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Effects of Low Calorie Diet and *Platycodon Grandiflorum* Extract on Fatty Acid Binding Protein Expression in Rats with Diet-induced Obesity

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Obesity can be defined as a metabolic disease due to an increased fat accumulation in the body caused by an imbalance of calorie intake and output. The prevalence of obesity has increased substantially over the past 2-3 decades in developed and developing countries. The health impact of weight gain is so marked that obesity has now been classified as a major global public health problem.

In order to investigate the effect of diet conversion and oral administration of *Platycodon grandiflorum* extracts on the treatment of obesity, male Spraque-Dawley rats were divided into four groups: a group converted to normal diet (Control group), a group maintained high fat (30%) diet (H), and two groups with *Platycodon grandiflorum* extract added to the previously mentioned two groups. All animals were fed high fat diet for 7 weeks to induce the obesity. Then they were divided as mentioned above. Animals were fed experimental diet and *Platycodon grandiflorum* extract (150 mg/ml/rat/day) for 7 weeks. Body weight, adipose tissue weight (subcutaneous, epididymal, peritoneal fat pads) and serum lipids (total cholesterol and triglyceride) showed some differences among groups. The *Platycodon grandiflorum* feeding markedly decreased both body weight and adipose tissue weight in control group compared to H, high fat diet maintaining, group. *Platycodon grandiflorum* extracts significantly decreased the concentrations of serum lipids compared to H group. Fat cell numbers and sizes were significantly reduced in the oriental medicinal herb extract administrated group.

Increased fatty acid binding protein (FABP) expression in high fat diet group was decreased by the dietary conversion to normal diet and the oral administration of *Platycodon glandiflorum* extracts. In contrast, there was no significant effect on FABP expression in the high fat maintenance group.

In this study, the conversion from high fat diet to low fat or normal diet had a beneficial effect on body weight loss and serum lipid profiles. Dietary *Platycodon glandiflorum* extracts had an additive beneficial effect on the prevention and treatment of obesity.

Key words: *Platycodon glandiflorum* extracts, High fat diet, Obesity, FABP

INTRODUCTION

Obesity is defined as an imbalance of energy metabolism due to excessive energy intake or decreased energy consumption, whi.ch accelerates the accumulation of excessive fat that can further causes various metabolic diseases such as hypertension, hyperlipidemia, fatty liver, arteriosclerosis, and diabetes.[1-4]

The purpose of obesity treatment is to maintain healthy body weight through behavioral modifications that include not only weight reduction but also appropriate dietary intake and regular exercise.[5-7]

Diet therapy is fundamental for the treatment of simple obesity, in which the food intake is restricted and the energy consumption is increased so that the energy intake becomes smaller than the energy consumption and the body obtains energy supply from the fat accumulated in the body.[7,8] The safest diet therapy for the obese is a nutritionally balanced low calorie diet (LCD). Balanced low calorie diet, a diet therapy using the food exchange group, is prescribed by health professionals and effective in the correction of dietary habits of obese people.[9]

In addition to changes in dietary habits, drug therapy has been often accompanied.

Platycodon grandiflorum, which is a perennial plant in Campanulaceae family, contains triterpenoid saponin, carbohydrates, and fibers. It has been known to be effective in anti-inflammation, lowering blood pressure. For studies on the lipid-lowering activity of *Platycodon*

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glandiflorum in the serum and liver, Fisher *et al.*[10] reported that fibers in *Platycodon glandiflorum* inhibited the progress of atherosclerosis by reducing cholesterol in white rats. Oakenfull *et al.*[11] and Sidhu & Oakenfull[12] reported that saponins reduced the serum cholesterol concentration by inhibiting the reuptake of bile acids in the intestine and increasing its fecal excretion. Also, lipid-lowering effects of *Platycodon glandiflorum* extract in the serum and liver tissues have been reported since its pharmacological actions were reported in the country.[11-14] These effects might be useful to treat and prevent obesity without side effects.

FABP (fatty acid binding proteins) in liver, heart, intestine, and adipose tissues were increased after the long-term intake of high fat diet or diet with highly concentrated sugars, and serum lipid lowering agents such as clofibrate and cholestyramine increased the absorption rate of free fatty acids and the amount of FABPs inside the liver cells.[15] Also, it was reported that FABP influenced the activity of enzymes related to lipid metabolism in *in vitro* experiments,[16-19] suggesting that the FABP content in tissues also could be changed when the metabolism related to obesity was changed and this protein had an important role in the intracellular lipid utilization. In addition, FABP content was increased by high fat diet which was understood as the high fat diet increased the oxidation of fatty acids and further increased the transport of fatty acids into the mitochondria inside the hepatocytes.[20-22]

Based on the above experimental results, this study was performed to investigate the effect of shifting to the low-calorie diet on the improvement or treatment of obesity in high-fat diet induced obesity, and also to investigate the effect of simultaneous administration of *Platycodon glandiflorum*, which has been used in the treatment of obesity using *Platycodon glandiflorum* extract, on the FABP expression in adipose tissues.

MATERIALS AND METHODS

1. Preparation & Oral Administration of *Platycodon Glandiflorum* Hot Water Extract

Oriental medicinal herb used in this experiment was *Platycodon glandiflorum* that was approved as a foodstuff among Oriental medicinal ingredients used for the treatment of obesity and preliminary experiments. *Platycodon glandiflorum* was obtained from products of Yeongcheon-gun, Gyeongsangbuk-do. *Platycodon glandiflorum* was extracted in 5 times volume of distilled water for 2 hours for the first extraction, and then the collected extract was mixed again with 5 times volume of distilled water and extracted for 2 hours for the second extraction. The final extract was collected and concentrated by using a vacuum evaporator (Buchi Rotavapor R-114, Switzerland), and then freeze-dried to use this experiments.

The administration of hot water extracts of Oriental medicinal herbs was decided as the same daily dose for human on the basis of 4 general prescriptions for obesity such as Bi-gam-whan, Che-gam-haeng-hyeol-ui-i-in-tang, Che-gam-bo-hyeol-an-shin-tang, and Che-gam-bang-pung-tong-seong-san.[23]

After the one-week of adaptation period, the experimental diet was given for 7 weeks along with the oral administration of hot water extract of *Platycodon glandiflorum* to examine the effect of the oral administration of *Platycodon glandiflorum* on the improvement of dietary obesity.

2. High-Fat Diet Induced Obese Rats

Experimental animals used in this study were 14-week old male Sprague-Dawley rats (Dae-Han Bio Link) with the average body weight of 438.04±3.09 g for the first experimental design and 7-week old male rats with the average body weight of 318.43±3.80 g for the second experimental design. These experimental animals were housed two per metabolic cage and maintained with regular feeding management everyday during the experimental period. The animal room was maintained at 22±2 ℃ and animals had free access to water and experimental feeds.

3. Experimental Diet Preparation and Experimental Group Design

Experimental diet was prepared on the basis of the AIN-93G.[24]

Basal diet provided 11.7% of its total energy from fat and high fat diet, in which corn oil and parts of corn starch in the basal diet were replaced by lard, provided 59.8% of its total energy from fat. Dietary obesity was induced by providing high fat diet for 7 weeks and then animals were divided into two groups in which one group was shifted to normal diet and the other group was

Table 1. Composition of basal and experimental diet

	Basal (%)	High Fat Diet (%)
Casein	16	15
Sucrose	10	10
Corn starch	59	31
Lard (80% contained)	-	37
Corn oil	5	-
Cellulose	5	2
Vitamin mix	1	1
Mineral mix	3.5	3.5
Choline bitartarate	0.2	0.2
DL-Methionine	0.3	0.3
Energy (Kcal/100g)	385	557
Energy from fat (%)	11.7	59.7

maintained on the high fat diet for another 7 weeks. Experimental groups in this study were divided into four groups such as a group maintained on high fat diet, a group shifted from high fat diet to normal diet, and two groups with the addition of *Platycodon glandiflorum* extract to the previously mentioned two groups. The composition of experimental diets was shown in Table 1.

4. Blood Sampling and Serum Lipid Concentration Analysis

Blood samples were obtained from the tail vein of rats at the 0, 2, 4 and 7 week (the last day) of the experiment and centrifuged. Plasma samples obtained from the centrifugation were used as samples for blood lipid concentration analysis. All plasma samples were stored at -80 ℃ before the analysis.

Total cholesterol and triglyceride concentrations were measured using analysis kit manufactured by Asan Pharmaceutical Co. Ltd.

5. Anatomical Observation and Tissue Treatment

Animals were anesthetized with ether and their livers and three adipose tissues such as subcutaneous adipose tissues, epididymal adipose tissues, and retro-peritoneal adipose tissues were isolated, weighed, and then quickly frozen in dry ice for samples for adipocyte staining. As previous report indicated,[25] when open the abdomen, subcutaneous adipose tissue was collected from white fat pad covered internal organ.

6. Fat Cell Number and Average Area of Various Adipose Tissues

It is necessary to measure the changes of body fat size and fat cell numbers in the observation of body fat increase. Among adipose tissues, the cell number and cell area of epididymal adipose tissue were measured.

Frozen epididymal adipose tissue was thinly sliced serially in depth with 40 μm by using freezing microtome (cryostate) and stained with Mayer's hematoxylin, and then the cell area was measured by using light microscopy and image analysis program.

7. Epididymal Adipose Tissue PPARγ and FABP Expression by RT-PCR

The RNA in epididymal adipose tissue was separated by guanidinium-thiocyanate method[26] using Triazol Reagent (Gibco BRL, Gaithersburg, MD).

FABP gene fragment and PPARγ2 gene fragment were amplified by using reverse transcription polymerase chain reaction (RT-PCR) with oligonucleotide primers to examine the changes in the expression of FABP gene and PPARγ2 gene.

Oligonucleotide primers were manufactured by Bioneer (Korea) and RT-PCR was performed by using Accupower RT-PCR premix (Bioneer, Korea).

Each primer was listed as below.

Gene name	primer site	primer sequence
FABP	sense(+36-+55)	5' TCT CCA GTG AGA ACT TCG AT 3'
	antisense(+335-+316)	5' TTC TTT ATG GTG GTC GAC TT 3'
PPARγ2	sense(+289-+308)	5' CAC TAT GAA GAC ATC CCG TT 3
	antisense(+926-+907)	5' TCG TAG ATG ACA AAT GGT GA 3
β-Actin	sense(+199-+207)	5' CTG AAG TAC CCC ATT GAA C 3'
	antisense(+658+639)	5' CAA CAT AGC ACA GCT TCT CT 3'

One ug of RNA, sense primer 20 pmol, and antisence primer 20 pmol were added to the RT-PCR premix in the PCR system 2700 (Perkin-Elmer, U.S.A.) and then RT-PCR was performed under the following conditions: for make cDNA template, 1 ug RNA was transcribed by M-MLV reverse transcriptase at 42 ℃ for 60 min to make cDNA then its cDNA was amplified for target mRNA expression at annealing temperature of 50 ℃ for 1 min, 30 cycle. Its amplified products The PCR products were separated on 1% agarose gel. Each mRNA expression level was identified as its target size.

8. FABP Content in Liver Tissue

Protein Separation in the cytosol

Isolated liver tissue was weighed and homogenized with 10 mM KCl-PO_4 buffer (pH 7.4) and centrifuged at 9,800 g for 20 minutes. The supernatant was centrifuged again at 38,000 g for 60 minutes and eliminated the lipid layer with a gauge. Then the supernatant was used as cytosol samples. All of these manipulations were per- formed at 4 ℃.

SDS-PAGE (Sodium Dodesyl Sulfate Polyacrylamide Gel Electrophoresis)

The protein content in the cytosol was measured by Bradford method[32] and 50ug of cytosolic protein was separated by using 12% SDS-PAGE (sodium dodesyl sulfate polyacrylamide gel electrophoresis) and stained with Ponceau S solution. Proteins with the molecular weight of 14 kDa was considered as FABP and then compared.

Western Blotting

After the SDS-PAGE electrophoresis was finished, western blotting was performed by using FABP antibody. Electrophoresis gel was transferred to the nitrocellulose membrane at 100 voltage for 1.5 hours, reacted in 5% skim milk solution for 1 hour, reacted with 1:500 diluted FABP antibody (Alpha Diagnostics Int., Cat# FABP12-S) for 12 hours, and then reacted with 1:2000 diluted anti-rabbit-IgG (whole molecule alkaline phosphatase

conjugate) for 2 hours. After washing the nitrocellulose membrane that was reacted with the antibody, it was reacted with ECL™ (Amersham Pharmacia Biothech RPN 2209) solution for 1 minute and measured for the intensity of bands appeared on the X-ray film.

9. Statistical Analysis

Statistical analysis for experimental results was performed by SPSS program and all measurements were expressed as Mean±SE. The significance test for analyzed values was performed by using one way-ANOVA. Duncan's multiple-range test was performed on analyzed values at the level of $p<0.05$ to analyze the significant differences among average values of each treatment group.

RESULTS AND DISCUSSION

1. Body Weight Changes in Experimental Animals

Body weight changes of obese rats in each group for 7 weeks and the weekly weight gain on the basis of the weight value at 0 week was presented in Table 2.

Table 2. Body weight of SD rats fed experimental diets and oriental medical herb extracts

	week	0	2	4	7
C[2]	DW	535.44±30.35[1)a]	549.86±33.36[ab] (4.17±1.28[ab])	586.37±28.82[ab] (9.06±1.67[ab])	632.74±32.23[b] (13.90±2.12[ab])
	PG[4]	510.63±18.57[a]	509.08±17.27[a] (2.28±0.55[ab])	546.87±21.43[ab] (-2.94±1.80[a])	569.08±37.55[ab] (8.35±3.43[b])
H[3]	DW	513.33±0.35[a]	517.05±0.73[a] (5.23±2.48[b])	586.01±1.41[b] (13.50±2.48[c])	657.43±2.48[b] (20.59±2.48[d])
	PG	500.65±6.30[a]	512.10±5.21[a] (2.42±0.44[ab])	550.34±4.19[ab] (8.28±0.88[b])	585.47±12.32[ab] (12.15±0.61[ab])

1) Mean±SE
2) Converted group to the control diet
3) High fat diet maintain group
4) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat
( ) : Body weight gain during experimental period

At the beginning of the experiment, the average body weight of 7-week old rats was 318.43±3.80 g and significantly increased to 516.19±5.98 g after 7 weeks of high fat diet. These obese rats were randomly selected and grouped for the following experiment.

In high fat diet maintaining group (H group) showed significant increase in body weight and maintained obesity when compared to control group (converted to normal diet). The body weight reduction was significant in control group.

In case of the oral administration of *Platycodon glandiflorum* extract, significant body weight reduction was observed both in H and control group. Also, the body weight reduction was significantly effective in control group along with the simultaneous administration of *Platycodon glandiflorum* extract.

Thus it is considered that the *Platycodon glandiflorum* extract has some synergistic effect in the diet therapy for obesity treatment.

2. Anatomical Observation & Adipose Tissue Weight

After 7 weeks of experimental diet and oral administration of *Platycodon glandiflorum* extract, blood samples were drawn from the tail vein and liver and adipose tissues were isolated and weighed as shown in Table 3.

Table 3. Various white adipose tissue weight of rats fed experimental diet and oriental medical herb extracts

		Liver (g)	Subcutaneous adipose tissue (g)	Epididymal adipose tissue (g)	Retro-peritoneal adipose tissue (g)
C[2]	DW	21.26±2.04[1)]	6.58±1.06[a]	6.09±1.03[ab]	11.31±1.72[a]
	PG[4]	20.16±1.34	5.87±0.64[bc]	5.85±1.07[ab]	10.42±1.71[ab]
H[3]	DW	23.61±2.52	11.71±1.18[c]	8.45±2.49[b]	22.31±4.15[d]
	PG	18.46±1.61	8.10±1.75[ab]	5.41±0.93[ab]	20.05±2.63[b]

1) Mean±SE
2) Converted group to the control diet
3) High fat diet maintain group
4) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

Liver weight was significantly higher in control group along with the oral administration of *Platycodon glandiflorum* extract. There was no significant difference between control group and *Platycodon glandiflorum* extracts administered group. However in H group, there was significant decrease in *Platycodon glandiflorum* extracts group.

Adipose tissues such as subcutaneous adipose tissues, epididymal adipose tissues, and retro-peritoneal adipose tissues were isolated and weighed. When open the abdomen, subcutaneous adipose tissue was collected from white fat pad covered internal organ.

In control group, all of adipose tissue weights were lower than H group, and particularly much lower in the group with simultaneous oral administration of Platycodon glandiflorum extract group. This effect indicated that the dietary conversion as well as Platycodon glandiflorum extract administration at the same time was important in body weight reduction.

From the result of liver and adipose tissue weights, it is considered that the oral administration of *Platycodon glandiflorum* extract not only helps to suppress the accumulation of body fat but also helps to degrade accumulated fats when converted from high fat diet to normal diet.

3. Epididymal Adipose Tissue Cell Area and Cell Number

The average cell area and average cell number of epididymal adipose tissues among isolated adipose tissues

Table 4. Epididymal adipose tissue cell area and cell number

group		Area (um^2)	Cell count
C[2]	DW	11197.00±1041.80[1),a]	72.86±1.64[ab]
	PG[4]	8665.40±507.83[ab]	100.23±2.00[ab]
H[3]	DW	15104.56±1136.29[a]	55.45±5.01[a]
	PG	6578.23±162.69[b]	125.20±2.92[b]

1) Mean±SE
2) Converted group to the control diet
3) High fat diet maintain group
4) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

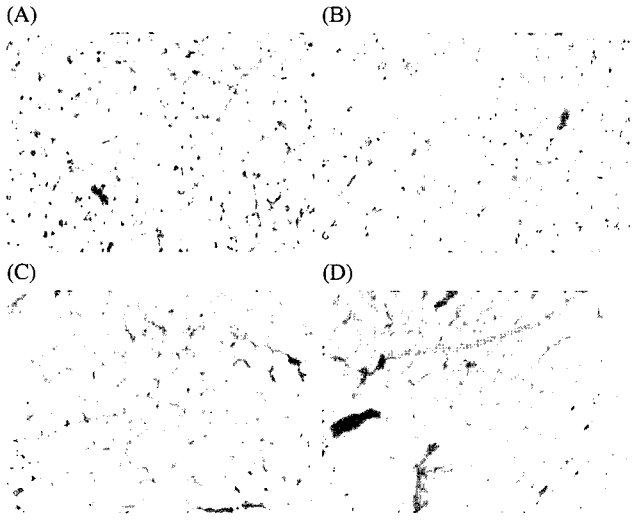

Fig. 1 Epidymal adipose tissues of diet-induced obese rats fed experimental diet
(A) Converted to control diet
(B) Diet conversion group and equally administered with PG extract group
(C) High fat diet maintain group
(D) High fat diet maintenance and equally administered with PG extract group
(PG) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

Table 5. Serum total cholesterol concentrations of the rats fed experimental diets and oriental medical herb extracts.

week		0	2	4	7
C[2]	DW	223.87±24.06[1)]	196.39±41.51	258.23±33.50	249.05±18.22
	PG[4]	190.24±22.42	161.21±52.64	184.25±24.63	222.19±26.26
H[3]	DW	198.03±48.90	241.19±34.18	286.00±16.29	294.44±36.60
	PG	242.14±25.58	234.92±47.39	229.33±41.72	235.48±63.24

1) Mean±SE
2) Converted group to the control diet
3) High fat diet maintain group
4) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

Table 6. Serum triglyceride concentrations of the rats fed experimental diets and oriental medical herb extracts.

week		0	2	4	7
C[2]	DW	68.41±13.15[1)]	67.41±4.44	66.32±3.26	63.25±4.08
	PG[4]	75.23±10.13	70.93±3.02	62.83±4.40	57.08±4.15
H[3]	DW	67.08±3.43	70.31±3.99	79.09±9.97	84.77±4.87
	PG	59.77±3.14	64.45±4.70	62.90±4.12	67.52±1.86

1) Mean±SE
2) Converted group to the control diet
3) High fat diet maintain group
4) Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

were shown in Table 4 and Fig. 1.

In control group, the fat cell area was decreased when compared to H group, showing that the fat cell size was decreased due to the dietary conversion. The number of fat cells was increased when compared to the H group, which suggested that the dietary conversion to normal diet reduced the size. This aspect was even greater in the case of oral administration of *Platycodon glandiflorum* extract to increase the dietary improvement effect.

4. Serum Total Cholesterol and Triglyceride Concentrations

Serum total cholesterol and serum triglyceride concentrations of obese rats fed experimental diet along with the oral administration of *Platycodon glandiflorum* extract were shown in Table 5 and 6.

Serum cholesterol concentrations at 7 week in control and H groups were 249.05±18.22 mg/ml and 294.44± 36.60 mg/ml, respectively, showing that the dietary conversion to normal diet was effective in the improvement of serum cholesterol. This result was consistent with the results of other studies[27)] in which serum lipid concentrations were improved with the administration of Deodeok (*Codonopsis lanceolata*) that has been known to contain large amount of saponin as in the case of Chinese bellflower root, a food name of *Platycodon glandiflorum*.

Serum triglyceride concentration at 7 week in control and H group were 63.25±4.08 mg/ml and 84.77±4.87 mg/ml, respectively, showing that the dietary conversion to low-fat/normal diet was effective in the improvement of serum triglycerides as in the case of serum cholesterol.

Also, experimental groups with the oral administration of *Platycodon glandiflorum* extract showed a beneficial effect in the improvement of serum lipid concentrations, although it was not statistically significant.

5. Changes in Hepatic Fatty Acid Binding Protein (FABP) Level

FABP levels in every experimental group were shown in Fig. 2.

In H group, significant changes in the FABP expression level was not observed with the oral administration of *Platycodon glandiflorum* extract when compared to the control group. This result was similar to the result of serum lipids concentration.

In contrast, FABP expression level in control group was significantly decreased between control group and control plus *Platycodon glandiflorum* extract administrated group. It is considered that the dietary conversion to normal diet or *Platycodon glandiflorum* extract administration was significantly effective in hepatic FABP level had already increased due to long-term high fat diet.

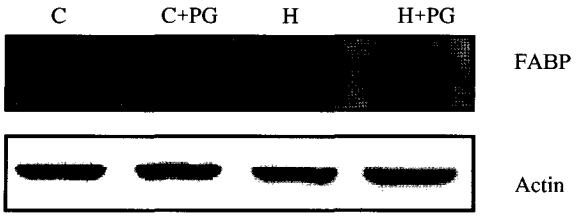

Fig. 2 Expression of hepatic fatty acid binding protein of SD rats with high fat diet group and converted group to low fat diet. In each group was devided into two groups according to the supplementation of *Platycodon glandiflorum* extract.
C : Converted group to the control diet
H : High fat diet maintain group
PG : Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

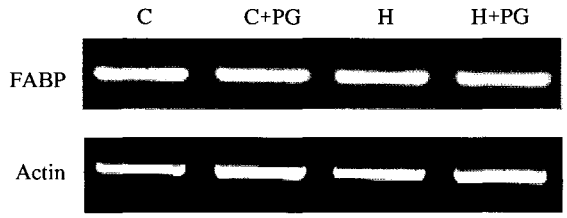

Fig. 3 Expression of epididymal adipose tissue fatty acid binding protein of SD rats with high fat diet group and converted group to low fat diet. In each group was devided into two groups according to the supplementation of *Platycodon glandiflorum* extract. The intensities of β-actin bands were compared to show that equal amounts of RNA was used for each RT-PCR reactions.
C : Conversion to control diet group
H : High fat diet maintain group
PG : Group administerred with *Platycodon glandiflorum* extract at 150 mg/day/rat

6. Epididymal Adipose Tissue PPARγ and FABP Expression by RT-PCR

The FABP(fatty acid binding protein)mRNA express- ion level in epididymal adipose tissue was shown in Fig. 3.

There was no difference in the expression level between control and H groups. It is considered that the dietary conversion or the administration of *Platycodon glandiflorum* extract did not affect the FABP expression of epididymal adipose tissue in the obese condition due to long-term high fat diet.

Also, this result was consistent with other results[28-30] in which the expression level of FABP was increased during the process of adipocyte differentiation or induced obesity and not further increased after the complete differentiation of adipocytes or complete development of obesity.

Form the above results, it was understood that *Platycodon glandiflorum* could suppress the FABP expression during the developmental process of obesity, but no longer had the inhibitory effect on the FABP expression after the obesity was fully developed because FABP had already expressed.

SUMMARY & CONCLUSION

This study was performed to investigate the effect of dietary conversion and *Platycodon glandiflorum* extract on obesity treatment and improvement.

Body weight in control group was decreased compared to H group, and the degree of its effect was more significant in administration *Platycodon glandiflorum* extract. It means that, the *Platycodon glandiflorum* extract had inhibitory effect on the fat accumulation. The change in serum lipid concentrations showed that the dietary conversion from high fat diet to normal diet was helpful in the improvement of serum lipid concentrations, and also the extract of *Platycodon glandiflorum* was helpful in serum lipid lowering effect.

The FABP mRNA expression level in epididymal adipose tissues showed that there was no difference in the expression level in this experiment. It is considered that the dietary conversion or the oral administration of *Platycodon glandiflorum* did not affect the already increased FABP mRNA level in epididymal adipose tissue caused by long-term high fat diet. The above results emphasize the fact that the diet therapy is very important for the treatment of obesity. In addition to diet therapy, it is suggested that the combinational use of oriental medicinal herb extract can be a beneficial effect on loss of side effect and hunger feeling that can be induced in the application of dietary therapy.

Platycodon glandiflorum that was used in this study is one of oriental medicinal herbs that have been traditionally used without adverse effects and can be further used as an ingredient in the development of effective treatments for obesity without side effects through the study on the mechanisms for the treatment and improvement of obesity.

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