crop that is widely used in cooking. The roots and bulbs of *Allium fistulosum* have traditionally been used for the treatment of febrile disease, headache, abdominal pain and diarrhea. Recently, *Allium fistulosum* was reported to have anti-fungal, anti-oxidative, anti-platelet and anti-hypertensive activity (12-14). However, the anti-obesity activity of *Allium fistulosum* has yet to be investigated. In this study, the anti-obesity effect of the 70% ethanol extract of *Allium fistulosum* L. (AFE) and its underlying mechanism were elucidated in high-fat diet-induced obese mice.

Materials and methods

Preparation of *Allium fistulosum* extract. *Allium fistulosum* was purchased in dried herb form from Hanherb Co. (Seoul, Korea) and was authenticated based on its microscopic and macroscopic characteristics by the Classification and Identification Committee of the Korea Institute of Oriental

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Abbreviations: FAS, fatty acid synthase; LDL, low density lipoprotein; FER, food efficiency ratio; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; AFE, *Allium fistulosum* extract; HDL, high density lipoprotein; HFD, high-fat diet; ND, normal diet; PPAR, peroxisome proliferators activated receptor; SREBP, sterol regulatory element binding protein

Key words: adipocytokine, *Allium fistulosum* L., anti-obesity, high-fat diet, lipogenesis

Table I. Sequences of primers used for RT-PCR analysis.

Genes	Forward	Reverse	Accession no.	Length (bp)
PPAR γ	CCCTGGCAAAGCATTGTAT	GAAACTGGCACCCCTTGAAAA	NM_011146	225
SREBP-1c	AGCTCAAAGACCTGGTGGTG	TCATGCCCTCCATAGACACA	NM_011480	216
FAS	CGCACCGGCTACCAAGCCAA	GCTTCCC GGTTGCCCTGTC	NM_007988	266

Medicine (KIOM). The committee was composed of nine experts in the fields of plant taxonomy, botany, pharmacognosy and herbology. A voucher specimen (no. JA-97) was deposited at the herbarium of the Department of Herbal Resources Research in KIOM. The dried bulbs and roots of *Allium fistulosum* (200 g) were extracted twice with 70% ethanol (with 2 h reflux), and the extract was then concentrated under reduced pressure. The decoction was filtered, lyophilized and serially stored at 4°C. The yield of dried extract from the initial crude materials was ~15.91% (w/w).

Animals and treatment. Male 4-week-old C57BL/6J mice were purchased from Daehan Biolink Co. (Eumsung, Korea) and maintained for 1 week prior to the experiments. The mice were housed in an air-conditioned animal room with a 12-h light/dark cycle at a temperature of 22±1°C and humidity of 50±10%. Mice were provided with a laboratory diet and water *ad libitum*. All experimental protocols for animal care involving the use of animals were conducted in accordance with the National Institutes of Health (NIH) guidelines and approved by the Committee on Animal Care of our institute. For the induction of obesity, the mice were fed a high-fat diet (Rodent diet D12492, Research Diet, New Brunswick, NJ, USA) providing 60% of energy as fat, 20% as protein and 20% as carbohydrates. Normal mice were fed a commercial standard chow diet (Orient Bio Inc., Seongnam, Korea). AFE was dissolved in normal saline and was orally administered to the mice at a dose of 400 mg/kg/day for 6.5 weeks. The dose of AFE used in these experiments was determined in preliminary experiments involving a dose range and also in previously published reports (15,16). The mice were randomly divided into three groups (n=7) and respectively fed a normal diet (ND), a high-fat diet (HFD) and a high-fat diet plus AFE (HFD + AFE) for 6.5 weeks. Body weight and food intake were measured twice a week.

Biochemical assay of serum. At the end of the experiment period, the mice were fasted for 15 h prior to being sacrificed. The mice were anesthetized with ether and then blood samples were obtained from the inferior vena cava. Blood samples were centrifuged at 2,500 rpm for 15 min at 4°C, and serum was obtained and stored at -70°C before analysis. Serum levels of triglyceride, total cholesterol, LDL-cholesterol and high density lipoprotein (HDL)-cholesterol were analyzed by an automatic analyzer (Hitachi 7080; Hitachi Co., Tokyo, Japan). The concentrations of serum leptin and adiponectin were measured with a mouse leptin and adiponectin ELISA kit (R&D, Minneapolis, MN, USA), respectively, according to the manufacturer's instructions. The absorbance was measured using a microplate spectrophotometer (BioRad, Hercules, CA, USA).

Adipose tissue weight and histology analysis. After collecting the blood, the white adipose tissues (subcutaneous, epididymal and retroperitoneal) were removed from the mice and then weighed immediately. For adipocyte staining, adipose tissues were fixed in 4% formalin solution for 1 day and embedded in paraffin. All tissues were cut with a thickness of 6 μ m and stained with H&E. To quantitate adipocyte size, the stained sections were analyzed using light microscopy (Olympus BX51; Olympus Optical Co., Tokyo, Japan) and an image analysis program (Image pro plus 5.0; Media Cybernetics, Silver Spring, MD, USA).

Reverse transcriptase-polymerase chain reaction (RT-PCR). The tissue was homogenized and total RNA was isolated with the easy-BLUE total RNA extraction kit (Intron, Seoul, Korea) according to the manufacturer's instructions. For cDNA synthesis, 1 μ g of total RNA was mixed with premix containing oligo dT primer and DEPC-treated water to a final volume of 20 μ l, then incubated at 45°C for 60 min. The reaction was stopped by heat inactivation at 95°C for 5 min. Then, cDNAs were amplified with primers specific for genes using *Taq* PCR master mix (Qiagen, Takyo, Japan) according to the manufacturer's instructions. The 20- μ l amplification mixture contained 1 μ l of cDNA and 10 μ l of 2X *Taq* PCR master mix containing 1.5 mM MgCl₂, 0.1 μ M of each primer and water. After 15 min of pre-incubation at 94°C, the PCR amplification was performed for 35 cycles using the following cycling conditions: 30 sec of denaturation at 94°C, 30 sec of annealing at 60°C and 1 min of extension at 72°C. Primers were designed using Primer3 software and the sequences available in the GenBank database. Table I shows the sequences of the gene-specific PCR primers. The relative expression levels of target genes were normalized using GAPDH as an internal control.

Statistical analysis. The differences between groups were examined using an unpaired Student's t-test. All data were presented as the means \pm SE. Significant differences were accepted when the p-value was <0.05.

Results

Changes in body weight, food intake and food efficiency ratio (FER). The body weight, body weight gain, food intake and FER of the mice fed the high-fat diet with oral treatment of AFE for 6.5 weeks are shown in Fig. 1 and Table II. The final body weight of mice fed the high-fat diet was significantly higher than that of mice fed the normal diet (p<0.001). However, the AFE treatment reduced body weight compared to the high-fat diet control group by ~10%. Body weight gain was significantly decreased in the AFE-treated group compared to the high-fat

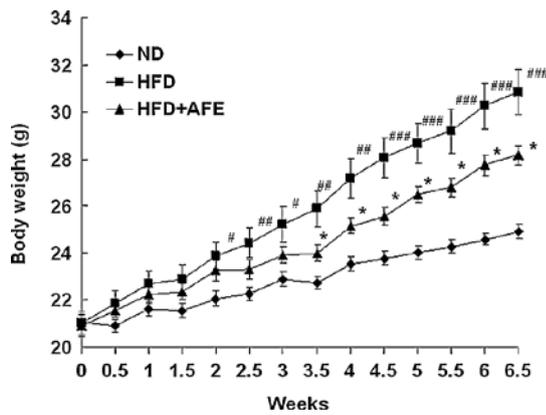


Figure 1. Effect of *Allium fistulosum* extract on body weight in obese mice fed a high-fat diet for 6.5 weeks. AFE were orally administered to the mice at a dose of 400 mg/kg/day. ND, normal diet; HFD, high-fat diet; HFD + AFE, high-fat diet + *Allium fistulosum* extract. Values are the mean \pm SE (n=6). Significant differences between the ND and HFD groups, #p<0.05; ##p<0.01 and ###p<0.001. Significant differences between the HFD and HFD + AFE groups, *p<0.05 and **p<0.01.

Table II. Effects of *Allium fistulosum* extract (AFE) on body weight gain, food intake and food efficiency ratio (FER) in high-fat diet-induced obese mice.

	ND	HFD	HFD + AFE
Body weight gain (g/mice)	3.84 \pm 0.23	9.81 \pm 0.59 ^a	7.46 \pm 0.63 ^b
Food intake (g/day)	4.65 \pm 0.29	2.50 \pm 0.07 ^a	2.59 \pm 0.13
FER	0.84 \pm 0.06	3.87 \pm 0.17 ^a	2.40 \pm 0.44 ^b

Body weight gain = final body weight - initial body weight. FER = body weight gain/food intake. Values are expressed as the means \pm SE (n=6). Significant differences between the ND and HFD groups, ^ap<0.001. Significant differences between the HFD and HFD + AFE groups, ^bp<0.05.

diet control group (p<0.05). However, AFE did not affect food intake. FER was higher in the HFD group than in the ND group. However, in the AFE-treated group, the FER was significantly decreased compared to the HFD group, by 38% (p<0.01).

Serum levels of lipid parameters. AFE treatment with the high-fat diet significantly suppressed the increase of triglyceride, total cholesterol and LDL-cholesterol concentrations compared to the high-fat diet control mice (p<0.05) (Table III). However, HDL-cholesterol concentration did not differ between the HFD and the HFD + AFE-treated groups.

Serum levels of leptin and adiponectin. The high-fat diet increased the serum leptin level significantly compared to the normal diet-fed mice (p<0.001). However, AFE-treated mice had a decreased serum leptin level compared to the high-fat diet control mice (p<0.05) (Table III). The concentration of serum adiponectin was significantly increased in the AFE-treated group compared to the high-fat diet group (p<0.05).

Table III. Effects of *Allium fistulosum* extract (AFE) on biochemical parameters in the serum of high-fat diet-induced obese mice.

	ND	HFD	HFD + AFE
Triglyceride (mg/dl)	68.0 \pm 6.5	88.7 \pm 11.2	48.2 \pm 3.8 ^c
Total cholesterol (mg/dl)	110.3 \pm 3.8	166.3 \pm 2.0 ^b	148.4 \pm 3.9 ^c
LDL-cholesterol (mg/dl)	4.8 \pm 0.1	5.9 \pm 0.3 ^a	4.5 \pm 0.2 ^d
HDL-cholesterol (mg/dl)	74.0 \pm 2.5	76.5 \pm 4.9	71.7 \pm 1.7
Leptin (ng/ml)	2.16 \pm 0.48	16.91 \pm 2.26 ^b	10.85 \pm 1.05 ^c
Adiponectin (ng/ml)	7.74 \pm 0.16	6.33 \pm 0.26	9.42 \pm 0.47 ^c

Values are expressed as the means \pm SE (n=6). Significant differences between the ND and HFD groups, ^ap<0.05 and ^bp<0.001. Significant differences between the HFD and HFD + AFE groups, ^cp<0.05 and ^dp<0.01.

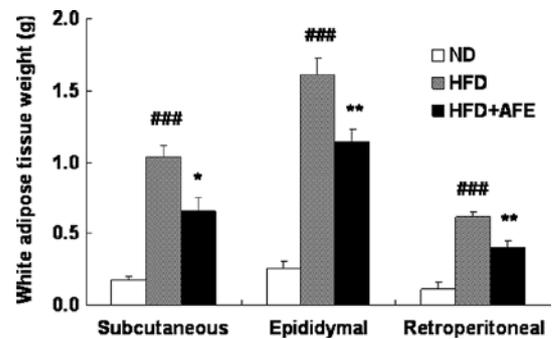


Figure 2. Effect of *Allium fistulosum* extract on white adipose tissue weight in high-fat diet-induced obese mice. ND, normal diet; HFD, high-fat diet; HFD + AFE, high-fat diet + *Allium fistulosum* extract. Values are the mean \pm SE (n=5). Significant differences between the ND and HFD groups, ###p<0.001. Significant differences between the HFD and HFD + AFE groups, **p<0.01.

Weight and histology of adipose tissue. To investigate whether AFE causes a decrease in adiposity, the mice were sacrificed and their adipose tissues were removed and weighed. The weight of various white adipose tissues, including subcutaneous, retroperitoneal and epididymal adipose tissues, was increased in the HFD mice compared to the ND mice. The weight of the white adipose tissues was significantly decreased by treatment with AFE (p<0.05) (Fig. 2). The adipose tissues were further examined histologically (Fig. 3A). The adipocyte size of the subcutaneous, retroperitoneal and epididymal adipose tissues were significantly larger than those of the HFD group (p<0.001) (Fig. 3B). When mice were treated with the high-fat diet and AFE, the size of the adipocytes was significantly decreased compared to those of the high-fat diet group (p<0.05).

Expression of genes involved in lipid metabolism. To understand the mechanism involved in the effect of AFE on lipid metabolism, the expression of the genes involved in lipogen-

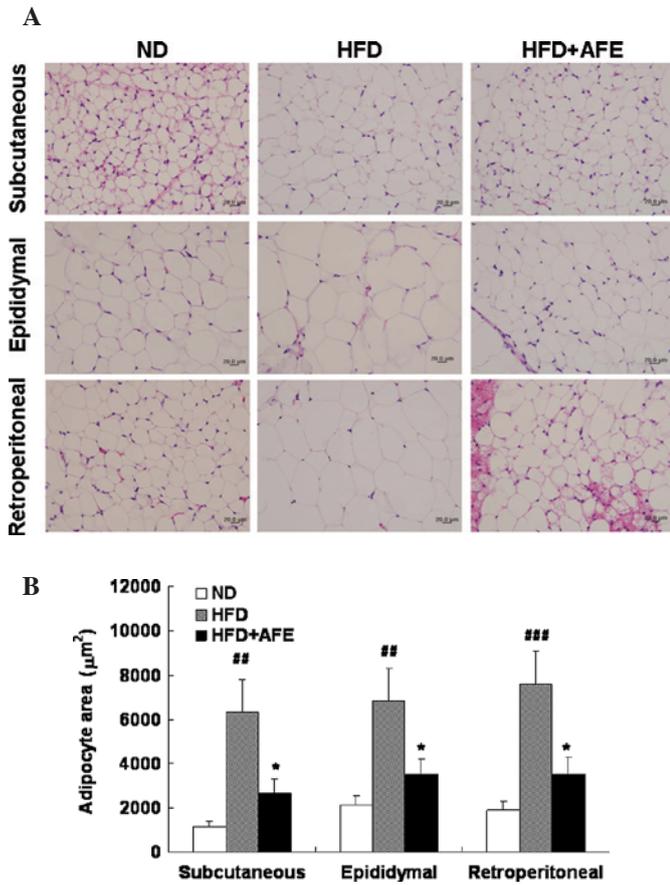


Figure 3. Histology of white adipose tissues in high-fat diet-induced obese mice. (A) Representative photographs and (B) adipocyte area of H&E-stained sections (magnification, x400). ND, normal diet; HFD, high-fat diet; HFD + AFE, high-fat diet + *Allium fistulosum* extract. Values are the mean ± SE (n=20). Significant differences between the ND and HFD groups, ^{##}p<0.01 and ^{###}p<0.001. Significant differences between the HFD and HFD + AFE groups, ^{*}p<0.05 and ^{**}p<0.01.

esis in adipose tissue was investigated (Fig. 4). Compared to normal mice, the high-fat diet induced increased mRNA levels of transcription factors, such as SREBP1c and PPAR γ as well as FAS, a lipid metabolizing enzyme, in the subcutaneous adipose tissue of obese mice. By contrast, AFE treatment decreased the mRNA expression of these genes compared to their levels in the high-fat diet group.

Discussion

In this study, AFE administration to high-fat diet-induced obese mice decreased adipocyte size as well as body weight and adipose tissue mass. In addition, AFE reduced the serum triglyceride, total cholesterol, LDL-cholesterol and leptin concentrations. Adipose tissue accumulation due to adipocyte hypertrophy (increased adipocyte size) induces changes in the secretion of adipocytokines, such as leptin, tumor necrosis factor- α , resistin and adiponectin, involved in the development of insulin resistance (17). Leptin, a protein mainly secreted by the adipocytes, plays a crucial role in regulating body weight by controlling the size of the adipose tissue mass (18). Plasma levels and mRNA expression of leptin are directly associated with adiposity and body weight changes in humans and rodents (19). Thus, the decreased serum

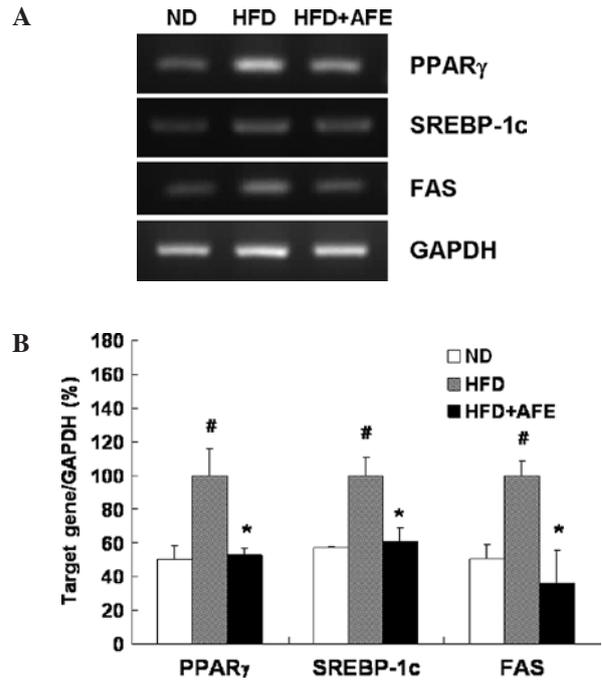


Figure 4. Effect of *Allium fistulosum* extract on PPAR γ , SREBP-1c and FAS mRNA expression in subcutaneous adipose tissue of high-fat diet-induced obese mice. (A) Representative bands and (B) relative changes in mRNA expression are shown. Values are the mean ± SE (n=3). ND, normal diet; HFD, high-fat diet; HFD + AFE, high-fat diet + *Allium fistulosum* extract.

leptin level in AFE-treated mice may be attributable to the decrease in adipose tissue mass. AFE treatment also elevated adiponectin levels in the serum of the high-fat diet-induced mice. Adiponectin is an adipose tissue-secreted protein that enhances insulin sensitivity and fatty acid oxidation (20). It has been shown that plasma adiponectin levels are reduced in individuals with insulin resistance, obesity and type 2 diabetes mellitus (21,22). Administration of adiponectin reduced weight gain induced by a high-fat diet in mice (23). It has been reported that circulating adiponectin levels are inversely correlated with body fat mass and insulin resistance (24,25). Therefore, the increased serum adiponectin level induced by AFE treatment ameliorated insulin resistance in the high-fat diet-induced obese mice, resulted in reduced serum lipid concentrations and body weight loss.

PPARs are well characterized transcription factors that are members of the nuclear hormone receptor superfamily (26). PPAR γ is primarily expressed in adipose tissue and plays an essential role in the regulation of genes involved in adipocyte differentiation, glucose homeostasis and fat tissue development (27). It has been shown that PPAR γ regulates the transcription of LPL, aP2, phosphoenolpyruvate carboxykinase, fatty acid transporters and uncoupling protein-2 in adipocytes (28,29). Sterol regulatory element binding proteins (SREBPs) are major transcription factors that regulate lipid homeostasis by directly activating the expression of genes required for the synthesis and uptake of cholesterol, fatty acid and triglycerides (30). In particular, SREBP-1c is a key lipogenic transcription factor that regulates the transcriptional expression of metabolizing enzymes of fatty acid biosynthesis, such as FAS and acetyl CoA carboxylase (31). FAS is an important lipogenic enzyme that catalyzes the biosynthesis of fatty acids from acetyl-coen-

zyme A precursors (32). It was reported that the transcription of FAS is activated through binding to its promoter region by SREBP-1 (33). In this study, AFE treatment in obese mice fed the high-fat diet decreased adipose tissue accumulation, adipocyte size and body weight. AFE treatment also significantly reduced the mRNA expression of PPAR γ and SREBP-1c, as well as FAS, in the subcutaneous adipose tissue. These results suggest that AFE may decrease weight gain and body fat mass by downregulation of SREBP-1c and PPAR γ expression, which leads to the inhibition of the transcription of lipogenic enzymes, such as FAS.

In conclusion, AFE treatment inhibited the expression of SREBP-1c, PPAR γ and FAS in the adipose tissue of high-fat diet-induced obese mice. These changes led to decreased adipocyte size, fat mass and serum lipid levels, and altered adipocytokine secretion. These results suggest that *Allium fistulosum* L. may be a promising candidate for the treatment of obesity.

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