

## Ginseng modifies the diabetic phenotype and genes associated with diabetes in the male ZDF rat

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### Abstract

Asian ginseng (*Panax ginseng*) and its close relative North American ginseng (*Panax quinquefolius*) are perennial aromatic herbs that are widely used in Oriental medicine and have been acclaimed to have various health benefits including diabetes treatment. In this study, we compared the effects of a diet containing rosiglitazone to a diet containing ginseng (*Panax quinquefolius*) in male Zucker diabetic fatty (ZDF) rats. Animals were assigned to one of three diets: control, rosiglitazone (0.1 g/1 kg diet), or ginseng (10 g/1 kg diet). During the 11-week study, body weight, food intake, organ weight, blood glucose, plasma cholesterol, and plasma triglyceride levels were evaluated. Animals treated with rosiglitazone or ginseng exhibited increased body weight ( $p < 0.05$ ) and decreased kidney weight ( $p < 0.05$ ) compared to control animals. The rosiglitazone group demonstrated decreased food intake and plasma triglyceride levels versus the other groups ( $p < 0.05$ ). The ginseng group revealed decreased cholesterol levels relative to the control group ( $p < 0.05$ ). Furthermore, ginseng and rosiglitazone had marked effects on the expression of genes involved in PPAR actions and triglyceride metabolism compared to controls. In conclusion, ginseng modified the diabetic phenotype and genes associated with diabetes in the male ZDF rat. These data are encouraging, and warrant further research to determine the therapeutic value of this medicinal herb in treating human diabetes.

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**Keywords:** Ginseng; Insulin resistance; Obesity; Gene expression; Peroxisome proliferator-activated receptor (PPAR); Zucker Diabetic Fatty (ZDF) rat

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### Introduction

Asian ginseng (*Panax ginseng*) and its close relative North American ginseng (*Panax quinquefolius*) are perennial aromatic herbs that are widely used in oriental medicine. Many claims are associated with over-the-counter ginseng supplements ranging from increasing resistance to stress and fatigue to improved well-being in

age-related debilitation. In the United States, ginseng is one of the highest selling herbal supplements. In experimental animals, the root extract of ginseng has been demonstrated to enhance learning and memory, produce anxiolytic effects, enhance libido, reduce risk of cancer and exert anti-diabetic effects (Blumenthal, 2001; McCabe, 2002; Cuddy, 2003; Huntley and Ernst, 2003; Tesch, 2003; Coleman et al., 2003). The anti-diabetic effects of ginseng have also been investigated (Kimura and Suzuki, 1981; Bao, 1981; Kimura et al., 1981a, b; Vuksan et al., 2001; Shan et al., 2002; Dey et al., 2002, 2003; Xie et al., 2002a, b, 2004b, 2005; Wang et al., 2003; Yun et al., 2004; Park et al., 2005; Jung et al., 2005; Vuksan et al., 2006). Cumulatively, these data strongly suggest that the anti-diabetic properties of ginseng warrant further preclinical investigation.

Ginsenosides, also called ginseng saponins, are thought to be the component responsible for the anti-diabetic actions of ginseng (Attele et al., 2002; Huntley and Ernst, 2003; Han et al., 2006a). Ginsenosides have been proposed to work through the peroxisome proliferator-activated receptors alpha (PPAR $\alpha$ ) and gamma (PPAR $\gamma$ ) (Yoon et al., 2003; Park et al., 2005; Han et al., 2006a). The PPARs are members of the nuclear hormone receptor family and are distributed in a variety of tissues. PPAR $\alpha$  ligands have shown to improve lipid profiles and increase insulin sensitivity. PPAR $\alpha$  may indirectly improve insulin sensitivity by increasing  $\beta$ -oxidation of fatty acids, which reduces lipid accumulation and toxicity in muscle and liver tissues (Li and Glass, 2004; Michalik et al., 2006). PPAR $\gamma$  has a large distribution in adipocytes and plays an important role in the adipogenesis and stimulates production of small insulin-sensitive adipocytes (Kintscher and Law, 2005). It is still unclear how PPAR $\gamma$  directly improves insulin sensitivity in mature adipocytes, but PPAR $\gamma$  does induce the expression of genes involved with the insulin signaling cascade (Kintscher and Law, 2005).

The current study was designed to investigate the effectiveness of ginseng root extract in treating the diabetic phenotype in the preclinical Zucker diabetic fatty (ZDF) rat model and address potential mechanism of action. Because of the similarities in the mechanisms of nuclear receptor pathways, we utilized the insulin-sensitizing thiazolidinedione, rosiglitazone, as a comparison to ginseng (Han et al., 2006a). Physiological parameters such as changes in body weight, organ weight, food intake, blood glucose, plasma cholesterol, and plasma triglyceride levels were evaluated. In addition to physiological effects, the genes known to be associated with PPAR activation and those involved in triglyceride metabolism and diabetes were measured for change in their transcript abundance relative to a control diet in order to better understand the antidiabetic effects of ginseng.

## Material and methods

### Animals and diet

Male ZDF rats (*fa/fa*) were obtained at 6 weeks of age from Genetic Models Inc. (Indianapolis, IN, USA). Animals were randomly placed into three diet groups: control diet (C,  $n = 8$ ); control diet + rosiglitazone (R,  $n = 8$ ); or control diet + ginseng (G,  $n = 7$ ). Casein, cellulose, vitamin mix, mineral mix, choline bitartrate, DL-methionine, L-cysteine, and *tert*-butylhydroquinon were obtained from ICN Biomedicals (Costa Mesa, CA). The experimental diets (Table 1) contained: 100 mg rosiglitazone/kg diet (R) or 10 g root extract of ginseng (*Panax quinquefolius*)/kg diet (G) (Sigma St. Louis). As previously described (Corbit et al., 2005), ginseng extract (containing approximately 7% ginsenosides) was prepared using a water extraction method utilizing the ginsenosides (from Indofine) as standards for HPLC analysis. All diet (Banz et al., 2006; Davis et al., 2007) and drug regimens are based on a modification of previous investigations and American Institute of Nutrition (AIN93) recommendations (Reeves et al., 1993; Banz et al., 2005; Davis et al., 2005a, b). All rats were housed in stainless-steel wire-mesh cages at 21 °C in a room with an automatically controlled 12:12h light:dark cycle. Each rodent had free access to water and respective diets in powdered form for the 11-week study. All experimental protocols for animal care and use were approved by the Institutional Animal Care and Use Committee.

### Physiological measures, tissue collection and biochemical analysis

Body weight, food intake, and non-fasted blood glucose levels were obtained weekly. Blood samples

**Table 1.** Composition of experimental diets

Ingredient (g/kg)	Diet group		
	Control	TZD	Ginseng
Casein	230	230.4	230
Sucrose	270.5	270.4	267.5
Cornstarch	310	310	303
Cellulose	50	50	50
Soybean oil	25	25	25
Lard	64	64	64
Vitamin mix	10	10	10
Mineral mix	35	35	35
Choline bitartrate	2.5	2.5	2.5
L-Cytine	3.0	3.0	3.0
<i>tert</i> -Butylhydroquinon	0.014	0.014	
Rosiglitazone	–	.1	–
Ginseng (root extract)	–	–	10

TZD = Thiazolidinediones (feed/add mixture of rosiglitazone).

were acquired through tail snip and analyzed with the Glucometer Elite<sup>®</sup> blood glucose meter (Mishawaka, IN, USA). At approximately 17 weeks of age, fasted animals were weighed and then sacrificed by decapitation. Blood was immediately collected into tubes containing heparin (25 µl/ml blood) and placed on ice. Plasma was extracted by centrifugation and subsequently utilized to measure glucose, insulin, cholesterol, and triglycerides levels. The liver, heart and right kidney were immediately extracted and weighed for further analysis and/or statistical comparisons. The remaining carcasses were frozen at  $-40^{\circ}\text{C}$  for body lipid analysis.

Quantitative determination of final glucose concentrations was carried out on plasma samples using the Glucose Reagent supplied by Beckman Coulter in conjunction with the Synchron CX Systems CX Multi<sup>™</sup> Calibrator (Beckman Coulter, Fullerton, CA) and Synchron Multi-Level Controls (Beckman Coulter, Cat # 657365). The CX-4 requires 30 µl of plasma for the timed endpoint assay that monitors the change in absorbance at 340 nm. The determination of total triglycerides and cholesterol were carried out on plasma samples using Triglycerides GPO Reagent and Cholesterol Reagent and carried out as described above for glucose measuring absorbance at 520 nm. The resultant concentration of glucose, total triglycerides, and cholesterol is expressed in mg/dl.

Quantitative determination of insulin was carried out on plasma samples using the ALPCO Ultrasensitive Insulin ELISA (Salem, NH). The colorimetric endpoint is read spectrophotometrically on a BioTek Elx808IU Ultra Microplate Reader at 450 nm. The resultant concentration of plasma insulin is expressed in ng/ml.

Body lipid analysis was based on a modification of a previously published protocol (Banz et al., 2005; Davis et al., 2005a, b). Briefly, each frozen carcass was weighed and then autoclaved for 60 min in a covered glass beaker. The autoclaved rat carcass was then combined with 3 ml of distilled water per gram of carcass weight and blended for 5 min. Following homogenization of the rat carcass, three 50 ml polypropylene tubes were filled with 7.7 ml of homogenate. The remaining homogenate was discarded. Each tube was then capped and weighed. Ten milliliters of methanol and 5 ml of chloroform were added to each tube and then capped and vortexed several times. Tubes were incubated at room temperature for 1 h. Following the incubation period, 5 ml of chloroform and 5 ml of KCl (1 M) were added to each tube. The tubes were then capped and vortexed and placed in an ice bath for 5 min. The samples were then centrifuged at 20g for 10 min. After centrifugation, the top layer was aspirated by pipette and the bottom layer was poured into disposable aluminum pans in the hood. The pellet that separated the two aqueous layers was discarded. Samples were left to evaporate overnight. On the next afternoon, the aluminum pans were heated

in a drying oven at  $80^{\circ}\text{C}$  for 15 min and then placed in a desiccator for 5 min. Finally, pans containing lipid were weighed and %lipid was calculated [ $\% \text{Lipid} = (\text{pan} + \text{lipid} - \text{pan weight}) / (\text{tube} + \text{homogenate} - \text{tube weight}) * 400$ ].

#### RNA isolations from liver, adipose, and muscle

Frozen liver tissues were ground into a fine powder in liquid  $\text{N}_2$  using a mortar and pestle. Adipose tissue and soleus tissues were homogenized and RNA was isolated using a QIAGEN RNeasy Mini Kit (QIAGEN Inc., CA, USA) according to the manufacturer's instructions. The quality of the RNA was determined by running a portion on 1.2% (w/v) formaldehyde agarose gel. The Spectronic UV-visible spectrophotometer was used to measure the concentration of RNA. Equal quantity of RNA (1 µg of RNA) from individual rats of each treatment (control, rosiglitazone, and ginseng) were pooled for DNase treatment and cDNA synthesis. Pooled RNA samples were loaded on a QIAGEN RNeasy mini column and treated with RNase free DNase (QIAGEN Inc., CA, USA) according to the manufacturer's instructions. Quality and concentration of RNA in the Dnase-treated samples were determined as described earlier (Banz et al., 2005; Davis et al., 2005a, b).

#### cDNA synthesis and quantitative real-time PCR

cDNA was synthesized from 2 µg of total pooled RNA for each group and quantitative real-time PCR was carried out as described earlier (Banz et al., 2005; Davis et al., 2005a, b). PCR conditions for PPAR- $\alpha$ , PPAR- $\gamma$ , CPT-1, and FAS were as described earlier (Banz et al., 2005; Davis et al., 2005a, b). Real-time quantitative PCR reactions for  $\beta$ -actin were run in duplicate and the other genes were run in triplicate. The annealing temperature was lowered to  $58^{\circ}\text{C}$  for ApoD and ApoAII genes and  $55^{\circ}\text{C}$  for UCP3, UCP2, IRS-1, Ob-Rb, HSL, RxR, and LPL. The rest of the conditions remained the same. Ct values of the genes were normalized by the average Ct values of  $\beta$ -actin for each pooled sample. The Fold changes were calculated using  $2^{(-\Delta\Delta\text{Ct})}$  and the standard deviation of fold-changes was determined (Bookout and Mangelsdorf, 2003).

## Results

### Body weight and food intake

At the start of the study body weight was not significantly different between rosiglitazone, ginseng, and control diets. At the end of the study, the rodents fed the rosiglitazone diet had a higher body weight ( $p < 0.05$ ) as compared to the control and ginseng groups

(Table 2). The ginseng-treated animals also exhibited increased body weight over control, but not to the same extent as did rosiglitazone treatment (Table 3). The rosiglitazone diet also increased ( $p < 0.05$ ) total body lipids versus the control and ginseng diet (Table 3). No differences were observed in body lipids between the control and ginseng groups.

Food intake between all groups was similar through the first 2 weeks (data not shown). At week 5, rodents fed the rosiglitazone diet exhibited a significant ( $p < 0.05$ ) decrease in food intake versus the ginseng diet. Rodents fed the rosiglitazone diet decreased food intake significantly versus the ginseng and control diet from weeks 7 through the end of the study (data not shown). The total food intake was significantly decreased ( $p < 0.05$ ) in the rosiglitazone group when compared to the control and ginseng groups (Table 3).

### Glucose, insulin, cholesterol, and triglycerides levels

Non-fasting blood glucose was monitored at weekly intervals throughout the study (data not shown). There were no changes in levels between control and treatment groups during the first 2 weeks of the study. However, rodents fed the rosiglitazone diet displayed a significant ( $p < 0.05$ ) decrease in non-fasting blood glucose levels versus the control and ginseng diet groups after week 2 and through the end of the study. The ginseng-treated animals exhibited a significant decrease in blood glucose levels versus the control group at week 6 only.

**Table 2.** Mean body weight and food intake in male ZDF rats after 11 weeks of diet treatment

Diet group	<i>n</i>	Body weight (g)	Body lipid (%)	Food intake (g)
Control	8	411.75 ± 11.7	28.65 ± 1.9	2117.87 ± 21.2
TZD	8	576.50 ± 18.6 <sup>a</sup>	42.13 ± 3.0 <sup>a</sup>	1813.34 ± 27.9 <sup>b</sup>
Ginseng	7	454.86 ± 15.2 <sup>c</sup>	25.21 ± 2.7	2151.30 ± 87.3

<sup>a</sup>TZD significantly increased in body weight and % body lipid versus control and Ginseng.

<sup>b</sup>TZD significantly decreased food intake versus Ginseng and control.

<sup>c</sup>Ginseng significantly increased in body weight versus control.

**Table 3.** Cholesterol, final glucose, triglycerides, and body lipid composition (% age) after 11 weeks of diet treatment

Diet group	<i>n</i>	Cholesterol (mg/dl)	Final glucose (mg/dl)	Triglycerides (mg/dl)
Control	7	107.57 ± 11.6	476.14 ± 43.8	285.43 ± 77.9
TZD	8	91.75 ± 3.4	252.00 ± 46.3 <sup>a</sup>	131.00 ± 18.1 <sup>b</sup>
Ginseng	7	78.86 ± 5.8 <sup>c</sup>	438.86 ± 50.9	201.29 ± 45.6

<sup>a</sup>TZD significantly decreased fasting blood glucose levels versus control and Ginseng.

<sup>b</sup>TZD significantly decreased triglyceride levels versus control.

<sup>c</sup>Ginseng significantly decreased cholesterol versus control.

Plasma samples from fasted rats were collected at the end of the experiment and plasma glucose, insulin, triglyceride, and cholesterol were measured (Table 4). Rodents fed the rosiglitazone exhibited significantly lower fasting plasma glucose levels versus the control and ginseng-fed rodents. No significant differences were observed in fasting plasma insulin levels (data not shown). The animals fed the rosiglitazone diet also exhibited a significant ( $p < 0.05$ ) decrease in triglyceride levels versus the control-fed rodents only. Rodents fed the ginseng diet showed a trend toward a decrease in triglyceride levels but a significant ( $p < 0.05$ ) decrease in cholesterol levels versus the control-fed rodents.

### Organ weight

At the end of the experiment the heart, liver, and right kidney were removed and weighed for comparison (Table 5). No significant differences were seen in heart weight or liver weight in the ginseng- and rosiglitazone-fed versus the control-fed rodents. Rodents fed the ginseng and rosiglitazone diets, however, were found to have a significant ( $p < 0.05$ ) decrease in kidney weight versus the control group; kidney weight was also decreased ( $p < 0.05$ ) in animals fed the rosiglitazone diet when compared to the ginseng-fed rats.

### Gene expression response

Changes in gene expression using real-time quantitative PCR indicated a mixed response in different tissues

**Table 4.** Diet effect on heart, liver, and kidney weights at 11 week of treatment

Diet group	<i>n</i>	Heart (g)	Liver (g)	Kidney (g)
Control	8	1.16 ± 0.03	22.51 ± 1.23	1.84 ± 0.04
TZD	8	1.34 ± 0.04	24.26 ± 1.26	1.39 ± 0.06 <sup>a</sup>
Ginseng	7	1.36 ± 0.13	22.63 ± 0.63	1.60 ± 0.10 <sup>b</sup>

<sup>a</sup>TZD significantly decreased kidney weight versus control and Ginseng.

<sup>b</sup>Ginseng significantly decreased kidney weight versus control.

**Table 5.** Genes and the primer sequences used to measure their transcript abundance (TA) in this study

Target gene	Forward primer (5'–3')	Reverse primer (5'–3')
PPAR $\alpha$	ACA GGA GAG CAG GGA TTT G	AGA AAG TAA GGA TGT GGG ACC
PPAR $\gamma$	AGA AGA CGG AGA CAG ATA TCA G	TGC AAT CGA TAG AAG GAA CAC
Apolipoprotein A2 (ApoAII)	TCA CCA TCT GTA GCC TAG AAG G	GCA TTC TGA AAG TAA GCC TTG G
Apolipoprotein D (ApoD)	ACC ATG CTG TTG CTC CTG G	CAC TTT GAT GTT TCC GTT CTC C
Fatty acid synthesis (FAS)	AGC ATA TCC CTG TAA ACA GGT GAC	TGT GGA TAG GAC TGA ATG CTG TGG
OBRB (Leptin Receptor)	CAC TTG ACT CTC CAC CAA CG CTG TAC	CAC ATA GAC CGC AC
Cartnitine palmitoyl transferase I (CPT-1)	TTT CCA GTG TCC TTG CTG C	ACA CAA TAG TCT TAC CTC CTC C
Insulin receptor substrate 1 (IRS-1)	ATG GCT ACA TGA TGA TGT CTC C	AGC TTA CCA CCA CCG CTC
Hormone-sensitive lipase (HSL)	AGC AGT TCA CAG TGC TTG AC	GTG GCT TTG TGG CAC AGA C
Retinoid X receptor (R $\times$ R)	ACA TTG GGC TTC GGG ACT G	CTT GCA GCC CTC ACA ACT G
Lipoprotein lipase (LPL)	AGA ATC GCT GTA ACA ACG TGG G	CGA GGG TGA AGG CAA TGT TCT C
Uncoupling protein 2 (UCP2)	TTG CAC GAG AGG AAG GGA TC TGA CCA	CAT CAA CAG GGG AG
Uncoupling protein 3 (UCP3)	AGA TTC CCG CAG TAC CTG G	GGT GGA TGT GGT AAA GAC CC

to ginseng and rosiglitazone treatments (Table 6). Ginseng diet increased the expression of PPAR $\gamma$  in liver and adipose tissues in contrast to no significant change in PPAR $\alpha$  in these tissue from animals on rosiglitazone. In muscle tissues, the two diets had significant opposite effects on the PPAR $\gamma$  expression (Table 6), with rosiglitazone increasing and ginseng decreasing muscle PPAR $\gamma$  expression. The ginseng and rosiglitazone diets significantly decreased the expression of PPAR $\alpha$  in adipose tissue. The decrease in PPAR $\alpha$  expression was also significant in muscle tissue of the animals on ginseng diet; muscle tissue from animals on the rosiglitazone diet showed no significant change in PPAR $\alpha$ . The other genes that were similar and significantly decreased in muscle tissue by both ginseng and rosiglitazone were CPT-1 and IRS. Ginseng also leads to a significant increase in expression of RxR in muscle tissue. The rosiglitazone diet group showed a significant increase in the expression of LPL and UCP3 in liver and FAS in adipose tissue. Changes were considered significant ( $p < 0.05$ ) when they were  $\geq 2$ -fold increased or decreased compared to controls. There were

no further changes in defined gene expression based on these set values (Table 6).

## Discussion

The current study demonstrated the effects of ginseng root extract in treating the diabetic phenotype in the preclinical ZDF rat model. When comparing the effectiveness of ginseng to the insulin-sensitizing PPAR $\gamma$  agonist rosiglitazone, we observed similar, yet distinct, therapeutic effects of ginseng. Transcription abundance of various genes known to be involved in the diabetic treatment response were also determined as a measure of their expression in order to help elucidate their potential roles in the physiological effects of ginseng.

Variable effects of ginseng on body weight, food intake, and body fat have been observed in rodent studies (Dey et al., 2002; Xie et al., 2002a, b, 2004b; Yun et al., 2004; Kim et al., 2005). In this study, the rats fed the rosiglitazone diet exhibited a much higher body

**Table 6.** Changes in transcript abundance of genes studied by real time RT-PCR

Gene	PPAR $\gamma$			PPAR $\alpha$			CPT-1		
	L	M	A	L	M	A	L	M	A
TZD	1.89 $\pm$ 0	$\uparrow$ 2.94 $\pm$ 0	0.79 $\pm$ .2	1.09 $\pm$ .4	0.69 $\pm$ .2	$\downarrow$ 0.45 $\pm$ .2	0.85 $\pm$ .6	$\downarrow$ 0.20 $\pm$ .1	0.63 $\pm$ .2
Ginseng	$\uparrow$ 4.78 $\pm$ .4	$\downarrow$ 0.31 $\pm$ 0.3	$\uparrow$ 2.63 $\pm$ .3	1.63 $\pm$ .4	$\downarrow$ 0.40 $\pm$ .1	$\downarrow$ 0.39 $\pm$ .2	1.30 $\pm$ .2	$\downarrow$ 0.36 $\pm$ 0	0.61 $\pm$ .4

  

Gene	FAS		RxR			ApoD	
	L	A	L	M	A	L	M
TZD	1.41 $\pm$ .0	$\uparrow$ 3.37 $\pm$ .1	0.89 $\pm$ .1	1.12 $\pm$ .4	1.33 $\pm$ .1	1.77 $\pm$ .4	0.70 $\pm$ .1
Ginseng	0.95 $\pm$ .1	0.67 $\pm$ .3	1.09 $\pm$ .6	$\uparrow$ 3.37 $\pm$ .1	1.78 $\pm$ 0	1.85 $\pm$ .2	1.88 $\pm$ 1.3

  

Gene	ApoAII	HSL	IRS	LPL	ObRb	UCP2	UCP3
	L	L	M	L	L	L	L
TZD	1.07 $\pm$ .1	0.80 $\pm$ .3	$\downarrow$ 0.37 $\pm$ .3	$\uparrow$ 3.09 $\pm$ 0	1.30 $\pm$ .5	1.02 $\pm$ .1	$\uparrow$ 3.36 $\pm$ 0
Ginseng	0.94 $\pm$ .3	0.73 $\pm$ .5	$\downarrow$ 0.35 $\pm$ .4	1.56 $\pm$ .5	0.63 $\pm$ .4	0.75 $\pm$ 0	1.75 $\pm$ .7

The transcript levels of the two treatments were compared to the control diet and fold changes were calculated as  $2^{(-\Delta\Delta Ct)}$  (Current protocols in Molecular Biology, 2005) Standard deviation in fold change represent experimental error and was calculated from  $\Delta\Delta Ct$  values. L = Liver, M = Muscle, A = Adipose. The direction of arrow indicates the significant up- or down regulation of the transcript levels.

weight when compared to ginseng, consistent with other studies (Davis et al., 2007). Ginseng itself increased body weight over that of controls. Similar to rosiglitazone treatment, the weight-enhancing effect of the ginseng diet may be related to the proposed PPAR $\gamma$  agonist effect of ginseng extracts (Yoon et al., 2003; Kintscher and Law, 2005; Lee et al., 2006). Indeed, there was a significant increase in PPAR $\gamma$  expression in adipose tissue of the ginseng diet group animals (Park et al., 2005; Lee et al., 2006; Han et al., 2006b; Shang et al., 2007). However, contrary to the food intake paradox (Davis et al., 2005a, b) associated with rosiglitazone, in which food intake decreases but body weight increases through increased adiposity, the ginseng group showed no differences in body lipids compared to the control group. This suggests that the body weight increase in the ginseng group constitutes an increase in lean body mass. Consistent with the increased body weight, the rosiglitazone diet also increased total body lipids versus the control and ginseng diet. The significant increased expression of FAS and LPL support the lipid accumulation effect of rosiglitazone in adipose tissues (Yoon et al., 2003; Park et al., 2005; Kintscher and Law, 2005). The total food intake of the rosiglitazone group decreased when compared to the control and ginseng groups. Also of note, RXR expression in muscle was significantly increased in the ginseng group but not the rosiglitazone group. This may have implications on how ginseng alters glucose tolerance, as ligands for RXR that do not activate transcription through the PPAR $\gamma$  heterodimer can be effective agents in lowering blood

glucose in animal models of insulin-resistant diabetes (Li et al., 2005).

Similar to the variable effects of ginseng on body weight (Dey et al., 2002; Xie et al., 2002a, b, 2004b; Yun et al., 2004; Kim et al., 2005), ginseng has also been shown to have variable effects on blood glucose levels (Sotaniemi et al., 1995; Vuksan et al., 2000a, b, 2001; Chung et al., 2001; Shan et al., 2002; Dey et al., 2002, 2003; Attele et al., 2002; Xie et al., 2002a, b, 2004a, b, 2005; Wang et al., 2003; Yun et al., 2004; Park et al., 2005; Jung et al., 2005). In this study, rodents fed rosiglitazone displayed a marked decrease in non-fasting blood glucose levels versus the control and the ginseng diet groups. The ginseng-treated animals only exhibited a significant decrease in blood glucose levels versus the control group at week 6. No differences were observed in fasting plasma glucose or insulin levels at the end of the study.

Ginseng has also been shown to decrease plasma lipid levels (Sotaniemi et al., 1995; Vuksan et al., 2000a, b, 2001; Chung et al., 2001; Shan et al., 2002; Dey et al., 2002, 2005; Attele et al., 2002; Xie et al., 2002a, b, 2004a, b, 2005; Wang et al., 2003; Yoon et al., 2003; Kim and Park, 2003; Cicero et al., 2003; Yun et al., 2004; Park et al., 2005; Jung et al., 2005; Lee et al., 2006). In this study, the animals fed the rosiglitazone diet, but not the ginseng diet, exhibited a decrease in triglyceride levels versus the control-fed rodents only. Conversely, the rodents fed the ginseng diet but not the rosiglitazone diet demonstrated a decrease in cholesterol levels versus the control-fed rodents. It has been

suggested (Sotaniemi et al., 1995; Vuksan et al., 2000a,b, 2001; Chung et al., 2001; Shan et al., 2002; Dey et al., 2002, 2003; Attele et al., 2002; Xie et al., 2002a, b, 2004a, b, 2005; Wang et al., 2003; Yoon et al., 2003; Yun et al., 2004; Park et al., 2005; Jung et al., 2005; Lee et al., 2006) that PPAR $\alpha$  is involved in the regulation of lipid metabolism by ginseng. The ginseng-induced lipid-lowering effect that we observed was limited to cholesterol, unlike the triglyceride-lowering effect observed with the rosiglitazone (PPAR $\gamma$  agonist) treatment. This observation supports the proposition that PPAR $\alpha$  is involved in the regulation of lipid metabolism by ginseng (Sotaniemi et al., 1995; Vuksan et al., 2000a,b, 2001; Chung et al., 2001; Shan et al., 2002; Dey et al., 2002, 2003; Attele et al., 2002; Xie et al., 2002a, b; Wang et al., 2003; Yoon et al., 2003; Yun et al., 2004; Xie et al., 2004a, b, 2005; Park et al., 2005; Jung et al., 2005; Lee et al., 2006).

No significant differences were seen in heart weight or liver weight in the ginseng- and rosiglitazone-fed rodents versus the control-fed rodents. Rodents fed the ginseng and rosiglitazone diets, however, demonstrated a decrease in kidney weight versus the control group. Limited studies (Yokozawa and Liu, 2000; Kang et al., 2006) have demonstrated that ginseng may have a protective effect on renal function. For example, treatment with ginseng components has been shown to prevent renal damage associated with diabetes (Kang et al., 2006).

In conclusion, ginseng modified the diabetic phenotype and genes associated with diabetes in the male ZDF rat. These data are encouraging, and warrant further research to determine the therapeutic value of this medicinal herb in treating human diabetes.

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