Preventive Effect of Geniposide on Metabolic Disease Status in Spontaneously Obese Type 2 Diabetic Mice and Free Fatty Acid-Treated HepG2 Cells

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Accumulation of visceral fat induces various symptoms of metabolic syndrome such as insulin resistance and abnormal glucose/lipid metabolism and eventually leads to the onset of ischemic cerebrovascular diseases. Geniposide, which is iridoid glycoside from the fruit of Gardenia jasminoides Ellis, is recognized as being useful against hyperlipidemia and fatty liver. In order to clarify the effect of geniposide on metabolic disease-based visceral fat accumulation and the relevant molecular mechanism, experiments were performed in spontaneously obese Type 2 diabetic TSOD mice and the free fatty acid-treated HepG2 cells. In the TSOD mice, geniposide showed suppression of body weight and visceral fat accumulation, alleviation of abnormal lipid metabolism and suppression of intrahepatic lipid accumulation. In addition, geniposide alleviated abnormal glucose tolerance and hyperinsulinemia, suggesting that geniposide has an insulin resistance-alleviating effect. Next, in order to investigate the direct effect of geniposide on the liver, the effect on the free fatty acid-treated HepG2 fatty liver model was investigated using genipin, which is the aglycone portion of geniposide. Genipin suppressed the intracellular lipid accumulation caused by the free fatty acid treatment and also significantly increased the intracellular expression of a fatty acid oxidation-related gene (peroxisomal proliferator-activated receptor: PPARα). From these results, it was confirmed that geniposide has an anti-obesity effect, an insulin resistance-alleviating effect and an abnormal lipid metabolism-alleviating effect, and the metabolite genipin shows a direct effect on the liver, inducing expression of a lipid metabolism-related gene as one of its molecular mechanisms.

Key words: geniposide; genipin; metabolic disease; fatty liver; HepG2

Obesity, diabetes, hyperlipidemia and hypertension, which are caused by hypernutrition and lack of exercise, are often found in the same person. These symptoms used to be called “the deadly quartet,” “Syndrome X” or “insulin resistance syndrome,” but these names have recently been collectively replaced with “metabolic syndrome (MS).” Since the presence of visceral fat accumulation-type obesity has been recognized as the major disease base. It should be noted that progression of MS increases the risk of future onset of ischemic cardiac diseases and cerebrovascular diseases, and the importance of “prevention” and “early therapy” of MS is emphasized.

Gardeniae fructus, the fruit of Gardenia jasminoides Ellis, is widely used in Asian countries as a natural colorant, and it is also used as a Japanese and Chinese traditional medicine since it has a homeostatic effect, an antiphlogistic effect, an analgesic effect, an antipyretic effect, a hepatoprotective effect and a hypolipidaemic effect. Geniposide, an iridoid glycoside contained in Gardeniae fructus, is reported to have a hepatoprotective effect, an antioxidant effect, a hypoglycemic effect, a vascular endothelial cell adhesion-suppressing effect, an anti-lipopolysaccharide (LPS) effect, a neuroprotective effect, and an anti-inflammatory effect. In addition, genipin, which is the aglycone portion of geniposide and is formed as a metabolite, is also reported to have an anti-inflammatory effect, a bile secretion-enhancing effect, and an anti-thrombotic effect. Geniposide is promising as a seed compound for developing therapeutic medicines for metabolic diseases. However, no publication has reported the effect of geniposide on various metabolic disease symptoms based on visceral fat accumulation.

MATERIALS AND METHODS

Reagents: Geniposide and genipin (Fig. 1) were supplied by Tsumura and Co. (Ibaraki, Japan). Palmitic acid powder was purchased from Sigma-Aldrich (MO, U.S.A.). The other reagents used were of the highest grade available.

Animal Experiments: Male TSOD mice and corresponding control animals (TSNO mice) were purchased from the Institute for Animal Reproduction (Ibaraki) at the age of 3 weeks. They were acclimated under controlled circumstances (temperature: 23±1℃, humidity: 55±5%, lighting hours: 12 h) for one week. During the acclimation period, the animals were given ordinary powder food (MF, Oriental Yeast Co., Ltd., Tokyo, Japan) and city water ad libitum for 24 h. Geniposide was mixed with MF at concentrations of 0.1% and 0.3% and given to the TSOD mice and TSNO mice ad libitum for 8 weeks starting from the age of 4 weeks. This study was approved by the Experimental Animal Ethics Committee of the...
**Measurement of Body Weight and Food Intake:** The body weight of the mice was measured at one-week intervals from the start of the experiment (4 weeks of age) to the end of the experiment (12 weeks of age). The food intake of each mouse was calculated as the daily mean intake at an interval of two weeks in each cage by subtracting the sum of the quantity spilled from the food box and the quantity remaining in the food box from the quantity originally placed in the food box.

**X-Ray Computed Tomography (CT) Analysis and Glucose Tolerance Test:** At 8 weeks after starting the treatment with the test feed (at 12 weeks of age), X-ray CT analysis was performed. Each mouse was placed in an X-ray CT device for experimental animals (La Theta 100, Hitachi Aloka Medical, Ltd., Tokyo, Japan) under anesthesia with pentobarbital (50 mg/kg, intraperitoneally (i.p.)), and scanning was performed from the xiphoid process to the sacrum at intervals of 1.5 mm. In the CT image, the visceral fat and the subcutaneous fat were distinguished using the abdominal muscle line as the boundary, and each weight was calculated with La Theta Software. Using the data obtained, the visceral fat weight and the subcutaneous fat weight were calculated for each of the 10 segments into which the range from the xiphoid process to the sacrum was divided. Also, at 8 weeks after starting the treatment with the test feed (at 12 weeks of age), as an oral glucose tolerance test, the mice were orally administered glucose (2 g/kg) after being fasted for 18 h. Blood samples were taken from the orbital venous plexus using a heparin-treated hematocrit tube immediately before the glucose administration (0 min) and 30, 60, 120 and 180 min after the glucose administration, and plasma samples were obtained by centrifugation. The plasma samples were stored at −30°C until determination of blood glucose levels.

**Anatomical Examination Items:** At 8 weeks after starting the treatment with the test feed (at 12 weeks of age), each mouse was anesthetized with diethyl ether under non-fasted conditions, and blood was taken from the abdominal inferior vena cava with a heparin-treated syringe, followed by liver isolation. The blood was centrifuged to obtain the plasma. The glucose, total-cholesterol (T-Cho), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) levels were determined with WAKO biochemical test kits (Wako Pure Chemical Industries, Ltd., Osaka, Japan), and the insulin level was determined with an enzyme-linked immunosorbent assay (ELISA) kit (Shibayagi Co., Ltd., Gurna, Japan). The quantity of intrahepatic fat was determined by the method of Freedman et al. The isolated liver was homogenized with 1 M NaCl, then chloroform/methanol (2:1) and 1 M NaCl were added and the suspension centrifuged (3000 rpm, 5 min) after shaking. The organic layer was taken and dried with a centrifugal thickener. The residue was dissolved in Triton X-100/methanol (2:1), and the resulting solution was used as the sample solution. The T-Cho and TG levels in the sample solution were determined with WAKO biochemical test kits.

**Cell Experiments** Fatty Acid Treatment: Palmitic acid complexed with bovine serum albumin (BSA) was made according to the method of Joshi-Barve et al. as follows: palmitic acid powder was added to a 10% solution of fatty acid free BSA and dissolved by shaking gently overnight at 40°C to yield a 0.5 mM solution of palmitic acid complexed to BSA.

**HepG2 Cells:** HepG2 cells obtained from RIKEN BRC were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal bovine serum (FBS), penicillin (100 unit/ml)–streptomycin (100 μg/ml) and kept at 37°C in a humidified atmosphere of 5% CO₂. The HepG2 cells in the sub-confluent state were exposed to palmitic acid for 48 h in the presence or absence of genipin. The normal group was exposed to fatty acid free BSA.

Lipid Levels in HepG2 Cells: Quantitative measurement of intracellular T-Cho level was performed using the method described by Gamble et al. In brief, the samples were collected and lipids were extracted by adding 1 ml of chloroform/methanol (2:1). The lipid phase was collected, dried in vacuum, and then dissolved in 2-propanol containing 10% Triton X-100. For quantitative measurement of intracellular TG level, the samples were collected with PBS supplemented with 1% TritonX-100 and sonicated. T-Cho and TG levels were measured using WAKO biochemical test kits. The lipid levels were normalized to protein content as determined by the Lowy method.

**Determination of mRNA Expression Levels in HepG2 Cells Using Real-Time Quantitative Reverse Transcription-Polymerase Chain Reaction (RT-PCR):** The total RNA was isolated from the HepG2 cells using the RNeasy Mini Kit (QIAGEN, Tokyo, Japan) according to the manufacturer’s instruction manual. Total RNA (1 μg) was reverse transcribed to cDNA in a reaction mixture using QuantiTect® Reverse Transcription kit (QIAGEN) according to the manufacturer’s instruction manual. The level of gene expression in the cells was measured using the real-time PCR system (Mini-opticon™ system, Bio-Rad Laboratories, Inc., Tokyo, Japan), and QuantiTect® SYBR Green PCR kit (QIAGEN). The primers used were followed: peroxisome proliferator-activated receptor α (PPARα) (NM_001101.3) Forward: 5’-CCG AGT CCA CGC GTG TGA A-3’ Reverse: 5’-GCT GCG GTC GCA CTT GTC AT-3’, β-actin (NM_001110.3) Forward: 5’-AAC ACC CCA GGC ATG TAC GTG-3’ Reverse: 5’-TCT CCT TAA TGT CAC GCA CGA-3’. Relative quantification of gene expression with real-time PCR data was calculated relative to β-actin.

**Statistical Analysis** The results are expressed as mean±S.E. In the animal experiments, the TSONO control.
group and the TSOD control group were compared by Student’s t-test, and a comparison between each geniposide-treated group and the corresponding control group was performed by analysis of variance (ANOVA) using Dunnett’s test. In the cell experiments, the normal group and the control group were compared by Student’s t-test, and the comparison between the control group and the genipin-treated group was performed by ANOVA using Dunnett’s test. A difference was considered significant if $p<0.05$.

RESULTS

Animal Experiments  Body Weight and Food Intake: The body weights were higher in the TSOD control group than in the TSNO control group (Fig. 2). In the TSOD mice, geniposide suppressed the body weight increase, and in the group given food containing 0.3% geniposide, the body weight increase was significantly suppressed at 5, 7 and 8 weeks after starting the treatment as compared with the control group. In the TSNO mice, the body weight increase was significantly suppressed at 7 and 8 weeks after starting the treatment in the group given the food containing 0.3% geniposide as compared with the control group. On the other hand, geniposide showed no influence on food intake in either the TSOD mice (TSOD control, TSOD 0.1%, TSOD 0.3%: 5.84±0.48, 5.57±0.10, 5.59±0.19 g/d at 8 weeks of age) or the TSNO mice (TSNO control, TSNO 0.1%, TSNO 0.3%: 4.97±0.27, 5.08±1.54, 4.74±0.58 g/d at 8 weeks of age).

Measurement of Visceral Fat and Subcutaneous Fat Weights: The visceral fat weights and subcutaneous fat weights calculated by X-ray CT analysis in all 10 segments showed a significantly larger accumulation in the TSOD control group as compared with the TSNO control group (Fig. 3). In the TSOD mice, geniposide suppressed visceral fat accumulation, and significant suppression was seen in the 8th and 9th segment in the group given the food containing 0.1% geniposide and in the 1st, 6th, 9th and 10th segments in the group given the food containing 0.3% geniposide. Furthermore, geniposide significantly suppressed subcutaneous fat accumulation in the 1st and 2nd segments in the group given the food containing 0.3% geniposide. On the other hand, in the TSNO mice, geniposide showed no influence on the weight of either visceral fat or subcutaneous fat.

Oral Glucose Tolerance Test: As shown in Fig. 4, the blood glucose level was significantly higher in the TSOD control
group than in the TSNO control group at 30, 60, 120 and 180 min after glucose loading. In the TSOD mice, geniposide suppressed the increase in blood glucose level. As compared with the control group, the increase in blood glucose level was significantly suppressed at 120 and 180 min after glucose loading in the group given food containing 0.1% geniposide, and at 30, 120 and 180 min after glucose loading in the group given food containing 0.3% geniposide. In the TSNO mice, geniposide showed no influence on blood glucose level changes after glucose loading.

Plasma Biochemical Test Values: Table 1 shows the plasma biochemical test values (glucose, insulin, TG, T-Chol, HDL/T-Chol, LDL/T-Chol) determined at the time of anatomy. The glucose, insulin, TG and T-Chol levels were significantly higher in the TSOD control group than in the TSNO control group. In the TSOD mice, geniposide suppressed the increases of insulin level and T-Chol level in a dose dependent manner and also tended to suppress the increase in TG level \((p=0.056)\) in the group given food containing 0.3% geniposide. Geniposide increased the ratio of HDL/T-Chol in a dose-dependent manner, and the effect was significant in the group given food containing 0.3% geniposide. The glucose level and the ratio of LDL/T-Chol were not influenced by geniposide. In the TSNO mice, geniposide showed no influence on the plasma biochemical test levels.

Liver Weight and Intrahepatic Fat Level: Table 2 shows the weights of the livers isolated at the time of anatomy and the intrahepatic fat levels. Significant liver hypertrophy was seen in the TSOD control group as compared with the TSNO control group. This liver hypertrophy in the TSOD mice tended to be suppressed by geniposide in the group given food containing 0.3% geniposide \((p=0.0764)\). As for the intrahepatic

Table 1. The Effect of Geniposide on Biochemical Parameters of Plasma

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.1%</th>
<th>0.3%</th>
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<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>154.4±8.1</td>
<td>158.8±8.9</td>
<td>156.3±8.5</td>
</tr>
<tr>
<td>Insulin (ng/ml)</td>
<td>1.30±0.30</td>
<td>1.23±0.22</td>
<td>1.21±0.21</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>103.9±10.0</td>
<td>130.2±21.4</td>
<td>112.4±9.2</td>
</tr>
<tr>
<td>T-Chol (mg/dl)</td>
<td>96.0±2.0</td>
<td>117.9±18.2</td>
<td>119.9±8.8</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.1%</th>
<th>0.3%</th>
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<tbody>
<tr>
<td>HDL/T-Chol</td>
<td>0.50±0.02</td>
<td>0.46±0.04</td>
<td>0.51±0.05</td>
</tr>
<tr>
<td>LDL/T-Chol</td>
<td>0.07±0.01</td>
<td>0.08±0.01</td>
<td>0.08±0.01</td>
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At 8 weeks after starting the treatment, blood was taken from the abdominal inferior vena cava and was centrifuged to obtain the plasma. Each biochemical parameter was determined using a biochemical test kit. Data represent the mean±S.E. values \(n=6–9\). Significantly different from the TSNO control group at \(p<0.05\) and \(p<0.01\). Significantly different from the TSOD control group at \(* p<0.05\) and \(* * p<0.01\). TG: triacylglycerol, T-Chol: total cholesterol, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol.

Table 2. The Effect of Geniposide on Liver Weight and Liver Lipids

<table>
<thead>
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<th></th>
<th>Control</th>
<th>0.1%</th>
<th>0.3%</th>
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<tbody>
<tr>
<td>Liver (g)</td>
<td>1.77±0.04</td>
<td>1.80±0.04</td>
<td>1.72±0.06</td>
</tr>
<tr>
<td>TG (mg/g liver)</td>
<td>5.50±0.72</td>
<td>4.70±0.26</td>
<td>4.94±0.37</td>
</tr>
<tr>
<td>T-Chol (mg/g liver)</td>
<td>6.71±0.25</td>
<td>7.28±0.26</td>
<td>6.64±0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.1%</th>
<th>0.3%</th>
</tr>
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<tbody>
<tr>
<td>Liver (g)</td>
<td>2.45±0.05††</td>
<td>2.31±0.09</td>
<td>2.29±0.04</td>
</tr>
<tr>
<td>TG (mg/g liver)</td>
<td>15.20±3.6††</td>
<td>9.44±1.61</td>
<td>9.29±0.82</td>
</tr>
<tr>
<td>T-Chol (mg/g liver)</td>
<td>8.06±0.57††</td>
<td>7.10±0.16**</td>
<td>6.95±0.33**</td>
</tr>
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</table>

The livers were isolated at 8 weeks after starting the treatment, and weighed. The quantity of intrahepatic fat was determined by the method of Freedman et al. Data represent the mean±S.E. values \(n=6–9\). Significantly different from the TSNO control group at \(p<0.05\) and \(p<0.01\). Significantly different from the TSOD control group at \(* * p<0.01\). TG: triacylglycerol, T-Chol: total cholesterol.

![Fig. 5](image-url) The Effect of Genipin on TG and TC Concentrations in HepG2-FFA

The HepG2 cells in the sub-confluent state were exposed to 0.5 m& s palmitic acid for 48 h in the presence or absence of genipin. The normal group was exposed to fatty acid free BSA. After 48 h, the cells were collected and measured TG and TC contents. The data represent the mean±S.E. values \(n=6\). Significantly different from the normal group with \(† p<0.01\). Significantly different from the control group with \(* p<0.05\) and \(* * p<0.01\).
fat values, both the TG level and T-Cho level were significantly higher in the TSOD control group than in the TSNO control group. In the TSOD mice, geniposide significantly suppressed the T-Cho level in a dose-dependent manner and tended to suppress the TG level (0.3%: \( p=0.087 \), 1.0%: \( p=0.088 \)).

**Cell Experiments**  Effect on Intracellular TG and T-Cho Levels: As shown in Fig. 5, the TG level and T-Cho level in HepG2 cells were increased significantly by addition of the free fatty acid, and these increases were suppressed by genipin in a dose-dependent manner. The suppressive effect was significant at concentrations of 50 and 100 \( \mu M \).

Intracellular PPAR\( \alpha \) mRNA Expression Changes: The expression of fatty acid oxidation-related gene PPAR\( \alpha \) mRNA was significantly decreased by addition of the free fatty acid. This decrease in PPAR\( \alpha \) mRNA expression was significantly suppressed by treatment with genipin (100 \( \mu M \)) (Fig. 6).

**DISCUSSION**

In this study, the possible effect of geniposide on metabolic diseases was investigated using spontaneously obese Type 2 diabetic TSOD mice (in vivo animal model) and free fatty acid-treated HepG2 cells (in vitro fatty liver model).

The TSOD control mice aged 12 weeks developed obesity, abnormal glucose/lipid metabolism, abnormal glucose tolerance and fatty liver, and showed various metabolic disease symptoms as compared with the TSNO control mice of the same age, similarly to previous results.\(^{23,24}\) Geniposide showed preventative effects on various metabolic disease symptoms in the TSOD mice. The body weight increase seen in the TSOD mice was significantly suppressed by geniposide from the 5th week after starting the treatment. Wu et al.\(^{5}\) reported that geniposide showed a suppressing effect on body weight increase in mice with diabetes induced by a high-fat diet and streptozotocin. This study also found an anti-obesity effect of geniposide. We consider that the anti-obesity effect of geniposide is due to its fat accumulation-suppressing effect and investigated the effect on the quantity of visceral fat and subcutaneous fat by X-ray CT analysis. Geniposide significantly suppressed the accumulation of visceral fat mainly in the 6th—10th segments, i.e., accumulation of perimesenteric fat, perirenal fat and peritesticular fat, and also partly suppressed the accumulation of subcutaneous fat. It was therefore shown that a fat accumulation-suppressing effect is involved in an anti-obesity effect of geniposide. This effect of geniposide on the accumulation of visceral fat has not previously been reported, and this study confirmed that reduction of the accumulation of visceral fat is one of the pharmacological effects of geniposide. Since geniposide suppressed the visceral fat accumulation that is the disease basis of MS, we then investigated the effects on other MS symptoms. We found that geniposide showed an alleviating effect on abnormal glucose/lipid metabolism. Visceral fat accumulation is caused by an increase in adipocyte count and adipocyte hypertrophy, and the hypertrophied adipocytes secrete adipocytokines inducing insulin resistance, leading to systemic insulin resistance. Since geniposide alleviated the abnormal glucose tolerance and hyperinsulinemia recognized in TSOD mice, geniposide was shown to have an insulin resistance-alleviating effect. It was previously reported that geniposide decreased the plasma insulin level in diabetes model mice,\(^5\) but the insulin resistance-alleviating effect of geniposide was demonstrated for the first time in the present study. It was reported that geniposide alleviates hyperglycemia by suppressing the expression of genes related to the enzymes involved in glyconeogenesis, such as glycogen phosphorylase and glucose-6-phosphatase,\(^5\) suggesting that the glyconeogenesis-suppressing effect is also involved as one of the mechanisms of the glucose metabolism-improving effect of geniposide recognized in the present study. In TSOD mice, which usually develop abnormal lipid metabolism, geniposide exhibited a plasma T-Cho level-suppressing effect, an HDL/T-Cho ratio-increasing effect and an intrahepatic fat level-decreasing effect. The ability of geniposide to alleviate abnormal lipid metabolism has also been recognized in high-fat-loaded rats\(^5\) or mice with diabetes induced by a high-fat diet and streptozotocin,\(^5\) and it was reported that the induction of expression of the fatty acid oxidation-related gene PPAR\( \alpha \) in the liver is involved as the action mechanism. In addition, an abnormal lipid metabolism-alleviating effect has been recognized with loganin (an iridoid glycoside like geniposide) and swertiamarin (a secoiridoid glycoside). Also, loganin has been reported to induce expression of PPAR\( \alpha \) and suppress expression of sterol regulatory element-binding protein (SREBP) and the cholesterol synthesis rate-determining enzyme HMG-CoA reductase,\(^{25}\) and swertiamarin has also been reported to suppress expression of HMG-CoA reductase.\(^{26}\) As mentioned above, it was suggested that geniposide acts on lipogenesis and lipolysis and alleviates an abnormal lipid metabolism. In the control TSNO mice, geniposide showed a body weight increase-suppressing effect slightly, but fat accumulation and other symptoms were not influenced by geniposide at all, suggesting that the effects of geniposide are exerted mainly on conditions arising after the onset of metabolic disease.

It has so far been reported that geniposide is effective in fatty liver in animal experiments,\(^5\) but it is unclear whether geniposide acts directly on the liver or acts indirectly on the liver through an action on another organ such as adipose tissue or pancreas, since there are inter-organ communication systems in the body. To investigate whether geniposide has a
direct effect on suppression of intrahepatic fat accumulation, the effect of geniposide was investigated using the fatty liver model HepG2-FFA, prepared by adding free fatty acid to human liver cancer cells (HepG2 cells). HepG2-FFA was used to investigate the basic disease status of fatty liver, to evaluate the drug effect and to clarify the mechanism of action.27,28) After oral administration, geniposide is decomposed by enterobacteria and metabolized into genipin, which is the aglycone portion, and which is taken up by the liver.29) Aburada et al.30) have reported that genipin and its glucuronide conjugate were detected at 44 μM and 100 μM in portal vein and bile respectively after intra-duodenal administration of 2 g/kg geniposide in Wistar rats. In this study, geniposide were continuously administered to TSOD mice at about 100 or 300 mg/kg/d, which calculated from food intake. Therefore, in the in vitro experiments, geniposide was used at concentrations of 10, 50 and 100 μM, which would be exist in liver of TSOD mice. Since genipin suppressed in a dose dependent manner the intracellular TG and T-Chol levels that in liver of TSOD mice. Since geniposide and loganin induces expression of PPARα mRNA. Since geniposide and loganin induces expression of PPARα in the liver in vivo,3,25) it has been shown that the fatty acid oxidative effect in the liver26) is involved in the mechanism of suppression of intrahepatic fat accumulation. However, it is difficult to explain the fat accumulation-suppressing effect of genipin solely by induction of PPARα expression, and we are also planning to investigate its effects on other factors such as SREBP and HMG-CoA reductase.

As mentioned above, geniposide was shown in this study to exhibit an anti-obesity effect by suppressing visceral fat accumulation and to alleviate the abnormal glucose/lipid metabolism that accompanies visceral fat accumulation. In addition, it was shown that genipin, a metabolite of geniposide, acts directly on the liver cells and induces expression of a lipid metabolism-related gene to alleviate fatty liver.

REFERENCES