

Full Length Research Paper

Anti-obesity effects of mogrosides extracted from the fruits of *Siraitia grosvenorii* (Cucurbitaceae)

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In this study, total mogrosides extracted from *Siraitia grosvenorii* as well as, mogrosides V and IV were tested for their effects on pancreatic lipase *in vitro*. The body weight and food intake, abdominal and epididymal fats weight, and hepatic triacylglycerol (TG) and total cholesterol (TC) contents were evaluated using male C57BL/6 mice fed with a high fat diet (HF) with or without different concentrations of total mogrosides for 11 weeks. Plasma TG was also evaluated after oral administration of lipid emulsions to mice. The results showed that total mogrosides as well as, mogrosides V and IV (600 µg/ml) demonstrated good inhibitory effects on pancreatic lipase activity. *In vivo*, total mogrosides suppressed the increase in body weight, abdominal and epididymal fats weight, TG and TC content in mice's liver; TG content in plasma was reduced at 1 to 3 h after oral administration of the lipid emulsion plus total mogrosides compared to those in the lipid emulsion groups. In addition, mice fed with HF plus 2% total mogrosides for 3 days had higher TG level in the feces compared to the HF group, which might be due to decreased dietary fat absorption in the intestine caused by inhibition of pancreatic lipase activity.

Key words: Mogroside, pancreatic lipase, high diet, obesity, mice.

INTRODUCTION

Obesity, the abnormal excessive growth of adipose tissue, normally results from the effects of excess high caloric western-style food intake (Spiegelman and Jeffery, 2001), which has caused many life style-related diseases such as ischemic heart disease, atherosclerosis and diabetics (Zhou et al., 2002; Idogun et al., 2006). Recent report from the International Obesity Task Force (IOTF) reveals that about 1.7 billion people, a quarter of the world population are suffering from the obesity (Friedrich, 2002). Thus, anti-obesity measure is being one of the most urgent tasks for human being to be conducted for the present and future. *Siraitia grosvenorii* C. Jeffrey (Cucurbitaceae) is a medicinal plant specially distributed in Guangxi province, China. Its dried fruits have been

used for the pharyngitis, pertussis and acute bronchitis therapy documented in Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2010). The saponins, a mixture of cucurbitane triterpene glycosides extracted from the fruits of *Siraitia grosvenorii* is normally named as mogrosides. Recently, mogrosides have shown significant anti-aging, anti-cancer, phthisis prevention, hyperglycemic, hypolipidemic and antioxidant effects (Konoshima and Takasaki, 2002; Takasaki et al., 2003; Takeo et al., 2002; Chen et al., 2011a; Zhou et al., 2009; Zhang et al., 2006; Qi et al., 2008; Song et al., 2007). It was widely accepted that mogrosides have diverse pharmacological effects. Although, mogrosides were frequently used for the diet of diabetics and obesity patients as an alternative of sugar due to its high sweetness, the anti-obesity effect of mogrosides has not been demonstrated clearly so far. Up to now, many Western medicines such as fenfluramine hydrochloride, orlistat and thyroxine have been explored for obese

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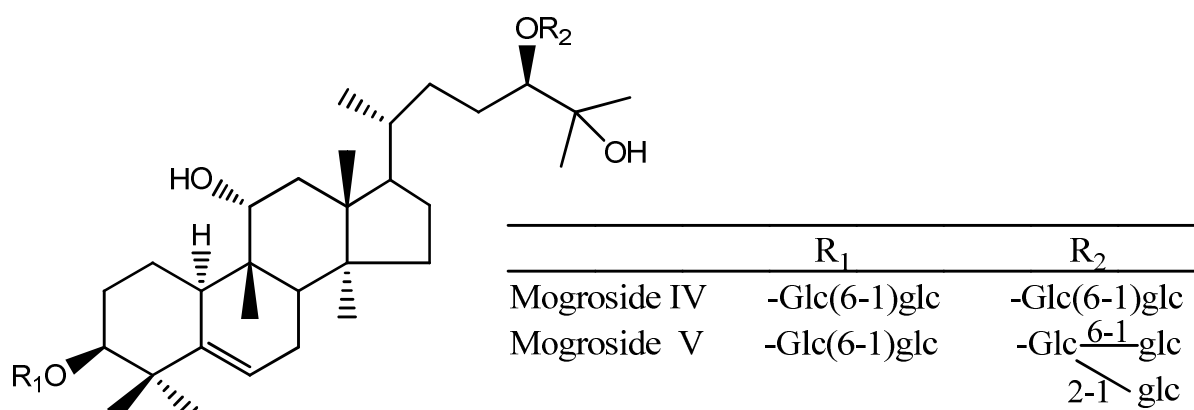


Figure 1. The Structures of mogrosides IV and V identified in the fruits of *Siraitia grosvenorii* C. Jeffrey. Glc, β -D-glucose.

therapy by means of suppressing appetite, inhibiting pancreatic lipase or inhibiting α -glucosaccharase, etc. However, Western medicines consumption on long term mostly caused adverse side effects. For instance, gastrointestinal side effects would occur when orlistat, a pancreatic lipase inhibitor was used clinically for long-term pharmacotherapy for obesity and overweight (Padwal, 2005). Therefore, it is necessary to develop new drugs with fewer side effects from medicinal plants for obesity and overweight therapy. In order to provide the scientific basis for the reported anti-obesity effects of mogrosides, we investigated their anti-obesity effects on obese C57BL / 6 mice. The results showed that mogrosides have a strong inhibitory effect on obesity both *in vitro* and *in vivo*.

MATERIALS AND METHODS

Assay kits for triacylglycerol, and total cholesterol were purchased from Nanjing Jiancheng Bioengineering Co. (Nanjing, China). Pancreatic lipase, 4-methylumbelliferyl oleate (4-MUO) and triolein were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Mogrosides IV and V were purchased from Chengdu Biopurify Photochemicals Co. (Chengdu, China) and the purity of these two compounds was over 99% as indicated by the manufacturer. Laboratory pellet chow was purchased from Samyang Oil and Feed Co. (Incheon, Korea). Beef tallow and casein were from Samwoo (Seoul, Korea). Vitamin and mineral mixtures were from Teklad (Madison, WI, U.S.A.). The fruits of *S. grosvenorii* C. Jeffrey were purchased from Linhai Chinese Medical Material Co. (Linhai, China), freeze-dried, powdered, and kept at -20°C . Voucher specimens (No. 0945) were deposited with the Department of Food Science and Technology, Chungnam National University, Korea. HPLC grade acetonitrile was purchased from Merck Co. (Merck, Darmstadt, Germany). Deionized water was purified by Milli-Q system (Millipore, Bedford, MA, USA). Other chemicals were of reagent grade.

Preparation of total mogrosides from the fruits of *Siraitia grosvenorii* C. Jeffrey

The dried powdered fruits of *S. grosvenorii* C. Jeffrey (3.7 kg) were extracted three times with 6000 ml of 80% aqueous ethanol at 60°C

by ultrasonication (60 kHz, heat power 330 W; JAC Ultrasonica 2010, KOPO, Korea) for 60 min. After filtration using filter paper (ADVANTEC, Dublin, CA, USA), the solvent was removed using an evaporator (EYELA N-N, Tokyo, Japan). The residue was dissolved in distilled water passed through macroporous resin D101, and then eluted with H_2O , 30 and 80% ethanol aqueous solution. Subsequently, the 80% ethanol fraction was collected and evaporated to dryness under vacuum at 60°C . The residue was re-dissolved in distilled water, and extracted further with acetic ether, water-saturated n-butanol. Consequently, 25 g of total mogrosides were obtained after the n-butanol fraction was evaporated to dryness using a rotary vacuum evaporator at 60°C . Figure 1 showed the structures of mogrosides IV and V.

Quantative analysis of Mogrosides IV and V content

Total mogrosides and two reference compounds mogrosides IV and V were dissolved individually in 70% aqueous ethanol and then filtered by a $0.2\ \mu\text{m}$ PTFE syringe filter before HPLC analysis. HPLC analysis was carried out on an Agilent 1100 series HPLC system (Palo Alto, CA, USA), equipped with vacuum degasser, quaternary gradient pump, auto-sampler and photo diode array (PDA) detector. A ZORBAX SB-C₁₈ column ($150 \times 4.6\ \text{mm}$, i.d., $5\ \mu\text{m}$) was used for separations at a column temperature of 40°C . The binary gradient elution system consisted of water (A) and acetonitrile (B). The separation was achieved using the following gradient program: 0 to 3 min (20 to 30% B), 3 to 8 min (30 to 35% B) and 8 to 9 min (35% B). The flow-rate and detection wavelength were set at 1.5 ml/min and 203 nm, respectively. The sample injection volume was 10 μl . A Bruker Esquire LC (Billerica, MA, USA) ion-trap mass spectrometer with electrospray ionization (ESI) was used in HPLC-MS method. ESI-MS conditions of HPLC-MS analysis were as follows: negative ion mode, drying gas N_2 , 8 l/min, temperature 250°C , pressure of nebulizer 12 psi, octapole voltage 2.35 V, ion-trap voltage 32.2 V and scan range 100 to 1700 u. ESI-MS/MSⁿ conditions were as follows: negative ion mode, separation width 0.9, fragment amplification 1.5 and scan range 100 to 1700 u.

Animals and diet composition

Male C57BL/6 mice were supplied by Samtako Bio. Korea Inc. (Osan, Korea) and housed for 1 week under 12 h /12 h light/dark

Table 1. Composition of the experimental diets.

Component	HF	HF + 0.5	HF + 1	HF + 2
Beef tallow	40	40	40	40
Casein	36	35.5	35.0	34.0
Corn starch	10	10	10	10
Sugar	9	9	9	9
Vitamin mixture	4	4	4	4
Mineral mixture	1	1	1	1
Total mogrosides	0	0.5	1.0	2.0

HF: high fat diet; HF+0.5: high fat diet + 0.5 % total mogrosides; HF+1: high fat diet +1 % total mogrosides; HF+2: high fat diet +2% mogrosides.

cycles (light 07:00 to 19:00 h) in a temperature and humidity-controlled room ($22 \pm 1^\circ\text{C}$). The animals were given free access to food and water. The animals were fed on a standard feed (Incheon, Korea) for 1 week and then, on experimental diet whose composition was listed in Table 1. To avoid auto-oxidation of the fat components, food was stored at -30°C . Laboratory chow pellet was used as a control diet. The experimental protocols were approved by the Ethical Committee of Chungnam National University.

Measurement of the pancreatic lipase activity

Pancreatic lipase activity was measured by a fluorometric assay using 4-MUO as a substrate (Bitou et al., 1999). Aliquots of 250 μl of extract solution and 500 μl of 0.1 mM 4-MUO solution in 13 mM Tris-HCl buffer (pH 8.0) containing 150 mM NaCl and 1.3 mM CaCl_2 were mixed, and an aliquot of 250 μl of the lipase solution (150 μg / ml of pancreatic lipase) in the aforementioned buffer was then added to start the reaction. After incubation for 30 min at 25°C , the reaction was stopped by adding 1 ml of 0.1 M citrate buffer (pH 4.2). The amount of 4-methylumbelliferone released by the action of the lipase was measured with a fluorescence spectrophotometer at excitation and emission wavelengths of 355 and 460 nm, respectively. Pancreatic lipase activity was also determined by measuring the oleic acid released from trioleoylglycerol. Briefly, a suspension of trioleoylglycerol (80 mg), lecithin (10 mg) and taurocholic acid (5 mg) in 9 ml of 0.1 M *N*-Tris methyl-2-aminoethane-sulfonic acid (TES, pH 7.0) containing 0.1 M NaCl was emulsified by sonication for 5 min. The resultant substrate emulsion (100 μl) was incubated with 50 μl of the lipase solution (50 μg / ml of pancreatic lipase) and 100 μl of extract solution for 30 min at 37°C . The amount of oleic acid was determined by the method of Tsujita and Okuda (1983). Lipase activity was expressed as mmol oleic acid released/ml of reaction mixture/min. The inhibitory activity (%) was calculated as $(1 - A/B) \times 100$ where A and B represent the enzyme activities with and without extract solution.

Estimation of body weight, abdominal and epididymal adipose tissue weight, hepatic TG and TC in male mice fed with a high-fat diet for 11 weeks

Male C57BL / 6 mice (3 weeks old) were randomly divided into five groups matched for body weight after 1 week of being fed with laboratory pellet chow. The control group continued to be fed with laboratory pellet chow *ad libitum*. The remaining mice fed with HF diet or HF diet plus 0.5, 1 or 2% total mogrosides for 11 weeks. The body weight of each mouse was measured once a week and the total amount of food consumption was recorded every day for 11 weeks. After the mice had been fed with these diets for 11 weeks, blood was taken by venous puncture under anesthesia with diethyl

ether, and the mice were then killed with an overdose of diethyl ether. Experiments were performed in a ventilated room. The plasma was prepared and frozen at -80°C until analysis. The liver, abdominal and epididymal adipose tissue were dissected and weighed. Liver TG and TC concentrations were measured using Triglyceride and Total Cholesterol Assay Kits.

Fat excretion in mice feces

Male C57BL / 6 mice (3 weeks old) were housed for 1 week in a room maintained at $22 \pm 1^\circ\text{C}$ with 60% relative humidity and given free access to standard laboratory pellet chow and water. The mice consumed the HF diet or the HF diet plus 0.5, 1 or 2% total mogrosides for 3 days. TG content in the feces obtained during the last 24 h was measured using a Triglyceride Assay Kit.

Plasma TG levels after oral administration of lipid emulsions to rats

Male C57BL / 6 mice were housed for 1 week under the same conditions as described above. After the mice had been deprived of food overnight, they were orally administered 1 ml of lipid emulsion consisting of corn oil (3 ml), cholic acid (40 mg), cholesteryloleate (1 g) and physiological saline (3 ml), plus total mogrosides (final concentration 250 mg/kg body or 800 mg/kg body). Blood samples were taken from the tail vein at 0, 1, 2, 3, 4 and 5 h after administration of the lipid emulsion with or without total mogrosides using a heparinized capillary tube, and centrifuged at $5000 \times g$ for 15 min at 4°C to obtain the plasma. The plasma TG concentration was determined using a Triglyceride Assay Kit.

Statistical analysis

The values of the experimental results were expressed as mean \pm S.E. Data were analyzed by one-way ANOVA, and then differences among means were analyzed using Scheffe's test. Differences were considered significant at $p < 0.05$. The analyses were performed using SPSS statistical software (version 19.0 for Windows).

RESULTS AND DISCUSSION

Evaluation of mogrosides IV and V content in fruits of *Siraitia grosvenorii* C. Jeffrey

Under the aforementioned chromatographic conditions,

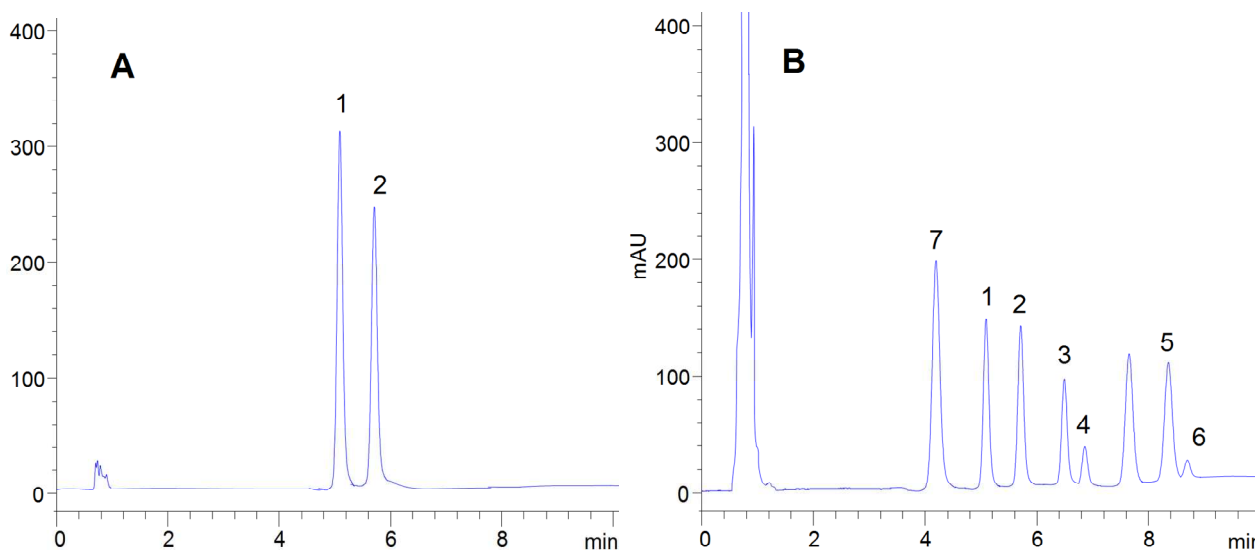


Figure 2. HPLC chromatograms of mixed standards (A) and mogrosides extracted from fruits of *Siraítia grosvenorii* (Cucurbitaceae). HPLC was performed on a ZORBAX SB-C₁₈ column (150 × 4.6 mm, i.d., 5 μm) at a column temperature of 40°C. The mobile phase consisted of water (A) and acetonitrile (B) using the following gradient program: 0 to 3 min (20 to 30% B), 3 to 8 min (30 to 35% B) and 8 to 9 min (35% B). The flow-rate and detection wavelength were set at 1.5 ml / min and 203 nm, respectively. The sample injection volume was 10 μl. Peaks: 1. Mogroside V; 2. Mogroside IV.

over 7 major compounds were identified from fruits of *S. grosvenorii* C. Jeffrey (Figure 2), 2 of which (mogrosides IV and V) were confirmed by comparing the mass spectra and retention times with that of reference compounds, while the others were tentatively assigned by matching the empirical molecular formula with that of the published known cucurbitane glycosides, and / or further confirmed by elucidating the low energy CID fragmentations' (data not shown) (Qi et al., 2005; Li, 2009). Peaks 3 to 6 were unambiguously assigned as mogroside III, 11-oxomogroside III, mogroside II and 11-oxomogroside II, respectively. The concentration of mogrosides IV and V in sample was calculated using formula from the standard calibration curve:

$y = 3334.5 x + 14.874$ and $y = 3598.6 x + 4.565$, respectively,

Where x and y represented the concentration and peak area, respectively.

The content of mogrosides IV and V was 7.8 mg/g dried fruit and 5.8 mg/g dried fruit, respectively. The method was validated by linearity ($r^2 \geq 0.9996$), precision (96.0 to 107.5%), intra- and inter-day accuracy (R.S.D. < 3.21%) (data not shown). The quantification method was rapid, accurate, and precise, and it could be used for the quality control of fruits of *S. grosvenorii*. In addition, the analysis of cucurbitane glycosides in *S. grosvenorii* fruits was of great significance to promote the understanding regarding the components responsible for its special pharmacological effects.

Effects of mogrosides IV, V and total mogrosides on pancreatic lipase activity *in vitro*

Obesity is associated with the development of type 2 diabetes, coronary heart disease, respiratory complication, etc (Kopelman, 2000). As one of strategies for preventing and / or treating obesity, inhibiting pancreatic lipase should be considered in the clinical treatment of obesity since a high fat diet could not be absorbed across the intestinal mucosa without pancreatic lipase decomposition (Chomczynski and Sacchi, 1987; Myers and Gelfand, 1991). One of the anti-obesity mechanisms involved should be suppressing the absorption of fat from diet through inhibiting pancreatic lipase. Although, its anti-obesity effect was lower than that of orlistat (one pancreatic lipase inhibitor), total mogrosides as well as, two reference standards mogrosides IV and V dose-dependently inhibited the pancreatic lipase 38.26, 5.59 and 3.34% respectively, compared to that in control at a concentration of 600 μg/ml (Figure 3). In addition, total mogrosides, mogrosides IV and V showed inhibitory activity against pancreatic lipase with IC₅₀ values 517.73, 289.09 and 256.00 μg/ml *in vitro*, respectively (Figure 3) which suggested that mogrosides IV and V might be good pancreatic lipase inhibitors.

Plasma TG levels after oral administration of lipid emulsions to mice

Previous studies have reported that mogrosides extract

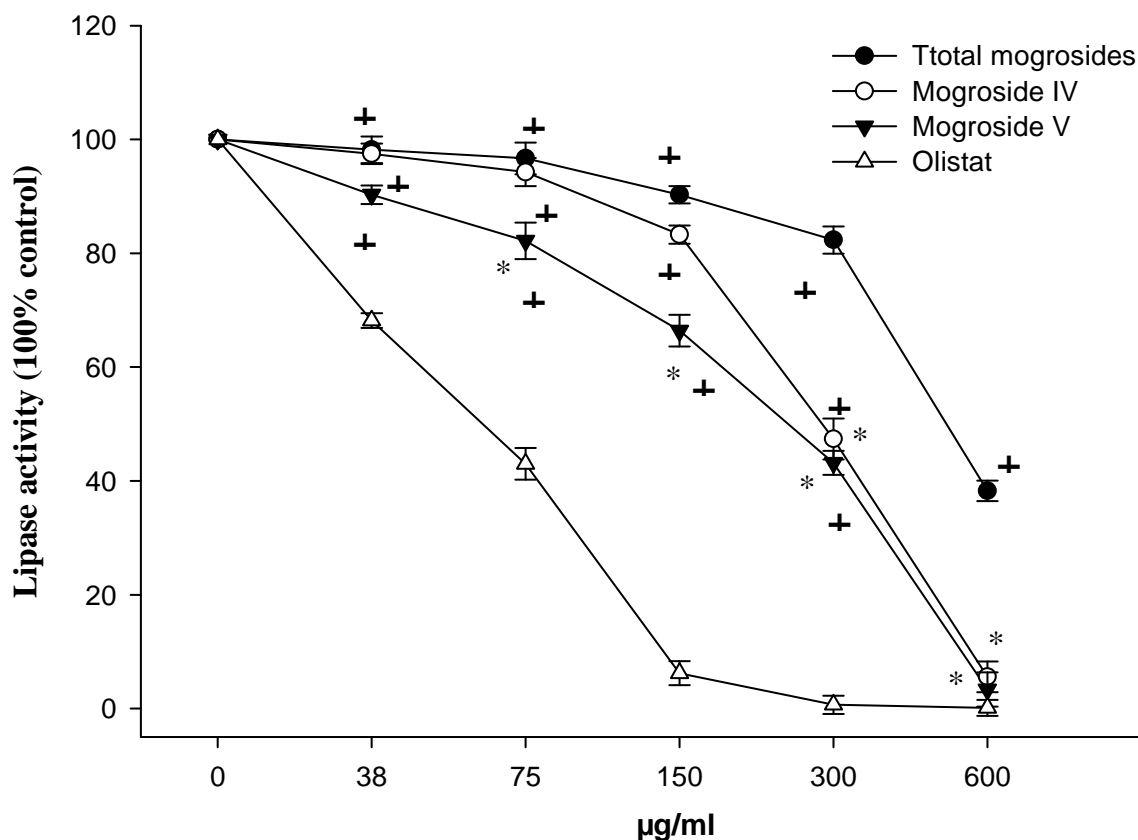


Figure 3. Effects of mogrosides extracted from the fruits of *Siraikia grosvenorii* C. Jeffrey on pancreatic lipase activity (*in vitro*). Values are mean \pm S.E. of three independent experiments. The effects of mogrosides aqueous methanol at concentrations ranging from 0 to 600 $\mu\text{g/ml}$ on pancreatic lipase activity were evaluated. * $p < 0.05$, significantly different from total mogrosides saponin; † $p < 0.05$, significant different from olistat.

effectively lowers glucose and lipid levels in blood and in plasma (Zhang et al., 2006; Qi et al., 2008; Takeo et al., 2002). As shown in Figure 5, total mogrosides (250 mg / kg body weight) prevented the increase in mice plasma TG concentration at 1 to 2 h after oral administration of lipid emulsion, while total mogrosides (800 mg/kg body weight) inhibited the increase in mice plasma TG concentrations at 1 to 3 h. After consumption of the high-fat diet plus 800 mg / kg total mogrosides at 2 h, the TG content in mice plasma was reduced to 0.83 ± 0.13 in comparison with that in the lipid emulsion group (1.95 ± 0.24). These results suggested that mogrosides extract consumption could suppress the time-dependent increase of plasma TG concentration in mice after oral administration of lipid emulsion, which was in accordance with the findings reported by Zhang et al. (2006) and Qi et al. (2008).

TG level in mice feces

As shown in Figure 4, TG level in mice feces could be

enhanced by the consumption of the HF diet for 3 days in comparison with that of the control group. Mice fed with the HF diet plus 1 or 2% total mogrosides had a significantly higher and a little higher TG levels in the faeces compared to the HF group, respectively, while HF diet plus 0.5% total mogrosides did not increase TG content. The reasons for this might be partially attributed to inhibition of absorption of dietary fat by inhibiting pancreatic lipase in the intestinal mucosa. Another reason might be due to the increase of gastrointestinal motility induced by total mogrosides since *S. grosvenorii* has been traditionally used for regulation of gastrointestinal motility and constipation therapy (Chen et al., 2011b). Interestingly, both mogrosides separated from *S. grosvenorii* fruits and cucurbitane glycosides isolated from *Hemsleya carnosiflora* (Dinan et al., 1997) had very similar structures and the latter had been proven to be significantly helpful for promoting the spontaneous motilities of animal's isolated intestine (Kasai et al., 1987). Therefore, mogrosides as well as, cucurbitane glycosides isolated from *H. carnosiflora* might result in a reduction of the absorption of dietary fat in the gastrointestinal tract.

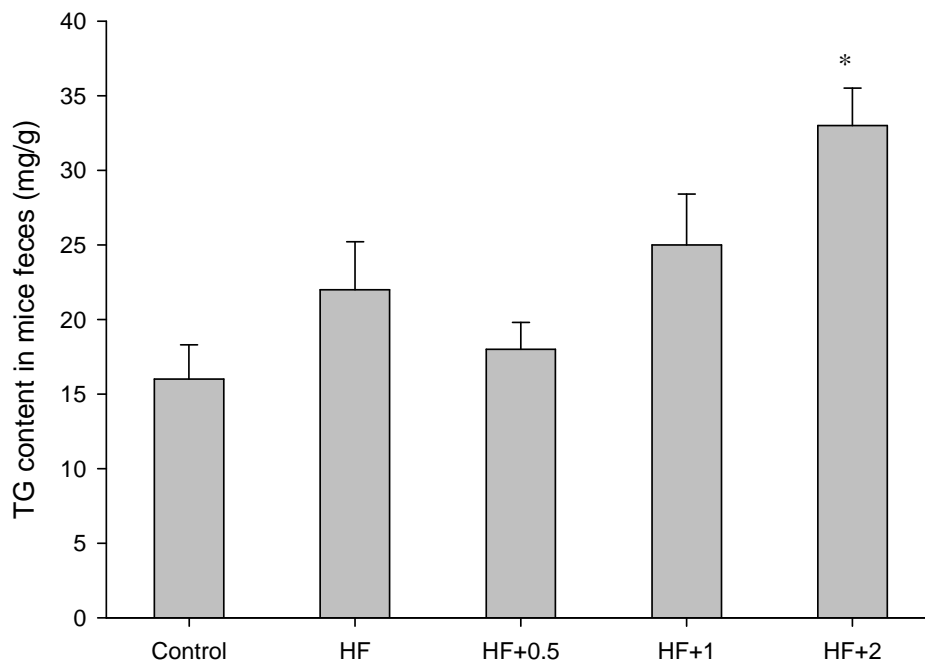


Figure 4. Effects of total mogrosides on TG content in mice feces consuming different diets for 3 d. Control: normal diet; HF: high fat diet; HF + 0.5: high fat diet plus 0.5 % total mogrosides; HF + 1: high fat diet plus 1% total mogrosides; HF + 2: high fat diet plus 2% total mogrosides. Values are mean \pm S.E. of 12 mice. * $p < 0.05$, significantly different from HF group.

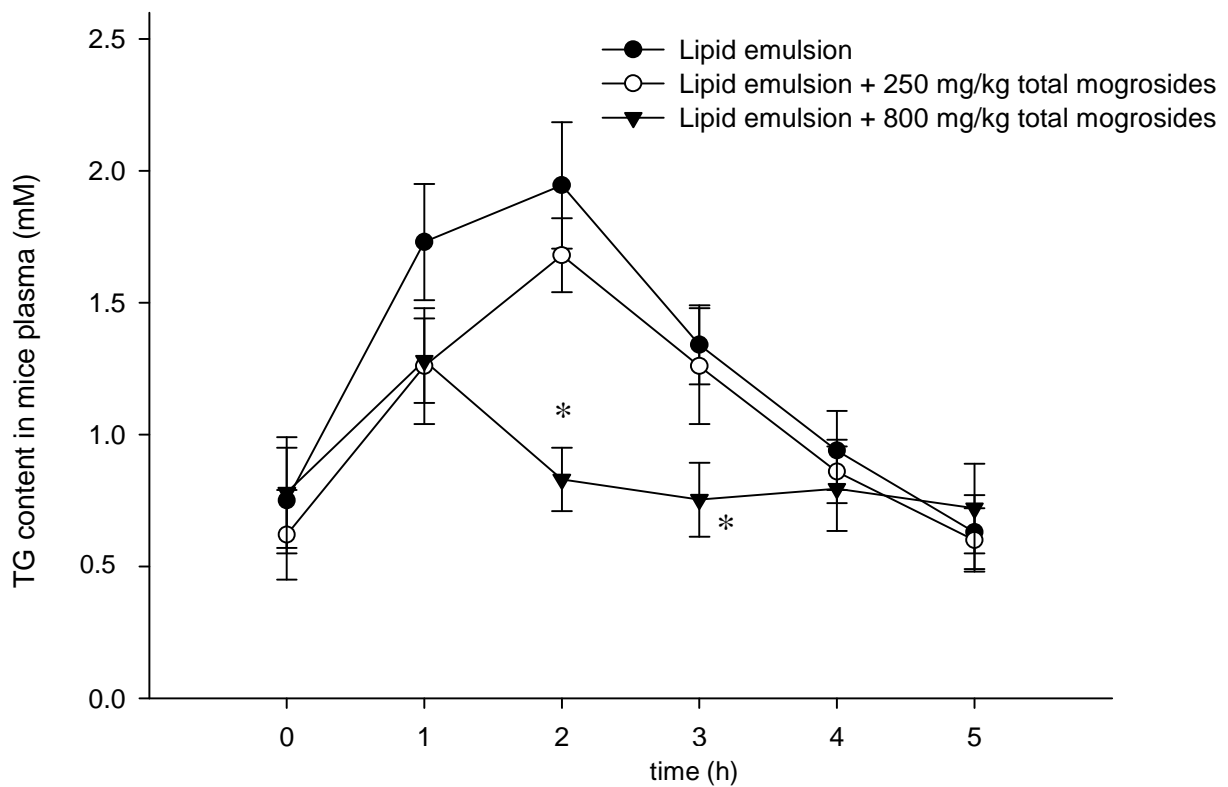


Figure 5. Effects of total mogrosides on mice plasma triacylglycerol levels after oral administration of a lipid emulsion. Values are mean \pm S.E. of 6 mice. * $p < 0.05$, significantly different from lipid emulsion group.

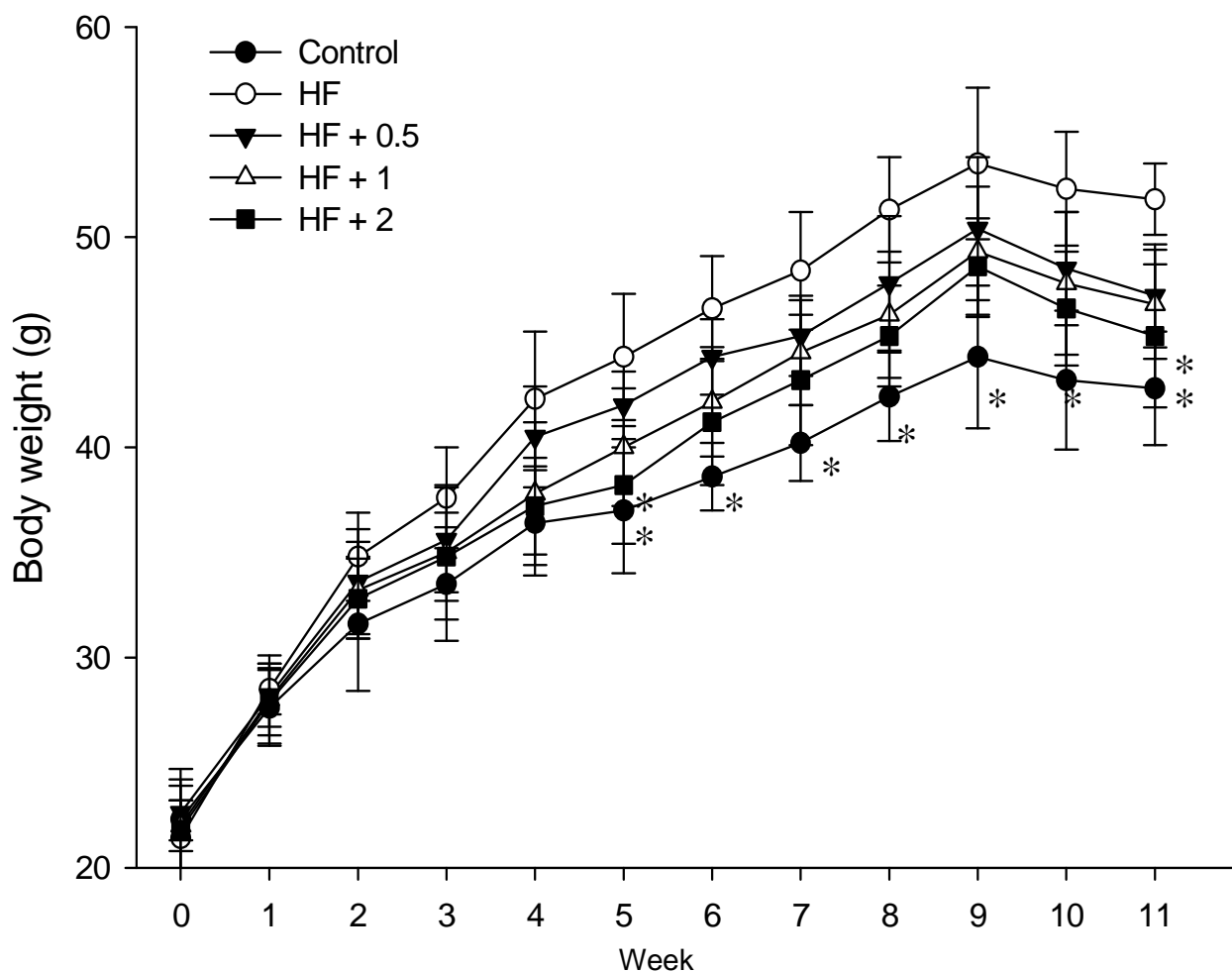


Figure 6. Effects of total mogrosides on body weight in mice fed with different diets for 11 weeks. Control: normal diet; HF: high fat diet; HF + 0.5: high fat diet plus 0.5% total mogrosides; HF + 1: high-fat diet plus 1% total mogrosides; HF + 2: high fat diet plus 2 % total mogrosides. Values are mean \pm S.E. of 12 mice. * $p < 0.05$, significantly different from HF group.

The results suggested that total mogrosides enhance fat excretion in feces and suppress fat accumulation *in vivo*.

Food intake; body, abdominal and epididymal fat weight, hepatic TC and TC in mice fed with a high-fat diet for 11 weeks

As known to all, obesity results from an imbalance between energy intake and energy expenditure. Obesity is normally closely related to the dietary habit and daily food intake. In this study, the mean food consumption was significantly different between HF group (3.3 ± 0.4 g / d / mouse) and control group (5.2 ± 0.3 g/d / mouse). However, there was no obvious difference in food consumption among the HF group (3.5 ± 0.4 g/d/mouse), HF diet plus 0.5% total mogrosides group (3.7 ± 0.3 g/d / mouse), HF diet plus 1% total mogrosides group ($3.9 \pm$

0.4 g / d / mouse) and HF plus 2% total mogroside group (3.6 ± 0.3 g / d / mouse). The body weight change of each group has been shown in Figure 6. Compared to the HF group, the body weight was reduced in groups fed with HF plus 0.5, 1 or 2% of total mogrosides, but there was no obvious dose-dependent relationship between body weight and total mogrosides amount. Subsequently, the fat weight in abdomen and epididymis where the fat is easily accumulated was further measured. In comparison with the control group, the abdominal and epididymal fat weights of the HF groups were increased from 14.6 to 30.3 mg / body weight (g) and 8.2 to 16.3 mg / body weight (g), respectively, whereas those of the HF diet plus 2% total mogrosides group were significantly reduced to 19.30 mg/body weight (g) and 10.40 mg / body weight (g) (Figure 7). In addition, long term consumption of the HF diet put a strain on the overall functioning of the liver, which ultimately resulted in the fatty liver development in

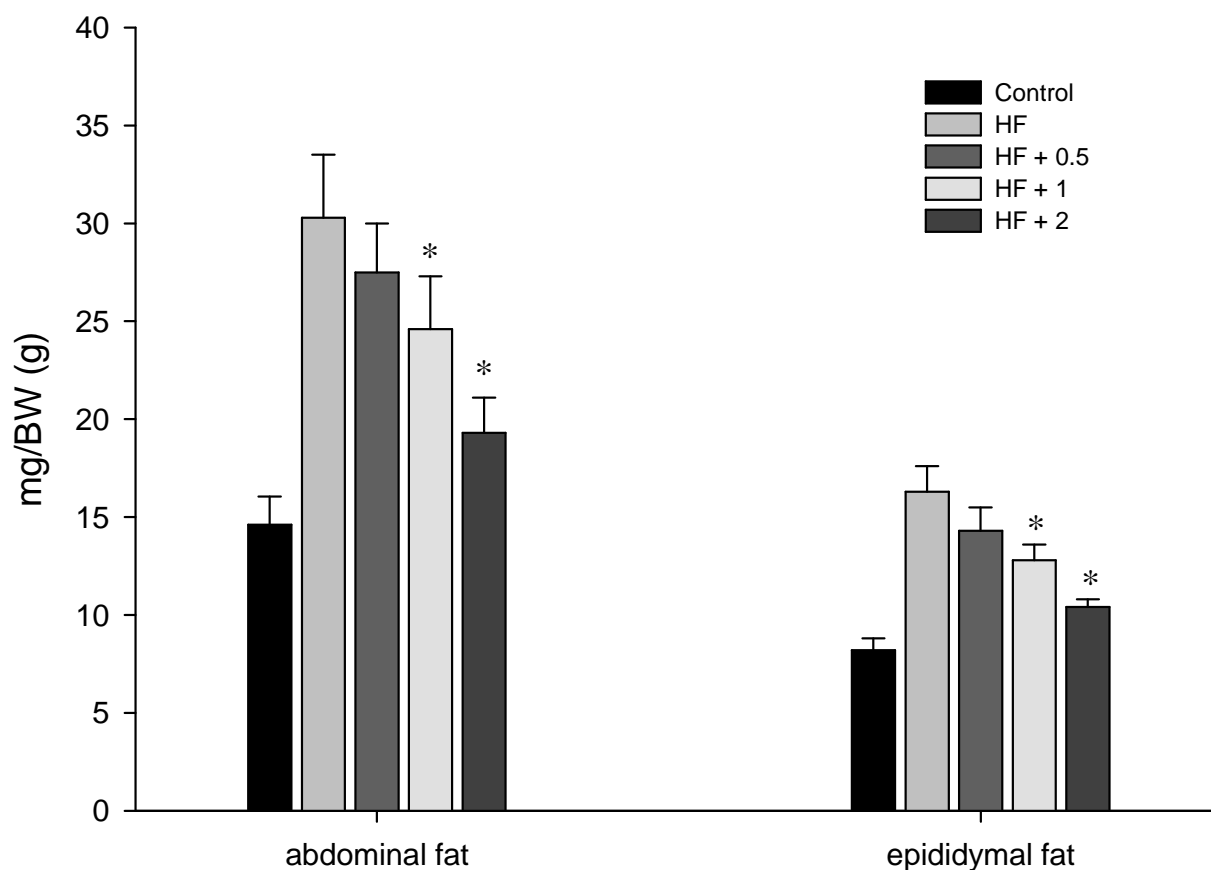


Figure 7. Effects of total mogrosides on abdominal and epididymal fat in mice fed with high fat diet for 11 weeks. Control: normal diet; HF: high fat diet; HF + 0.5: high fat diet plus 0.50 % total mogrosides; HF + 1: high fat diet plus 1% total mogrosides; HF + 2: high fat diet plus 2% total mogrosides. Values are mean \pm S.E. of 14 mice. * $p < 0.05$, significantly different from HF group.

mice. As shown in Figure 8, the mice in the HF groups had an increase in liver weight and the accumulation of hepatic TG and TC in comparison with the control group, whereas adding 1 or 2% total mogrosides into the HF diet for consumption could significantly reduce the hepatic TG level, liver weight and hepatic TC content compared to the HF group (Figure 8A to C). Up to now, many kinds of triterpenoid saponins isolated from different sources including *Panax ginseng* (Yun et al., 2004), *Platycodi radix* (Zhao et al., 2005), *Aesculus turbinata* (Kimura et al., 2008), etc had shown strong inhibitory effects on pancreatic lipase *in vitro* and had suppressed the increase of body weight induced by a high fat diet *in vivo*. Mogrosides extracted from *S. grosvenorii* also belonged to the triterpenoid saponins and have shown the same effects as mentioned earlier. However, some studies had reported that the oral bioavailability of glycosides was extremely low *in vivo* due to their hydrophilic nature (Chao et al., 2006; Yang et al., 2007). On the contrary, the aglycones derived from the deglycosylation of glycosides had the relatively high bioavailability *in vivo* and better

absorbability in the intestine. Therefore, the anti-obesity effects of aglycones from the deglycosylation of mogrosides *in vivo* would be worth studying further.

Conclusions

In the present study, total mogrosides extracted from *S. grosvenorii* as well as mogrosides V and IV (600 μg / ml) demonstrated good inhibitory effects on pancreatic lipase activity *in vitro*. *In vivo*, total mogrosides suppressed the increase in body weight, abdominal and epididymal fats weight, TG and TC content in mice's liver. In addition, TG content in plasma was reduced at 1 to 3 h after oral administration of the lipid emulsion plus total mogrosides compared to those in the lipid emulsion groups. The anti-obesity effects of mogrosides extracted *S. grosvenorii* on high fat diet-treated mice may be partly due to the inhibitory actions of mogrosides on pancreatic lipase activity. The results suggested that mogrosides may be an effective crude drug for the treatment of obesity and fat

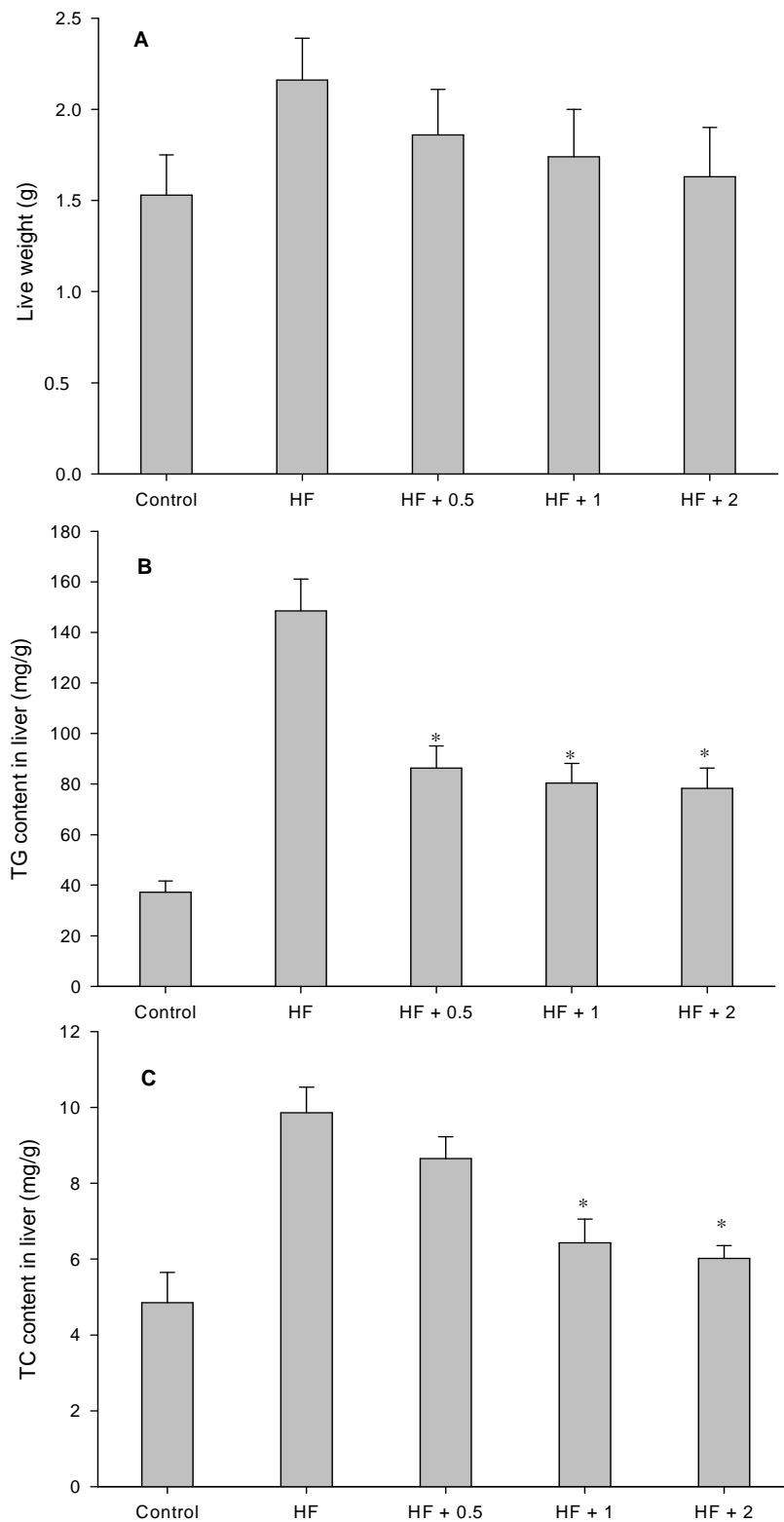


Figure 8. Effects of total mogrosides on liver weight (A), TG content in liver (B) and TC content in liver (C) of mice fed with high fat diet for 11 weeks. Control: normal diet; HF: high fat diet; HF + 0.5: high fat diet plus 0.50 % total mogrosides; HF + 1: high fat diet plus 1% total mogrosides; HF + 2: high fat diet plus 2% total mogrosides. Values are mean \pm S.E. of 14 mice. * $p < 0.05$, significantly different from HF group.

liver caused by a high-fat diet.

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