The Functional Assessment of *Alpinia pricei* on Metabolic Syndrome Induced by Sucrose-containing Drinking Water in Mice

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This study was designed to test whether *Alpinia pricei* (AP), a member of the ginger family indigenous to Taiwan, reduced metabolic syndrome induced by sucrose-containing drinking water in C57BL/6J mice. Mice given a chow diet were divided into a control group (C) or a test group given 30% sucrose water (SW) to drink *ad libitum*. After 22 weeks, mice in the SW group were subdivided into SW and SW + AP groups, the latter receiving a chow diet with an ethanol extract of AP (1500 mg/kg dosage). Four weeks later, bio-indexes associated with metabolic syndrome were measured. Compared with the C group, the SW group had significantly higher body weight, visceral fat weights, serum and tissue lipid, serum insulin level and the area under the curve for blood glucose of the insulin tolerance test ($p < 0.05$). These indicators in the SW + AP group were lower than in the SW group except for serum lipid, although slightly higher than the C group. The SW + AP group also showed significantly lower serum levels of leptin and tumor necrosis factor-α and a significantly higher level of adiponectin than the SW group. These results indicated that visceral adiposity and insulin resistance induced by sucrose water drinking might be alleviated by AP supplementation. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Alpinia pricei; metabolic syndrome; sucrose-containing drinking water; C57BL/6J mice.

INTRODUCTION

Metabolic syndrome has become a major global public health problem. It is indicated by the clustering of certain risk factors, including insulin resistance, central obesity, hypertension and dyslipidemia, which dramatically increases the risk of developing cardiovascular disease and type 2 diabetes mellitus (Reaven, 1998; Plutzky, 2000). Obesity (especially abdominal or visceral adiposity) has been postulated to play a crucial role and is recognized as a necessary component in the definition of metabolic syndrome (Zimmet *et al.*, 2005). Adipose tissue is known to serve not only in energy storage, but also as an endocrine organ that releases adipocytokines e.g. tumor necrosis factor-α (TNF-α), leptin, adiponectin, resistin and free fatty acids into circulation to regulate both systemic lipid and glucose metabolism and inflammatory responses (Ahima and Flier, 2000). Lipotoxicity stress (i.e. overloading adipose tissue beyond its storage capacity, which leads to the deposition of lipids into non-adipose tissues) and chronic obesity-induced inflammatory responses are believed to be involved in the pathogenesis of insulin resistance (Unger, 1995; DeFronzo, 2004; Solinas *et al.*, 2007).

Recently, polyphenols, such as epigallocatechin gallate (EGCG) in green tea (Wolfram, 2007; Potenza *et al.*, 2007), resveratrol in grape skin and red wine (Lagouge *et al.*, 2006) and flavonoids from licorice (Mae *et al.*, 2003) have been shown to confer multifaceted benefits on metabolic health. The aim of this study is to identify functional foods that could prevent or ameliorate metabolic syndrome, specifically *Alpinia pricei* (AP), a species of *Alpinia zerumbet* indigenous to Taiwan. To accomplish this, a method that would induce metabolic syndrome in mice was necessary.

Alpinia zerumbet, a plant frequently seen in Asia, belongs to the ginger family. Traditionally, its leaf is used for wrapping food, and its rhizome is used for cooking as a ginger substitute. The phenolic compounds of curcumin and curcuminoids are present in turmeric (*Curcuma longa* Linn, Zingiberaceae) and are well known for their antiinflammatory, antioxidative and anticarcinogenic effects (Srimal and Dhawan, 1973; Ammon and Wahl, 1991; Quiles *et al.*, 1998). Recently, dietary curcuminoids were reported to prevent liver triacylglycerol (TG) accumulation and epididymal adipose tissue weight gain in rats fed a high fat diet through an induction of fatty acid catabolism (Asai and Miyazawa, 2001). In addition, the hypoglycemic effect of curcuminoids was also observed in KK-A[y] mice, a spontaneous type 2 diabetic model (Nishiyama *et al.*, 2005). Thus, the potential of ginger family plants to treat metabolic syndrome merits study. To induce symptoms resembling human metabolic syndrome, a sucrose-containing drinking water strategy that had been successfully used in rats (El Hafidi *et al.*, 2001; Aguilera *et al.*, 2004) was used in C57BL/6J mice.

MATERIALS AND METHODS

Preparation of ethanol extract of *Alpinia pricei*. *Alpinia pricei* was collected from Ping-tung County located in southern Taiwan in March, 2006. Its authenticity was confirmed by the Department of Forestry, National Chung-Hsing University. The voucher specimen (YHT20060610 (TCF)) was deposited in the herbarium of the same university. The air-dried roots (2 kg) of *A. pricei* were treated with 10 L of 70% ethanol at room temperature, and the residue was collected after removing the solvent by evaporation under reduced pressure. The yield of AP ethanol extract was 8.3% (g/g).

Animals and diet. Twenty-four male C57BL/6J mice were purchased from the National Applied Research Laboratories (Taipei, Taiwan) at 7 weeks of age. After acclimatization with standard rodent chow diet (6 g water, 51 g crude carbohydrate, 23.5 g crude protein, 4.5 g crude lipid, 6 g crude fiber and 9 g ash/100 g diet; Fwusow Industry Co. Ltd, Taiwan) for 1 week, the mice were divided into two groups to receive the chow diet with either plain water (control group, C; $n = 8$) or 30% sucrose water (test group, SW; $n = 16$) for *ad libitum* hydration. At 20 weeks, all mice were switched from a pellet chow diet to a powdered one to help them become accustomed to it. At 22 weeks, mice in the test group were further divided into SW and SW + AP groups of eight mice each. Sucrose water was supplied continuously, but the two groups of mice were fed either a powdered chow diet without (SW) or with 5% (g/g) ethanol extract of AP (equivalent to 1500 mg/kg body weight) (SW + AP). The animals were kept in a room maintained at 23 ± 2 °C on a controlled 12 h light: dark cycle. The body weight gain was recorded weekly. The protocols for animal care and handling were approved by the Institutional Animal Care and Use Committee of the China Medical University.

Assessment of insulin sensitivity. After the AP treatment for 3 weeks, the insulin sensitivity of all mice was assessed by the oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) methods. For the OGTT, the mice were fasted overnight, then tail blood was collected before (0 min) and at 30, 60, 90 and 120 min after oral administration of a 2.5 M glucose solution (1.5 g/kg body weight). For the ITT, the mice were fed for 3 h after overnight fasting, then tail blood was collected before (0 min) and at 30, 60, 90 and 120 min after i.p. injection of a 0.1 U/mL solution of insulin (0.75 U/kg body weight). Blood glucose levels were measured using a MediSense Optium glucometer (Abbott Laboratories, MA), then the area under the curve for blood glucose (AUC_{glu}) over the 2 h was calculated.

Tissue sampling and preparation. After the AP treatment for 4 weeks, all mice were killed by carbon dioxide asphyxiation after overnight fasting. Blood was collected from the orbital capillary. Liver, adipose tissue (epididymal and retroperitoneal fats) and gastrocnemius muscle were excised and weighed. A small portion of liver and muscle was frozen at −20 °C for the analysis of lipid content. Serum samples were obtained by centrifugation of blood at 3000 × **g** for 10 min, then stored at −20 °C for the analysis of insulin, lipids and adipocytokines.

Measurement of biomedical index. The enzyme-linked immunosorbent assays were used to measure serum insulin (Linco, St Charles, MO), adiponectin (R & D, Minneapolis, MN), TNF-α (eBioscience, San Diego, CA) and leptin (R & D, Minneapolis, MN). Lipids in liver and skeletal muscle were extracted by the method of Folch *et al.* (1957). TG and total cholesterol (TC) in serum and tissue extract were measured by enzymatic methods using commercial kits (Randox Lab, Crumlin, Northland, UK).

Statistical analysis. Data are expressed as the mean ± SD. The significance of differences between groups was analysed statistically by one-way ANOVA and Duncan's multiple range tests. The data were transformed to log values for the statistical analysis if the variances were not homogeneous. The General Linear Model of the SAS package (SAS Institute, Cary, NC) was used for statistical analyses, and differences were considered significant at $p < 0.05$.

RESULTS

Induction of metabolic syndrome by sucrose water

The final body weight and the relative visceral fat (epididymal and retroperitoneal fats) masses of mice in the three groups are shown in Fig. 1. After 26 weeks,
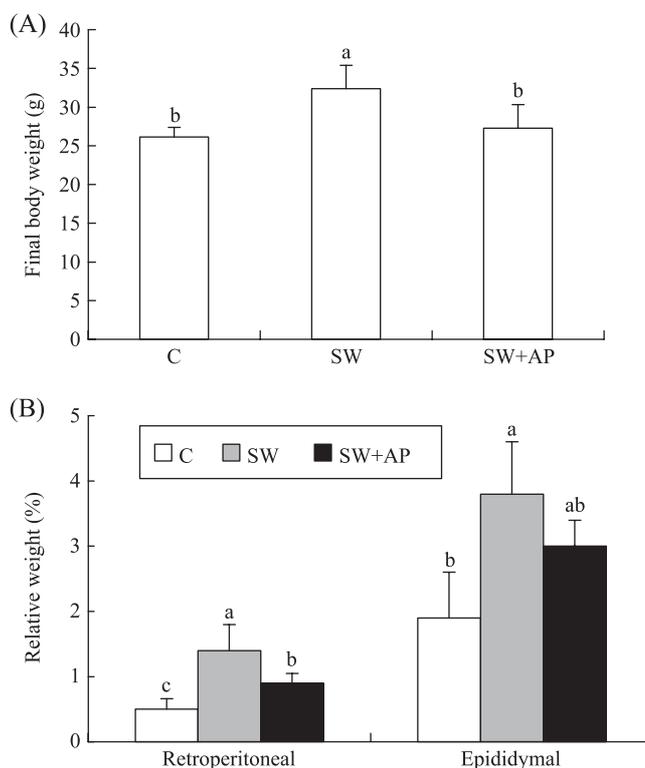

Figure 1. The final body weight (A) and the relative adipose tissue weight (B) of mice fed experimental diets. The relative tissue weight (%) is the tissue weight divided by the body weight × 100. C, normal control; SW, sucrose water induced metabolic syndrome; SW + AP, sucrose water induced metabolic syndrome + *Alpinia pricei*. Values are mean ± SD, $n = 8$. The significance of differences among C, SW and SW + AP groups were analysed by one-way ANOVA and Duncan's multiple range test. Values not sharing a superscript letter between groups are significantly different ($p < 0.05$).

Table 1. The lipid content in serum, liver and muscle of mice fed experimental diets

	C	SW	SW + AP
Serum			
TG (mmol/L)	1.00 ± 0.23[b]	1.50 ± 0.57[a]	1.50 ± 0.49[a]
TC (mmol/L)	2.62 ± 0.43[b]	3.29 ± 0.57[a]	3.82 ± 0.83[a]
Liver			
TG (mmol/g)	0.14 ± 0.22[b]	0.18 ± 0.06[a]	0.16 ± 0.004[ab]
TC (mmol/g)	0.18 ± 0.03[b]	0.32 ± 0.14[a]	0.26 ± 0.15[ab]
Muscle			
TG (mmol/g)	0.013 ± 0.004[b]	0.021 ± 0.003[a]	0.017 ± 0.002[ab]

C, normal control; SW, sucrose water induced metabolic syndrome; SW + AP, sucrose water induced metabolic syndrome + *Alpinia pricei*.
TG, triacylglycerol; TC, total cholesterol.
Values are mean ± SD, $n = 8$. The significance of differences among C, SW and SW + AP groups were analysed by one-way ANOVA and Duncan's multiple range test. Values not sharing a superscript letter between groups are significantly different ($p < 0.05$).

the final body weight of the SW group was significantly higher than that of the C group ($p < 0.0001$, Fig. 1A), and the difference could be observed as early as 3 weeks after induction of the experiment (data not shown). The SW group also had a significant increase in the relative epididymal and retroperitoneal fat weights compared with the C group ($p < 0.0001$, Fig. 1B).

The lipid content in serum, liver and muscle of mice fed experimental diets is shown in Table 1. Sucrose water significantly increased the TG and TC levels in serum ($p < 0.01$) and in liver ($p < 0.05$) as well as the TG concentration in muscle ($p < 0.05$) of the SW group compared with the C group.

The fasting blood glucose level was similar between the SW and C groups (Fig. 2A), as was the AUC_{glu} over 2 h of OGTT (data not shown). However, insulin resistance caused by sucrose water was demonstrated by the significantly higher level of serum insulin and AUC_{glu} over 2 h of ITT in the SW group compared with the C group ($p < 0.05$, Fig. 2B, C, respectively). Table 2 shows the concentrations of adipocytokines in the serum of mice fed experimental diets. The serum levels of leptin and TNF-α were significantly increased in the SW group compared with the C group ($p < 0.0001$). However, there was no difference in the adiponectin level between the SW and C groups.

Therefore, it appears that metabolic syndrome indicators including visceral adiposity, hyperlipidemia and insulin resistance were induced successfully in this model. The next step was to test the target substance.

(A)

(B)

(C)

Figure 2. The fasting blood glucose (A), serum insulin (B) and the area under the curve for blood glucose (AUC_{glu}) over 2 h of insulin tolerance test (ITT) (C) of mice fed experimental diets. C, normal control; SW, sucrose water induced metabolic syndrome; SW + AP, sucrose water induced metabolic syndrome + *Alpinia pricei*. Values are mean ± SD, $n = 8$. The significance of differences among C, SW and SW + AP groups were analysed by one-way ANOVA and Duncan's multiple range test. Values not sharing a superscript letter between groups are significantly different ($p < 0.05$).

Table 2. The adipocytokine levels in serum of mice fed experimental diets

	C	SW	SW + AP
Adiponectin (ng/mL)	13517 ± 1323[b]	13530 ± 2946[b]	21626 ± 3789[a]
Leptin (pg/mL)	447 ± 155[c]	2038 ± 1024[a]	884 ± 257[b]
TNF-α (pg/mL)	2.22 ± 1.03[b]	3.57 ± 1.35[a]	0.73 ± 0.34[c]

C, normal control; SW, sucrose water induced metabolic syndrome; SW + AP, sucrose water induced metabolic syndrome + *Alpinia pricei*.
Values are mean ± SD, $n = 8$. The significance of differences among C, SW and SW + AP groups were analysed by one-way ANOVA and Duncan's multiple range test. Values not sharing a superscript letter between groups are significantly different ($p < 0.05$).
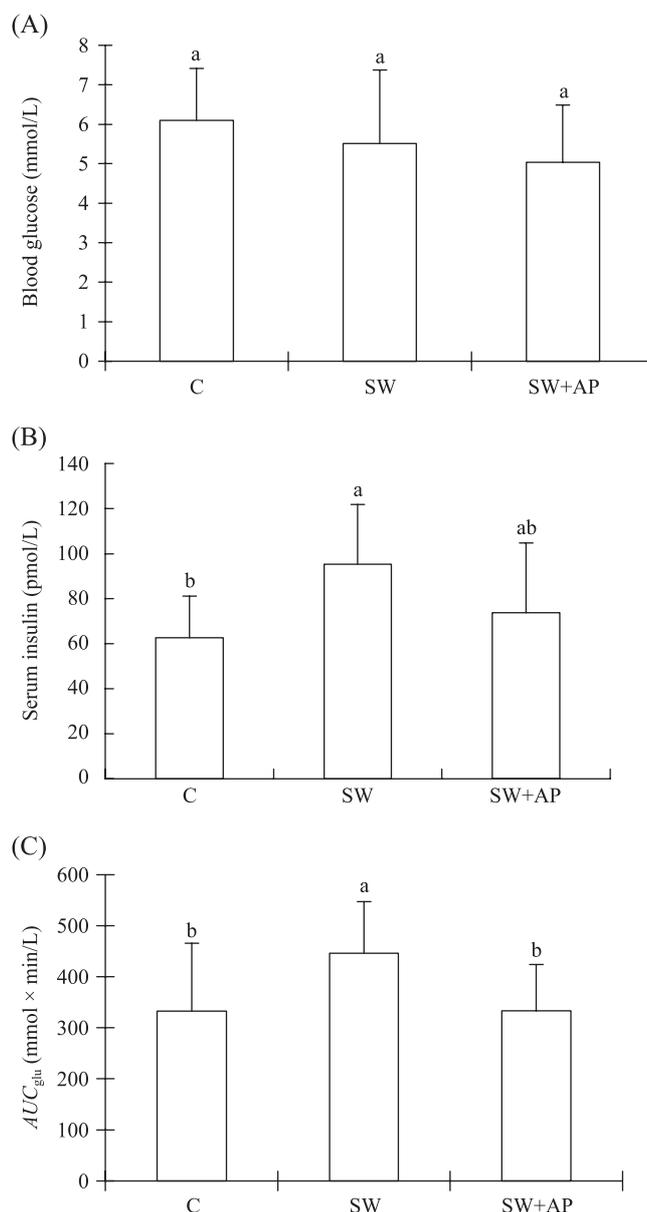
Effect of AP on ameliorating the metabolic syndrome

Compared with the SW group, the SW + AP group showed significant reductions in final body weight and relative retroperitoneal fat weight (Fig. 1A, B), although the retroperitoneal fat in the SW + AP group was still higher than in the C group. The increase of relative epididymal fat weight in the SW group was blunted by AP administration, since there was no difference between the SW + AP and C groups. The food intake was not different between the SW and SW + AP groups (data not shown).

In addition, the increased TG and TC concentrations in liver and TG concentration in muscle that were induced by sucrose-water consumption all decreased following AP administration, since there was no difference between the SW + AP and C groups in these levels (Table 1). However, serum lipids (TG and TC) in the SW + AP group were still significantly higher than those in the C group, and the SW and SW + AP groups were the same.

Although the fasting blood glucose (Fig. 2A) and the AUC_{glu} of OGTT (data not shown) did not differ among the three groups, insulin resistance was lowered by AP administration, as demonstrated by the serum insulin and ITT results. Because the SW + AP and the C groups had the same levels of fasting insulin, the hyperinsulinemia observed in the SW group was evidently alleviated by AP (Fig. 2B). The increased AUC_{glu} over 2 h of ITT in the SW group dropped significantly following AP administration to a level comparable to that of the C group (Fig. 2C).

AP administration conferred benefits to several adipocytokines. Compared with the C group, the levels of leptin and TNF-α in the SW group were much higher, but these levels were significantly reduced by AP administration to levels that were still higher than the C group for leptin and lower than the C group for TNF-α (Table 2). For adiponectin, the SW + AP group showed a significantly higher level than those of the SW and C groups ($p < 0.0001$).

DISCUSSION

Recently, encouraging results from using polyphenols for multifaceted protection against metabolic disturbances have emerged. For example, EGCG found in green tea has been shown to reduce adipose tissue weight, increase insulin sensitivity, favorably modify lipid profiles, reduce systolic blood pressure and enhance endothelial function in human and animal studies (Wolfram, 2007; Potenza *et al.*, 2007). Resveratol, a polyphenol in red wine and grape skin, protects mice from many detrimental effects of a high-calorie diet. The benefits include increased longevity, insulin sensitivity and mitochondrial capacity (Lagouge *et al.*, 2006). With peroxisome proliferator-activated receptor (PPAR)-γ activation effects, flavonoids from licorice were found to be effective in preventing and ameliorating diabetes in KK-A[y] mice, ameliorating abdominal obesity in high fat diet-fed C57BL mice and preventing hypertension in spontaneously hypertensive rats (Mae *et al.*, 2003). These results prompted us to identify other functional foods that could prevent or ameliorate metabolic syndrome.

In this study, metabolic syndrome indicators including visceral adiposity, hyperlipidemia and hyperinsulinemia were induced by sucrose-containing drinking water in C57BL/6J mice. The ethanol extract from AP rhizomes at 1500 mg/kg dosage administered for 4 weeks reversed some alterations of the metabolic parameters induced by sucrose water consumption. Reductions in body weight gain, visceral fat accumulation and insulin resistance were observed, but there was no effect on serum lipids. Although the time frame (2 h) for measuring ITT in this study might be too long to avoid the secondary effect of the insulin bolus, the changes in circulating insulin levels in sucrose-fed mice and AP administered mice supported the expected changes in insulin sensitivity.

High-sucrose (or fructose) diets, as well as high fat diets, are frequently used for diet-induced metabolic syndrome in animal models (Dobrian *et al.*, 2000; Mann, 2002; Fried and Rao, 2003). By adding sucrose to the drinking water (30%), metabolic syndrome symptoms, including abdominal obesity, hypertension, hyperlipidemia and hyperinsulinemia were induced in Wistar rats fed the chow diet with normal fat content (El Hafidi *et al.*, 2001; Aguilera *et al.*, 2004).

In this study, it was also shown that a high fat diet was not necessary to induce central obesity and insulin resistance in obesity- and diabetes-prone C57BL/6J mice, this finding disagreed with some previous reports; namely, Surwit *et al.* (1995) and Sumiyoshi *et al.* (2006), who failed to induce obesity and hyperinsulinemia in C57BL/6J mice when they replaced starch with an equal amount of sucrose in solid food with normal fat content. There are some differences between the two strategies (i.e. sucrose drinking water and a sucrose-containing diet) which are discussed below. When mice are subjected to a sucrose drinking water protocol, the dietary effects are similar to the over-consumed junk foods (or sweetened beverages) of modern human life, which result in a higher energy intake but lower nutrient value (can be observed in El Hafidi *et al.*, 2001; Aguilera *et al.*, 2004 and in our study). However, when sucrose was incorporated in a well-balanced diet, the energy intake remained the same, and the nutrient intake was adequate rather than deficient as in a modern diet (Surwit *et al.*, 1995; Sumiyoshi *et al.*, 2006). In the present study, the energy and nutrient intakes between the test and control groups during the first 4 weeks were compared. Due to the energy content in the drinking water (120 kcal/100 mL), the solid food intake in the test group dropped to only 57% of the control group. This caused a lower nutrient intake in the test group, while the total energy intake in the test group was still significantly higher than that of the control group (due to the large quantity of sucrose water consumption, the total energy intake in the test group was 21 kcal/d vs 11 kcal/d for the control group). It is possible that the negative effects of high sucrose intake might be accelerated by nutrient imbalance, which remains to be investigated fully.

The induction of the metabolic syndrome by sucrose water might be attributed to the disturbance of lipid metabolism, peroxidative stresses and inflammatory responses. Clinical studies have confirmed that sucrose (particular its product, fructose) can induce weight gain and features of metabolic syndrome (Johnson *et al.*, 2007). Fructose has been shown to enhance hepatic *de novo* lipogenesis and to contribute to visceral adiposity by postprandial hypertriglyceridemia (Stanhope and Havel,

2008). Fructose enters glycolysis via fructose-1-phosphate, bypassing an important allosteric enzyme, phospho-fructokinase, and thus providing an unregulated amount of substrate for lipogenesis. This is in accordance with the TG accumulation in liver and muscle observed in this study. The association between visceral adiposity and hyperinsulinemia, hyperlipidemia and hypertension has been well established (Matsuzawa *et al.*, 1994). In addition, the ectopic lipid accumulation (in liver and muscle) also contributes to insulin resistance (Unger, 1995; DeFronzo, 2004). According to the lipotoxicity hypothesis, the TG metabolites, including long-chain fatty acyl-CoA, diacylglycerol and ceramide, decrease insulin sensitivity in these peripheral tissues by interfering with insulin signaling and impairing insulin secretion (Prentki and Corkey, 1996; McGarry, 2002). Meanwhile, as aforementioned, the sucrose water-fed mice consumed 57% less nutrient intake than the controls, which could have compromised their antioxidative-defense ability, and hence initiated insulin resistance. In accordance with a previous observation in rats (Aguilera *et al.*, 2004), a significant increase in the serum level of TNF-α in sucrose water-fed mice was also observed. The increased TNF-α could have come from macrophages recruited by hypertrophic adipocytes. Further, it has been shown that chronic obesity-induced inflammation is involved in insulin resistance through activation of Jun kinases (JNKs) (Solinas *et al.*, 2007). The activated JNKs (mainly JNK1) result in phosphorylation in insulin receptor substrate at inhibitory sites that disrupt downstream events of insulin signaling (Solinas *et al.*, 2007).

The dietary benefits of plants of the ginger family in reducing the symptoms of metabolic syndrome are worth exploring, since the effects of turmeric-based curcumin and curcuminoids on reducing liver/plasma lipids and blood glucose levels were reported recently. Using rats fed high fat diets, Asai and Miyazawa (2001) reported liver TG and TC concentrations, plasma TG in VLDL fraction, and epididymal fat tissue weight were significantly lowered by supplementation with 1% (g/g) curcuminoids. Since hepatic acyl-CoA oxidase activity was increased in curcuminoid fed rats, the lipid-lowering effect of curcuminoids was attributed to PPARα activation. Curcuminoids were also found to be PPARγ ligands in transactivation assays, and when the turmeric extract was fed to KK-A^y mice, the increase of blood glucose in KK mice was effectively suppressed (Nishiyama *et al.*, 2005). Many efforts are now being made to screen for dual PPARα and γ-agonists from food or diet origins, not only for resolving the problems of insulin resistance, hyperlipidemia and central obesity simultaneously, but also for safety concerns (Mae *et al.*, 2003; Berger *et al.*, 2005). The benefits of ginger on glucose metabolism are also supported by other evidence, e.g. a blood-glucose-lowering effect of ginger was reported in rabbits (Mascolo *et al.*, 1989) and rats (Ahmed and Sharma, 1997; Akhani *et al.*, 2004). Using a preadipocyte cell line 3T3-L1, gingerol, a pungent component in ginger, was found to enhance the adipocyte differentiation and insulin-stimulated glucose uptake (Sekiya *et al.*, 2004).

In this study, supplementation of AP in sucrose-fed mice attenuated the increase of visceral adiposity, serum insulin and AUC_{glu} of ITT, but not serum lipids. It is difficult to address reasons for the lack of a beneficial effect on serum lipids since the lipid profiles were not measured. A cholesterol-fed hamster or rabbit,

or an apoE knock-out mouse model might be more appropriate for studying the functional food effect on the lipoprotein profile. In addition, the amelioration effect of AP on insulin resistance accompanied by the reductions of lipid content in tissues (visceral, liver and muscle) suggests that a mechanism mediated through alterations in lipid metabolism might be involved. Since the food intake was not apparently changed by AP administration, the effect of AP on intestinal fat absorption, hepatic fatty acid oxidation/lipogenesis and thermogenesis will be studied in the future.

Meanwhile, the shift of adipocytokine levels in experimental mice further supports the beneficial effects of AP on reducing adiposity and insulin resistance. The increase of serum level of TNF-α in the SW group was significantly reduced by AP administration (Table 2). The role of TNF-α in the impairment of insulin signaling has been well established (Feinstein *et al.*, 1993; Hotamisligil *et al.*, 1996). Ginger extract has been reported to inhibit TNF-α production in LPS stimulated macrophages (Tripathi *et al.*, 2008). In addition, the activation of NFκB through p38 and the down-stream pro-inflammatory signaling could be inhibited by curcumin and gingerol (Divya and Pillai, 2006; Weber *et al.*, 2006; Nonn *et al.*, 2007). It is not clear whether the TNF-α lowering effect of AP was associated with curcumin, gingerol or other related compounds. However, AP might exert its metabolic health effects through an antiinflammatory mechanism.

The beneficial effect of AP on insulin sensitivity was also supported by the increase of circulating adiponectin (Table 2), which is the only known adipocyte derived hormone whose levels are down-regulated in obesity and diabetes mellitus (Arita *et al.*, 1999). The increase of adiponectin by AP administration was not unexpected since Yamazaki *et al.* (2008) had shown that curcumin and gingerol could stimulate adiponectin production in cultured mouse and human preadipocytes. Adiponectin increases insulin sensitivity by enhancing fatty acid oxidation in muscle and insulin-mediated suppression of glucose production in liver (Yamauchi *et al.*, 2001; Combs *et al.*, 2001). Recently, the antiinflammatory property of adiponectin was also noticed (Takemura *et al.*, 2007). Leptin, although its role on glucose metabolism is controversial, has a good correlation with fat mass, which is consistently observed (Maffei *et al.*, 1995). In this study, the changes of leptin levels in the three groups paralleled the changes of their adipose weights.

This study is the first to test the physical functions of AP based on the well-known healthy effects of ginger family plants. The results show the potential of AP in treating metabolic syndrome, especially on reducing visceral adiposity and ameliorating insulin resistance, which might be mediated with the reduction of lipid accumulation in liver and muscle and an antiinflammatory effect. The functional components, action mechanisms and safety concerns for long term consumption of AP merit further study.

Acknowledgement

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