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Peucedanum japonicum Thunb (PJT) Extracts Enhance Adiponectin Secretion in Human Metabolic Stem Cells Screening System and in Healthy Individuals

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Abstract

Adiponectin is an adipocyte specific-secreted protein playing a major role in regulating insulin sensitivity and lipid metabolism. *Peucedanum japonicum* Thunb (PJT) grown on the cliff of Tokunoshima Island in Japan contains rich polyphenolic compounds and exerts hypolipidemic properties. In this study we studied the efficacy of PJT on the adiponectin secretion in the adipocytes differentiated from human Metabolic Stem Cells (MSC) and in healthy individuals. Three types of PJT extracts of each (water, 50% ethanol, 100% ethanol extracts), rutin, or chlorogenic acid as phytochemical candidates of the PJT extracts was dropped directly onto the differentiated adipocytes from MSC of obese patients at day 8 and adiponectin levels in the culture medium were measured at day 10 and 12. The efficacy of PJT on adiponectin secretion (1260 mg/day for 3 months) was examined for 46 healthy individuals in an open labeled-preliminary study. Chlorogenic acid and rutin showed that they had more positive effects on adiponectin secretion than PJT extracts. In the study of healthy individuals, serum adiponectin levels of the elder individuals significantly increased after the trial. PJT extracts might have an adiponectin secretion-enhancing properties, attributing partly to rutin and chlorogenic acid.

Keywords: Adiponectin; Metabolic stem cells; Polyphenol; *Peucedanum japonicum* Thunb; Clinical intervention

Abbreviations: PJT: *Peucedanum japonicum* Thunb; MSC: Metabolic Stem Cells; BMI: Body Mass Index; DMSO: Dimethyl Sulfoxide; PBS: Phosphate Buffered Saline; APR: Adiponectin Production Ratio; MAPK: Mitogen-activated protein kinase; JNK: c-Jun N terminal kinase; ERK: Extracellular Signal-Regulated Kinase; PPARγ: Peroxisome Proliferator-Activated Receptor γ; Glut-4: Glucose Transporter Type-4; FXR: Farnesoid X Receptor; RORγ: Retinoid-related orphan receptor γ; HPLC: High Performance Liquid Chromatography

Introduction

The prevalence of obesity has increased markedly in the last 10–50 years especially in industrial countries, and obesity constitutes a serious threat to health based on its association with the metabolic syndrome [1]. Obesity has become the primary threat to health worldwide in the last decade, leading to metabolic syndrome including type 2 diabetes mellitus, hypertension, coronary artery disease, cancer, respiratory complications, and osteoarthritis [1-3]. Though novel dietary approaches have been expected for improving metabolic syndrome currently, most of food factors are effective in responder-dependent manner, which has given the restriction to practical usage [4]. Recently we have constructed human Metabolic Stem Cells (MSC) screening system, which is able to overcome the restriction to the practical usage of food factors due to the responder-dependent effects and to identify potential responders to specific food factors for tailor-made medical intervention [5].

Adiponectin is an adipocyte specific-secreted protein playing a major role in regulating insulin sensitivity and lipid metabolism [6]. As the plasma adiponectin levels are negatively correlated with body mass index (BMI), pathological condition with low plasma adiponectin levels are closely linked with obesity and obesity-related complications such as insulin resistance, diabetes mellitus, and cardiovascular disease (Hypoadiponectinemia) [7-9]. Over 5000 reports worldwide, therefore, have indicated that it could be crucial to improve the obesity and obesity-related complications with hypoadiponectinemia in addition to reducing body weight.

Peucedanum japonicum Thunb (PJT) grown on the cliff of Okinawa Islands comprising Tokuno-shima Island of Japan contains rich phenolic compounds and has been used as a folk medicine traditionally [10-14]. Recently the hypolipidemic efficacy of PJT has been indicated using mice model with high-fat diet in some studies [15,16]. And PJT has been identified as an antiobesity and antidiabetic candidate in vitro [17,18]. PJT also contains several phenolic acids and flavonoids constituents including isoquercitrin, rutin (flavonoids), neochlorogenic acid, cryptochlorogenic acid, chlorogenic acid (Phenolic acids), which have been demonstrated as hypolipidemic compounds [10-12,16].

In this study, we studied the efficacy of three types of PJT extracts (water, 50% ethanol, 100% ethanol extracts) on the adiponectin secretion in human Metabolic Stem Cells screening system with the adipocytes differentiated from human MSC of 8 obese individuals (MSC screening system). Then, the effects of PJT constituents, chlorogenic acid and rutin, on adiponectin secretion were assessed by using the MSC screening system for the purpose of the identification of phytochemicals enhancing adiponectin secretion. Finally, a preliminary clinical study was performed for 46 elder residents in Isen-cho, Tokunoshima, Japan with open-labeled PJT daily intake (1260 mg/day) for 3 months.

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Materials and Method

Preparation of PJT extract and PJT constituents

PJT leaves (0.5 g) were washed with tap water, dried, and ground to a fine powder. The PJT powder was immersed in 20 ml of water, 20 ml of 50% ethanol, or 20 ml of 100% ethanol at 60°C for 0.5 h, and was shaken at room temperature for 4 hours, respectively. The extracts were dried up (water, 50% ethanol, 100% ethanol extracts), to prepare 0.56 mg/mL (A1) and 5.6 mg/mL (A10) water extracts, 0.62 mg/mL (B1) and 6.2 mg/mL (B10) 50% ethanol extracts, and, 0.18 mg/mL (C1) and 1.8 mg/mL (C10) 100% ethanol extracts in dimethyl sulfoxide (DMSO), respectively, before filter sterilization (MN Sterilizer PES, 0.22 μm, Macherey-Nagel). Stock solutions of rutin and chlorogenic acid were prepared in DMSO (Sigma-Aldrich Co. LLC. St. Louis, MO, USA).

Isolation of human MSC from patients undergoing elective surgery and the differentiation of MSC into mature adipocytes

Adipose tissues from various regions (subcutaneous, pelvic, and extra-peritoneal) were obtained from 8 obese patients (Age 23-77 years) undergoing elective surgery (Table 1). MSC were prepared and isolated as reported previously [19]. Briefly, fat tissues were washed several times in phosphate buffered saline (PBS). After removal of blood vessels, tissues were minced with scissors and digested with 10 ml of type 2 collagenase solution (0.1%, Sigma-Aldrich Co. LLC. St. Louis, MO, USA) for 1 h in a 37°C water bath under constant shaking, followed by filtration using a mesh filter and centrifugation at 780 × g for 10 min. The isolated cells were suspended in Preadipocyte Medium (PM-1, Zen-bio®), and were plated onto a 100 mm dish and incubated at 37°C under 5% CO_2. Cultured by days 3 to 5, a small number of spindle-shaped cells were apparent in visible symmetric colonies. After the preadipocytes were cultured as growing precursor cells, they were plated in 96-well plates and grown to confluence in PM-1 with the appropriate volume of Adipocyte Differentiation Medium (DM-2, Zen-bio®) at 37°C and 5% CO_2 to be differentiated into adipocytes. All patients gave informed consent and the above procedures were conducted with the approval of Ethics Review Committee of Osaka University Hospital.

Measurements of adiponectin productions

At 8 days after the differentiation from MSC, adipocytes were plated on fresh Adipocyte Medium (AM-1, Zen-bio®) and incubated every 48 h with or without the PJT extracts (at 1% v/v, 0.56 mg/mL (A1) and 5.6 mg/mL (A10) water extracts, 0.62 mg/mL (B1) and 6.2 mg/mL (B10) 50% ethanol extracts, 0.18 mg/mL (C1) and 1.8 mg/mL (C10) 100% ethanol extracts, were prepared in DMSO, respectively), or phytochemical candidates of PJT (rutin or chlorogenic acid) at the final concentration of 50–250 μM. Adiponectin levels in the culture medium were measured on day 10 and day 12 after differentiation (called day 10^{th} and 12^{th} adiponectin level, respectively) using an enzyme-linked immunosorbent assay (ELISA) kit (Otsuka Pharmaceuticals, Tokushima). The day 10^{th} and 12^{th} adiponectin levels were divided by the 10^{th} and 12^{th} adiponectin levels in DMSO, respectively, to obtain normalized day 10^{th} and 12^{th} adiponectin levels. Then, the normalized day 12^{th} adiponectin level was divided by the normalized day 10^{th} adiponectin level to obtain Adiponectin Production Ratio (APR).

Case No.	Age	Gender	BMI	Disease
1	25	Male	48.5	Severe obesity
2	65	Male	24.5	Colon cancer
3	63	Male	25.6	Prostate cancer
4	64	Male	25.2	Pancreatic cancer
5	23	Female	47.0	Severe obesity
6	65	Male	26.9	Liposarcoma
7	41	Female	37.6	Severe obesity
8	64	Female	42.6	Thoracic Aortic Aneurysm
9	77	Female	28.7	Left ovarian immature teratoma
10	36	Male	26.9	Submucosal tumor

Age, gender, body mass index (BMI), and diseases requiring surgery were shown.
Table 1: Baseline characteristics of patients from whom metabolic stem cells were isolated.

Treatment with PJT for residents in Isen-cho, Tokunosima-island in Japan

Forty-six healthy individuals (Average age, 66 years; BMI, 27; Men/women, 3/2; no history of the PJT usage) in Isen-cho, Tokunoshima-island in Japan were recruited for the clinical intervention with PJT intake from August through November 2012. They received commercially available PJT products 1260 mg/day (Ma-zaku®, Choujushokuzai-kenkyusho, Tokyo, Japan) for 3 months. The above procedure was conducted with the approval of Ethics Review Committee of Isen-cho town hall. Informed consent was obtained from all participants. Serum adiponectin levels were measured with an ELISA kit (Otsuka Pharmaceutical, Tokushima, Japan). Significant differences between serum adiponectin concentrations before and after PJT treatment were analyzed by paired t-test.

Statistical analysis

Values are expressed as mean ± SEM. A p-value of <0.05 denoted the presence of a statistically significant difference.

Results

Adiponectin secretion enhancing property of PJT extracts for obese individuals

The normalized day 10^{th}, 12^{th} adiponectin levels, and APR have changed to the following rates, respectively (N=8; *, $p<0.05$ vs. control; **, $p<0.01$ vs. control.); 184% (**), 193%, and 88% in water extract A1, 94%, 211% (*), and 213% (**) in water extract A10, 276% (**), 277%, and 87% in 50% ethanol extract B1, 100%, 197% (*), and 210% (**) in 50% ethanol extract B10, 259% (**), 185%, and 69% (*) in 100% ethanol extract C1, 77%, 153%, and 188% (*) in 100% ethanol extract C10, compared with controls of each (set DMSO controls as 100%, respectively) (Figure 1). Interestingly, it was shown that PJT water extract also has an adiponectin secretion property, to a lesser extent, than PJT ethanol extracts. These results indicated that PJT extracts were adiponectin secretion-enhancing food factors for the general intervention for obese patients. We have confirmed that there was no potential variability of adipose cell metabolism and the dynamics of adiponectin among the adipose tissues from various regions of the obese patients (Data not shown).

Potential contribution of PJT constituents, rutin and chlorogenic acid, to adiponectin secretion-enhancing property of PJT

Since ingredients identified in PJT extracts excluding rutin and chlorogenic acid have not been shown yet to exhibit adiponectin secretion property, we have selected rutin and chlorogenic acid as the phytochemical candidates in PJT extracts for the purpose of the identifications of phytochemicals enhancing adiponectin secretion (See Discussion), and investigated the effects of those two compounds on adiponectin secretion by using the MSC obtained from 2 patients during surgery (Case No. 9 and 10, Table 1). As a result, in Case No. 9, the normalized day 10^{th} and 12^{th} adiponectin levels, and APR have changed

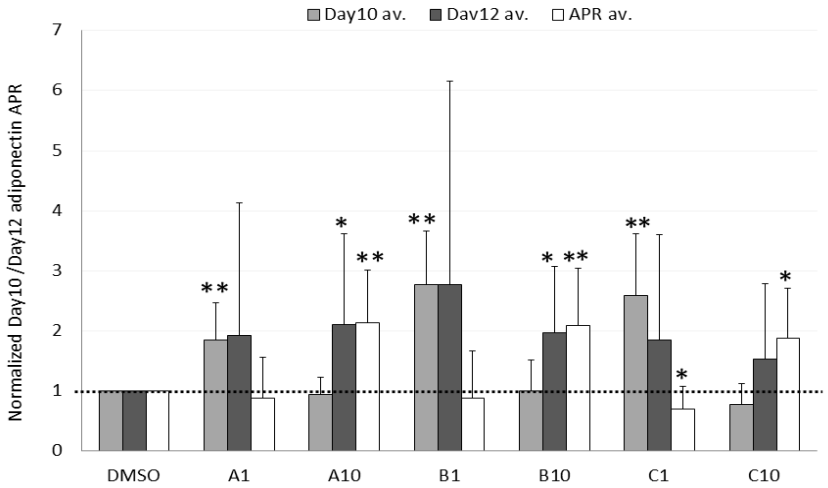

Figure 1: Examination of the effects of PJT extracts (A, water; B, 50% ethanol; C, 100% ethanol) on adiponectin secretion.
Based on the normalized day 10th and 12th adiponectin levels, and APR, the adiponectin secretion-enhancing properties of PJT extracts were examined. After the mature adipocytes differentiated from MSC were incubated every 48 h with or without the prepared PJT extracts (0.56 mg/mL (A1) and 5.6 mg/mL (A10) water extracts, 0.62 mg/mL (B1) and 6.2 mg/mL (B10) 50% ethanol extracts, 0.18 mg/mL (C1) and 1.8 mg/mL (C10) 100% ethanol extracts, prepared in DMSO) at 1% v/v, adiponectin levels in culture medium were measured for 8 individuals. The values in each patient were measured 3 times, respectively (n=3 wells per patient, respectively). * indicates $p<0.05$ vs. control and **, $p<0.01$ vs. control.

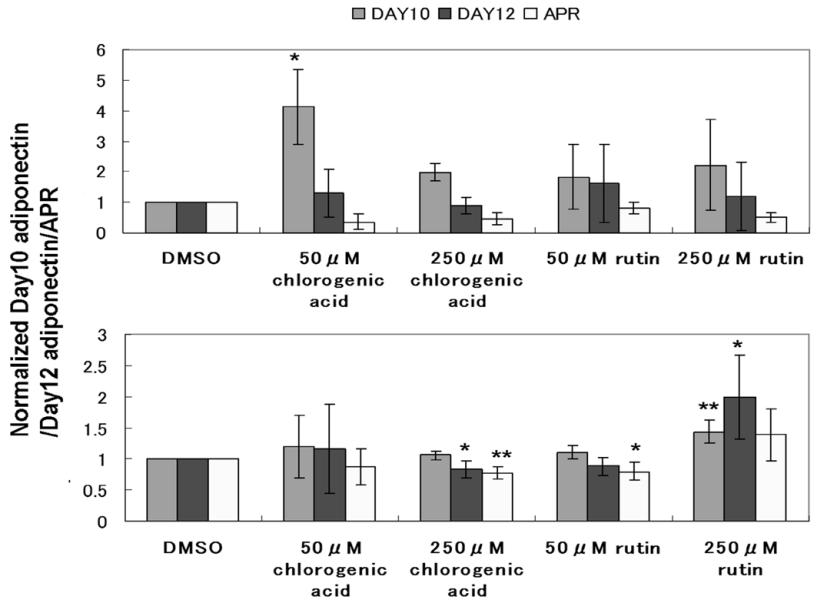

Figure 2: Examination of the effect of PJT constituents (chlorogenic acid and rutin) on adiponectin secretion.
Based on the normalized day 10th and 12th adiponectin levels, and APR, the adiponectin secretion-enhancing properties of PJT constituents, chlorogenic acid and rutin, were examined. After the mature adipocytes differentiated from MSC were incubated every 48 h with or without the PJT constituents (at the concentrations of 50–250 μM, prepared in DMSO) at 1% v/v, adiponectin levels in culture medium were measured. The values in each patient were measured 3 times, respectively (n=3 wells per patient, respectively). * indicates $p<0.05$ vs. control and **, $p<0.01$ vs. control.

up to the following rates, respectively; 198% (*), 88%, and 47% in 250 μM of chlorogenic acid, 413% (*), 130%, and 36% in 50 μM chlorogenic acid, compared with controls of each (set as 100%) (Figure 2).

In Case No. 10, the normalized day 10th and 12th adiponectin levels, and APR have changed to the following rates, respectively (*, $p<0.05$ vs. control; **, $p<0.01$ vs. control); 105%, 83% (*), and 78% (**) in 250 μM of chlorogenic acid, 121%, 116%, and 88% in 50 μM chlorogenic acid, 144% (**), 199% (*), and 139% in 250 μM of rutin, 111%, 88%, and 80% (*) in 50 μM of rutin, compared with controls of each (set as 100%) (Figure 2), indicating that the former patient, and the latter could be responders to chlorogenic acid, and rutin, respectively, in enhancement of adiponectin secretion. On the other hand, however, general enhancement of adiponectin secretion was observed on dropping PJT extracts directly onto the differentiated adipocytes from MSC in culture (Figure 1), which could suggest the existence of other phytochemicals in PJT extracts, or the synergetic effects among the phytochemicals in PJT extracts (See Discussion).

Treatment with PJT products in healthy adults

Finally we performed an open-labeled clinical study for the 46 individuals in order to clarify the influence of PJT intake on serum adiponectin secretion in healthy individuals (Table 2). They received PJT products (1260 mg/day followed by 3 months) with dietary and exercise intervention. An individual was found to be infected with Helicobacter pylori in September (at the beginning of the clinical trial) and administrated with Rabeprazole sodium for extermination for one week, who was judged to be a defector from this trial. 45 individuals completed the study. After PJT intakes for 3 months, the baseline levels of serum adiponectin (8.49 ± 3.41 μg/mL) significantly increased to 9.21 ± 4.16 μg/mL (7.81% increase, p=0.05, Figure 3). The improvement of movement of the bowels could be observed in 20% of the residents (Data not shown).

Gender (n)	Male (n=26)	Female (n=20)	Total (n=46)
Age (years)	61 ± 22	75 ± 16	69 ± 25
Body weight (kg)	69.7 ± 18.8	55.9 ± 8.45	63.6 ± 18.1
Waist circumference (cm)	89 ± 11	89 ± 7	89 ± 8
BMI (kg/m^2)	27 ± 4.7	26 ± 4.5	26 ± 4.8
Serum adiponectine (μg/ml)	7.0 ±4.0	9.0 ± 5.0	7.8 ± 4.3
Systolic BP (mmHg)	134 ± 16	138 ± 15	134 ± 16
Diastolic BP (mmHg)	82 ± 14	78 ± 12	79 ± 14
GOT (AST) (IU/l)	23.0 ± 23.0	22.0 ± 6.0	22.0 ± 9.5
GPT (ALT) (IU/l)	19.0 ± 29.5	19.0 ± 11.0	19.0 ± 23.3
γGTP (IU/l)	44.0 ± 62.0	17.0 ± 7.5	22.0 ± 31.8
Total cholesterol (mg/dl)	171 ± 37	203 ± 23	194 ± 47
HDL cholesterol (mg/dl)	47.8 ± 11.7	56.0 ± 12.0	50.0 ± 13.0
LDL cholesterol (mg/dl)	99.0 ± 48.0	127.0 ± 27.0	119.0 ± 42.0
Neutral fat (mg/dl)	145.0 ± 103.5	95.0 ± 44.0	114.0 ± 82.3
Creatinine (mg/dl)	0.8 ± 0.1	0.7 ± 0.2	0.8 ± 0.2
Uric acid (mg/dl)	6.7 ± 1.6	5.3 ± 1.5	6.3 ± 2.0
eGFR (ml/min/1.73m^2)	79.0 ± 16.5	76.0 ± 25.0	78.0 ± 22.0
Fasting glucose (mmol/l)	93.0 ± 8.3	100.5 ± 26.8	94.0 ± 18.0
HbA1c (%)	5.1 ± 0.8	5.1 ± 0.4	5.1 ± 0.5
Amylase (IU/l)	71.0 ± 30.5	60.0 ± 23.0	64.0 ± 24.0

Median values are shown with the interquartile range (IQR) in brackets. BMI-Body Mass Index; Systolic BP-Systolic Blood Pressure; Diastolic BP-Diastolic Blood Pressure; GOT (AST)-Glutamic Oxaloacetic Transaminase; GPT (ALT)-Glutamic Pyruvic Transaminase; Γgtp-Γ-Glutamyl Transpeptidase; HDL Cholesterol-High Density Lipoprotein Cholesterol; LDL Cholesterol-Low-Density Lipoprotein Cholesterol; Egfr-Estimated Glomerular Filtration Rate; Hba1c-Glycated Hemoglobin A1C.

Table 2: Baseline characteristics of healthy individuals in clinical trial.

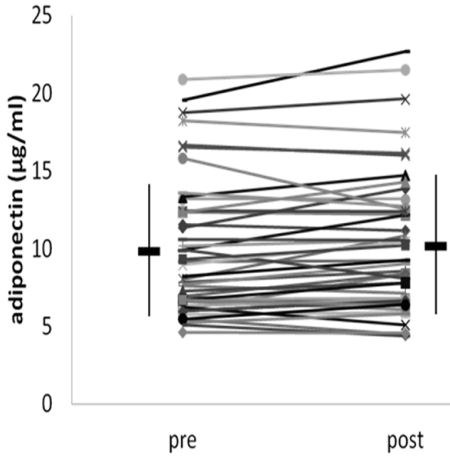

Figure 3: Treatment with PJT in residents in Isen-cho, Tokunosima-Island in Japan.
Forty-six healthy individuals (Average age, 66 years; BMI, 27; Men/women, 3/2; no history of the PJT usage) in Isen-cho in Japan were recruited. They received Ma-zaku® 500 mg/day for 6 month. Serum adiponectin levels were measured before and after PJT treatment with ELISA. After PJT intakes for 5 months, serum adiponectin levels significantly increased to 8.49 ± 3.41 to 9.21 ± 4.16 μg/mL (7.81% increase, p=0.05, paired t-test).

Discussion

In this study, interestingly, PJT aqueous extract also has been indicated to exert adiponectin secretion property. In obesity, the expansion of adipose tissues leads to overproduction of the pro-inflammatory adipokines including tumor necrosis factor-α (TNF-α), leptin, adipocyte fatty acid binding protein, and resistin, resulting in dysfunction of adipocytes, thereby contributing to the pathogenesis of metabolic syndrome [20,21]. The synthesis of pro-inflammatory cytokines is accompanied with activation of the mitogen-activated protein kinase (MAPK) family, a key component of the signaling pathways [22]. MAPK family includes c-Jun N terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 kinases. The production of adiponectin in adipocytes has been indicated to be inhibited by production of TNF-α regulating JNK signaling pathway [23-25]. In platelet physiology, aqueous extracts of some medicinal plant have been reported to affect the MAPK phosphorylation including p38, JNK, or ERK2 [26,27]. PJT aqueous extract also might contain compounds modulating the activation of some MAPK signaling pathways to ameliorate adiponectin secretion.

The normalized day 10th and 12th adiponectin levels, and APR have been upregulated in most cases by both of 50% ethanol extract and 100% ethanol extracts markedly (Figure 1). The reason for adiponectin is decreased with an increase in the PJT extraction, it is considered to be cell toxicity. Adiponectin promoting effect is reduced by a large amount of additives [28,29]. About the molecular basis responsible for the enhanced adiponectin secretion in PJT ethanol extract, it might upregulate adiponectin secretion *via* activation of the nuclear hormone receptor, peroxisome proliferator-activated receptor γ (PPARγ) [20,30]. And PJT ethanol extract might increase the expressions of glucose transporter type-4 (Glut-4), adiponectin, and fatty acid binding protein *via* the activation of Farnesoid X receptor (FXR), which participated in glucose and lipid metabolism, by PPARγ-dependent and -independent pathways [31]. And also, accompanied with the induction of PPARγ, the induction of retinoid-related orphan receptor γ (RORγ) has been suggested to function as an active transcription factor in the regulation of gene expression during adipocyte differentiation [32]. The molecular bases of these are supported by the lipid-lowering effects of PJT extracts in high fat-diet induced obese mice [16]. In PJT ethanol extract, thus, most parts of the molecular basis responsible for the enhanced adiponectin secretion might be occupied by the up-regulation of PPARγ-dependent pathways.

The increase in PPARγ expression could be sufficient to initiate adipogenesis *in vitro* and *in vivo* [33] and it is efficient to enhance the induction of preadipocyte differentiation and expansion of the capacity to store lipids for the normalization of adipokine-secretory profile. Activation of PPARγ gene, therefore, improves hypertrophy and metabolic dysfunction of adipocytes. For example, Thiazolidinediones, a PPARγ ligand and antidiabetic agent, contributes to improving insulin resistance due in part to PPARγ action to augment glucose

transporter Glut-4 and adiponectin expression [34]. PPARγ signaling pathways, thus, are potentially interesting targets for anti-inflammatory drug development [35]. As PJT ethanol extract increases a PPARγ level [16], PJT ethanol extract which promoted adiponectin secretion in this study, might contain the high-potent PPARγ agonist candidates. It may, therefore, be significant to identify the PPARγ agonist candidate constituents in PJT ethanol extract and to verify the efficacy as a PPARγ agonist in the future.

In the assessment of this study for the purpose of the identification of phytochemicals with adiponectin secretion activity, the constituents of PJT extracts, chlorogenic acid and rutin, had the equivalent, or more positive effects on adiponectin secretion than PJT extracts in the responder dependent-manner, respectively (Figure 1 and 2). In previous works, rutin has been shown to enhance adiponectin secretion [36], on the other hand, chlorogenic acid to improve adiponectin levels with body weight, lipid metabolism, and obesity-related hormones in mice [14]. Since ingredients identified in PJT extracts excluding rutin and chlorogenic acid have not been shown to exhibit adiponectin secretion property yet, we have selected rutin and chlorogenic acid as the candidates of phytochemicals in PJT extracts. Actually, from the results of content analysis in PJT extract (w/w%) by using high performance liquid chromatography (HPLC), the contents of rutin in water, 50% ethanol, and, 100% ethanol extract were 0.68, 0.93, and 1.23 w/w% in extract, respectively, while those of chlorogenic acid were 1.27, 1.19, 0.73 w/w% in extract, respectively, indicating that any PJT extracts in this study could contain the phytochemicals affecting adiponectin secretion (Data not shown). And also these results could support the results of the *in vitro* experiments of dropping PJT extracts directly onto the MSC adipose cells in culture (Figure 1). On the other hand, however, the potent responder-dependent effects of rutin and chlorogenic acid on adiponectin secretion suggest the other candidates of phytochemicals in any PJT extracts in this study (Figure 2). Furthermore, in a previous work rutin enhanced adiponectin secretion without regulating PPARγ level [37], which suggests that the enhancement of adiponectin secretion by rutin in this research depends on PPARγ-independent manners. On the other hand, as mentioned above, in PJT ethanol extract most parts of the molecular basis responsible for the enhanced adiponectin secretion, might be occupied by the up-regulation of PPARγ owing to the unknown phenolic compounds with high hydrophobicity [16], rather than by rutin and chlorogenic acid independent of PPARγ transcriptional activity.

Taken together, these results suggest that rutin and chlorogenic acid, though they have responder-dependent effects, may be ones of phytochemicals in PJT extracts, and that PJT extracts could contain physiologically active substances promoting adiponectin secretion other than rutin and chlorogenic acid. In future, further study would be required.

However, the model of dropping botanical extracts directly onto the adipose cells in culture may inefficient to explore bioactivity of the botanicals in general for the purpose of the identification of PJT phytochemicals, since the native food compounds can be altered through the processes such as digestion, absorption, and transport,, to become active metabolites reaching to the target tissue in humans. In future, the researches comprising PJT metabolites need to be performed.

In conclusion, PJT extract may provide promising dietary strategies up-regulating adiponectin secretion in healthy adults and for clinical intervention.

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