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Momordica charantia Extract Protects C57BL/6j Mice from High-Fat-Diet-Induced Obesity and Insulin Resistance*

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Abstract: In order to investigate the protective effects of *Momordica charantia* extract (MCE) on obesity and insulin resistance, C57BL/6j mice fed in a high-fat diet (HFD) were used as animal model. Obese mouse model was successfully made after 2-week HFD induction. The mice were then randomly divided into normal control, model control, MCE dose of 13.5, 27.0, and 54.0 g/kg treated groups. Mice in normal and model control groups were treated with 0.5% CMC-Na, and other groups were treated with MCE (i. g.), respectively, with the same volume twice a day for ten weeks. It was shown that the body weight, epididymal and total visceral white adipose tissue weight were decreased by treatment of MCE 54.0 g/kg without the change of food intake. The increased serum TG, CHO, LDL-C, glucose, insulin concentration and insulin resistance index were significantly inhibited. The concentration of TG was also decreased by the treatment of MCE 27.0 g/kg; while the concentration of HDL-C was increased by the treatment of MCE 13.5, 27.0 and 54.0 g/kg, respectively. The adipocyte hypertrophy induced by HFD was mitigated by MCE dose-dependently.

Key words: MCE; high-fat diet; obesity; insulin resistance
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苦瓜提取物对高脂肪喂食诱导的肥胖和胰岛抵抗 C57BL/6j 小鼠保护作用研究

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摘 要: 通过高脂肪喂食诱导的 C57BL/6j 小鼠动物模型研究苦瓜提取物对肥胖和胰岛抵抗的保护作用。小鼠喂养 2 周后成功建立肥胖小鼠模型, 随机分为正常对照组, 肥胖小鼠模型组和不同浓度的苦瓜提取物灌胃组, 灌胃质量分数分别为 13.5、27 和 54 g/kg。以 10 周为期, 每天以同等体积流质灌胃两次, 其中, 正常对照组和模

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型组用 $w=0.5\%$ 羧甲基纤维素钠灌胃，药物组用不同浓度的苦瓜提取物灌胃。记录小鼠每日食物摄入量和每周体质量。同时测定内脏白色脂肪组织质量、血清甘油三酯（TG）、胆固醇（CHO）、低密度脂蛋白胆固醇（LDL-C）、高密度脂蛋白胆固醇（HDL-C）、血糖和胰岛素水平，最后根据 HOMA 法计算胰岛素抵抗指数，HE 染色确定附睾白色脂肪组织的脂肪细胞是否肥大。结果显示，54 g/kg 苦瓜提取物组对小鼠摄食无影响，但小鼠体质量、附睾和内脏白色脂肪组织总质量减少，该剂量的苦瓜提取物显著抑制被提升的血清 TG、LDL-C、葡萄糖、胰岛素浓度和胰岛素抵抗指数；而 27 g/kg 苦瓜提取物则显著降低 TG 浓度；13.5、27 和 54 g/kg 苦瓜提取物分别显著升高 HDL-C 水平；苦瓜提取物能剂量依赖性地减轻高脂饮食诱导的脂肪细胞肥大。

关键词： 苦瓜；高脂喂食；糖尿病；胰岛素抵抗；肥胖

Obesity results from chronic imbalance between energy intake and expenditure, and is characterized by over 30 kg/m^2 Body Mass Index (BMI), which is the most widely used measure for determine the prevalence of obestiy[1]. Overweight and obesity are the fifth leading cause of global deaths, accounting for at least 2.8 million adults' deaths annually. And the alarming prevalence of childhood obesity is of particularly noteworthy since 1970s. The prevalence of obesity has been more than doubled for children and nearly 43 million children under the age of five were outweight in 2010. The obesity pandemic, if left out of control, will reach unprecedented proportions in 2050 with 165 million adults in the USA[2].

The global increase in prevalence of obesity has led to an increased need for the treatment of obese persons. It is well known that both diet and exercise are best for prevention and treatment. However, both ways require self-discipline and persistence. Another possible adjunct is drug treatment. But it may have only modest effects, accompanied by side effects and potential for drug abuse. Furthermore, the weight lowering effect lasts as long as the period when the drug is being taken. Unfortunately, as soon as the administration is stopped, the weight is regained[3-4]. Interestingly, in the Eastern world including Chian, there are some alternative therapies having been used, which herbal medicine is involved[5-6].

Momordica charantia, also is referred to as bitter melon or bitter gourd, is a popular vegetable as well as an herb in China. It has been used as an herb for at least 600 years in South China and nowadays widely cultivated in Asia[7], Africa and South America. Bitter melon is received widespread attention in the scientific community due to its beneficial effects such as anti-diabetic, anti-cancer and anti-inflammatory [8-11]. Although various parts (roots, stems, leaves and fruits) of *Momordica charantia* are used traditionally, studies have shown that the fruit extract of *Momordica charantia* has potent hypoglycaemic properties[12-13]. It has been reported that juice extract of fresh *Momordica charantia* fruit without seeds could reduce adiposity, lower serum insulin, improve insulin sensitivity, and normalize glucose tolerance in rats fed with a high-fat-diet (HFD) [14-16]. Lyophilised power of *Momordica charantia* fruit including seeds could reduce insulin resistance and inhibit adipocyte hypertrophy in diet-induced obese (DIO) rats[17]. Recent *in vitro* studies showed that juice of immature *Momordica charantia* could inhibit primary human adipocyte differentiation[18]. Moreover, 95% ethanol extract of *Momordica charantia* seedless fruit could depressed blood glucose in streptozotocin-diabetic rats[19]. However the effects of ethanol extract of *Momordica charantia* fruit on obesity and insulin resistance in diet-induced obese mice has not been reported yet.

Considering that C57BL/6j mice are very susceptible to diet-induced obestiy[20], the present study was designed to develop this animal model to examine the anti-obesity and anti-diabetic effects of *Momordica charantia* in C57BL/6j mice fed in a high-fat diet.

1 Materials and methods

1.1 Chemicals and Reagents

Serum triglyceride (TG), cholesterol (CHO) and glucose test kits were purchased from Roche Company (Shanghai, China); low density lipoprotein cholestrerl (LDL-C) and high density lipoprotein cholesterol (HDL-C) test kits were purchased from Leadman Company (Beijing, China); Insulin (mouse) ultrasensitive ELISA kits was purchased form ALPCO Company (America); Haematoxylin and eosin solution were purchased from Baso Company (Guangzhou, China). Other chemicals were of reagent grade.

1.2 Preparation of *Momordica charantia* extract (MCE)

Immature *Momordica charantia* fresh fruit was purchased from a local market, and was throughly washed with water and dried at room temperature. 45 kg of fruit was then cutted into slice and extracted with 360 L ethanol/water (70∶30, *V*/*V*) for 2 h. After filtration, the fruit was re-extrated with 270 L ethanol/

water (70:30, *V/V*) for 1.5 h, and filtered again, all the filtrates were combined and subjected to vacuum evaporation. The resulted gummy residues were weighted and stored at 4 ℃. Before using, it was diluted and adjusted with 0.5% CMC-Na to 1.8, 0.9 and 0.45 g (crude drug) /mL.

1.3 Animals and diets

Male C57BL/6j mouse (11 ~ 13 g) were obtained from Beijing HFK Bioscience Co., Ltd (Beijing, China). Mice were group-housed in standard individual ventilated cages with wood shavings as litter. The cages were a controlled environment an temperature (22 ± 1) ℃ and humidity 45% ~55% with a 12 h /12 h modified dark-light cycle. There were four mice in each cage. Food and water were available *ad libitum*. Animal care and use were conducted with the approval of Shenyang Pharmaceutical University Institutional Laboratory Animal Care and Use Committee. All efforts were made to minimize pain and suffering and to reduce the number of animals used. After adaption for 3 days, the mice were assigned into low-fat diet group and high-fat diet group. The compositions of low-fat diet and high-fat diet were shown in Table 1. The mice in high-fat diet group were induced obestiy (diet-induced obesity, DIO) after 2 weeks (weeks -2 to -1), and then separated into high-fat diet control group (HFD-Control) and MCE 13.5, 27.0, 54.0 g/kg groups (indicated as HFD-13.5MCE, HFD-27MCE, and HFD-54MCE, respectively). The mice in low-fat diet group were separated into low-fat diet control group (LFD-Control) and MCE 54.0 g/kg groups (LFD-54MCE) as well. The mice in MCE groups were given intragastrically with MCE; and mice in control groups (LFD-Control and HFD-Control) were given 0.5% CMC-Na with the same volume (15 mL/kg) twice a day for ten weeks . The dietary was also continued .

Table 1 Composition of tested diets

Composition	Low-fat diet	High-fat diet
Barley power/(g·kg^{-1})	200	140
Dehydrated vegetable /(g·kg^{-1})	100	70
Bean flour /(g·kg^{-1})	200	140
Casein /(g·kg^{-1})	10	7
Bone meal/(g·kg^{-1})	50	35
Corn starch /(g·kg^{-1})	160	112
Bran/(g·kg^{-1})	160	112
Fish meal/(g·kg^{-1})	100	70
Salt /(g·kg^{-1})	20	14
Milk power /(g·kg^{-1})	–	100
Yolk power/(g·kg^{-1})	–	100
Lard oil /(g·kg^{-1})	–	100
Concentrated cod liver oil	–	100 drops

The food intake of mice in each cage was recorded daily and body weight of mice were measured weekly throughout the study.

1.4 Collection of serum and adipose tissue

After 10 week of treatment, mice were fasted for 20 h. After the blood was removed, the mice were killed by decapitation. The white adipose tissues (WATs, including epididymal, mesentery, and perirenal WAT) were dissected according to the defined anatomical landmarks. The weights of tissues were measured. Visceral fat was defined as the sum of epididymal, mesentery, and perirenal WAT. They were then fixed in 4% buffered formalin until use. The collected blood was kept at room temperature for 10 min for coagulation. Then, the serum was obtained from the coagulated blood by centrifugation at 2 000 r/min for 15 min at 4 ℃. The separation of the serum was finished within 30 min. The serum was immediately frozen at −80 ℃ until analysis.

1.5 Measurement of serum lipid, glucose and insulin levels

The serum TG, CHO, LDL-C, HDL-C and glucose concentrations were measured using commercial assay kits according to the manufacturer's directions with MODULAR P800 automatic biochemistry analyzer (Roche, Germany). Serum insulin levels were measured by ELISA using a commercial assay kit according to manufacturer's directions, the OD value was readed at 450 nm with Synergy HT multifunctional microplate reader (Bio-tek, America). The degree of insulin resistance was estimated by a homeostasis assessment model (HOMA-IR), which was calculated according to the formula: HOMA-IR = serum glucose (mmol/L) (serum insulin (mU/L) /22.5[21].

1.6 Histological analysis of WAT

Epididymal adipose tissues from the mice were embedded in paraffin. Standard sections of 4-μm thickness were cut with Leica RM2245 manual rotary slicer (Shanghai, China), and stained with hematoxylin and eosin. which was viewed under an inverted optical microscope (Olympus IX71, Japan) and photographed at a final magnification of 400 ×.

1.7 Statistical analysis

Data are expressed as the mean ± SEM. The statistical significance of differences between the mean values for the treatment groups was analyzed with one-way or two-way analysis of Variance (ANOVA) followed by Dunnet *t*-tests using the software SPSS 13.0 (Chicago, USA). $P < 0.05$ was considered statistically significantly.

2 Results

2.1 Effects of the MCE on body weight and food intake

The weekly body weights and food intakes of mice were shown in Fig. 1 and Fig. 2. The body weight of the HFD-control group was significantly increased compared with the LFD-control group during MCE treatment after DIO except at eighth week. The body weight of the HFD-54MCE group was significantly decreased compared with the HFD-Control group at ninth and tenth week after MCE treatment. However, there was no significant difference in the body weight of the HFD-27MCE and HFD-13.5MCE group compared with the HFD-Control group (Fig. 1). During the MCE treatment period, the food intake did not differ significantly among all the groups except those mice in HFD-54MCE group, which ate less than those in HFD-Control group at second week after MCE treatment (Fig. 2).

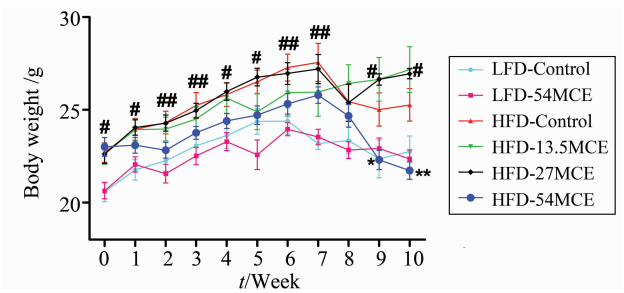

Fig. 1　Effect of MCE on body weight of mice after ten weeks treatment

LFD: low-fat diet; HFD: high-fat diet; MCE: *Momordica charantia* extract. Data are expressed as the mean ± SEM ($n = 8 \sim 12$). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs LFD-Control group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs HFD-Control group.

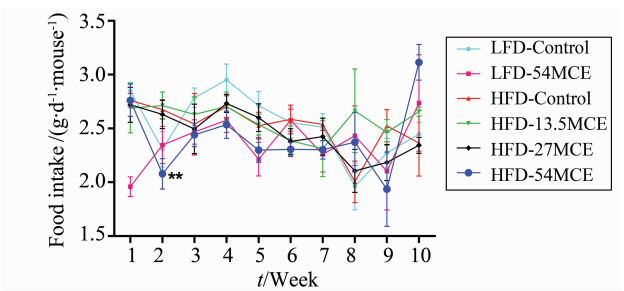

Fig. 2　Effect of MCE on food intake of mice after ten weeks treatment

LFD: low-fat diet; HFD: high-fat diet; MCE: *Momordica charantia* extract. Data are expressed as the mean ± SEM ($n = 8 \sim 12$). $^{**}P < 0.01$ vs HFD-control group.

2.2 Effects of the MCE on the WAT weights

The mesentery, perirenal and epididymal WAT weights were shown in Fig. 3. There were no significant differences in mesentery WAT weight among the six groups. The perirenal, epididymal and total visceral WAT weights were significantly increased in the HFD-Control group compared with the LFD-control group. However, the epididymal and total visceral WAT weights were decreased signifgicantly after treatement with MCE 54 g/kg for ten weeks, but treatement with MCE 13.5 and 27 g/kg had no obvious effect on WAT weights.

2.3 Effects of the MCE on the serum biochemical parameters

The serum biochemical parameters were shown in Table 2. The significantly increased serum TG, CHO, LDL-C, glucose, and insulin levels, and decreased HDL-C were observed in the HFD-control group compared with the LFD-control group. The serum TG, CHO, LDL-C, glucose and insulin levels were significantly reduced in the HFD-54MCE group compared with the HFD-control group, but not significantly in the HFD-13.5MCE and HFD-27MCE group. However, HDL-C levels was restored in all the MCE-treated groups. Although there were no significant difference on HOMA-IR between HFD-control group and LFD-control group, the HOMA-IR in HFD-54MCE group was decreased markedly compared with HFD-Control group. Moreover, the concentration of LDL-C in serum was significantly decreased in LFD-54MCE group compared with LFD-Control group.

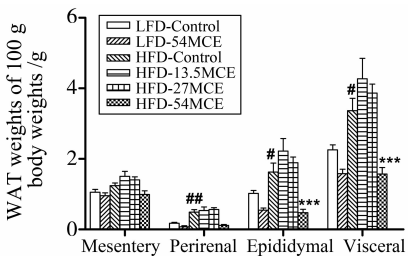

Fig. 3　Effect of MCE on visceral white adipose tissue weight of mice after ten weeks treatment

LFD: low-fat diet; HFD: high-fat diet; MCE: *Momordica charantia* extract. Data are expressed as the mean ± SEM ($n = 8 \sim 12$). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with LFD-control group; $^{***}P < 0.001$, compared with HFD-control group.

2.4 Histological analysis of the epididymal WAT

The sizes of the epididymal adipocytes in each groups were shown in Fig. 4. The sizes of the adipocytes were significantly larger in the HFD-control group than those in the LFD-control group. Interestingly, after treatment with MCE 54 g/kg for ten weeks, the hypertrophy of epididymal adipocytes were considerably

Table 2 Effects of the MCE on serum biochemical parameters in HFD-induced obese mice after ten weeks treatment[1)]

Group	TG / ($mmol \cdot L^{-1}$)	CHO/ ($mmol \cdot L^{-1}$)	LDL – C/ ($mmol \cdot L^{-1}$)	HDL-C/ ($mmol \cdot L^{-1}$)	Glucose/ ($mmol \cdot L^{-1}$)	Insulin / ($ng \cdot mL^{-1}$)	HOMA-IR
LFD-Control	1.14 ± 0.03	2.52 ± 0.07	0.50 ± 0.03	3.10 ± 0.11	5.53 ± 0.39	0.62 ± 0.03	4.21 ± 1.09
LFD – 54MCE	1.09 ± 0.09	2.43 ± 0.09	$0.28 \pm 0.02^{\#\#}$	2.83 ± 0.06	5.30 ± 0.59	0.62 ± 0.06	5.18 ± 0.46
HFD-Control	$1.35 \pm 0.10^{\#}$	$4.00 \pm 0.22^{\#\#\#}$	$0.80 \pm 0.04^{\#\#\#}$	$1.80 \pm 0.05^{\#\#\#}$	$7.58 \pm 0.69^{\#\#}$	$1.31 \pm 0.32^{\#}$	12.47 ± 5.18
HFD – 13.5MCE	1.23 ± 0.11	4.25 ± 0.16	0.69 ± 0.04	$2.50 \pm 0.17^{*}$	8.78 ± 0.49	1.08 ± 0.22	10.82 ± 1.97
HFD – 27MCE	$1.12 \pm 0.08^{*}$	4.22 ± 0.09	0.78 ± 0.04	$2.54 \pm 0.21^{*}$	7.20 ± 0.40	1.24 ± 0.43	11.20 ± 5.10
HFD – 54MCE	$1.13 \pm 0.09^{*}$	$3.37 \pm 0.20^{**}$	$0.46 \pm 0.04^{***}$	$3.03 \pm 0.05^{**}$	$6.20 \pm 0.57^{*}$	$0.55 \pm 0.03^{*}$	$3.68 \pm 0.25^{*}$

1) LFD: low-fat diet; HFD: high-fat diet; MCE: *Momordica charantia* extract. Data are expressed as the mean ± SEM ($n = 8 \sim 12$). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs LFD-Control group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs HFD-Control group.

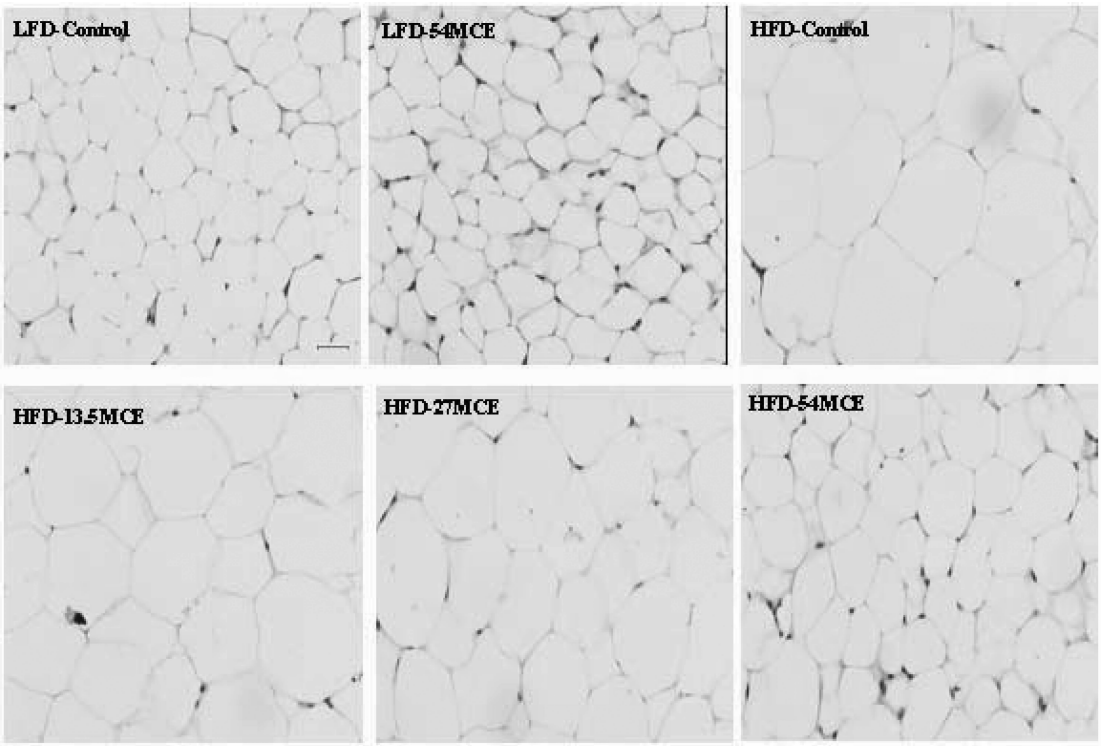

Fig. 4 Representative histological section of epididymal white adipose tissue, stained with haemotoxylin and eosin, from each of the six treatment groups
Scale bar: 100 microns; LFD: low-fat diet; HFD: high-fat diet; MCE: *Momordica charantia* extract.

decreased compared with the HFD-control group, but the effects of MCE 13.5 and 27 g/kg were not as significant as those of MCE 54 g/kg.

3 Discussion

The present study demonstrated that MCE reduced body weight and visceral white adipose tissue weight without affecting food intake and controlled hyperlipidemia, hyperglycemia and hyperinsulinemia by significantly decreasing serum lipids, glucose and insulin levels in C57BL/6j mice fed in a high-fat diet. Moreover MCE could inhibit proliferation and hypertrophy of adipocyte in epididymal adipose tissue.

C57BL/6j mice are preferred to use in many anti-obesity experiments for its susceptibility to diet-induced obesity. Some studies have shown that obesity was induced within 4 weeks after introduction of HFD to C57BL/6j mice[22-24]. However, in the present study, obesity was induced after fedding in HFD for two weeks. The inhibitory effects of *Momordica charantia* on adiposity has been reported *in vivo* and *in vitro*. Adiposity was reduced in rats fed with HFD when 0.75% or higher freeze-dried *Momordica charantia* juice supplemented into the diet for 15 weeks[15]. Adipocyte hy-

pertrophy and lipogenic gene expression were inhibited in diet-induced obese rats when 5% lyophilised *Momordica charantia* powder supplemented into the diet for 9 weeks[17]. Visceral obesity and body weight gain were inhibited in mice on high-fat diet after treatment with P and G fraction extracts of *Momordica charantia* for 4 weeks[9]. The differentiation of primary human adipocyte was inhibited by *Momordica charantia* juice[18]. In accordance with these results, after 10 weeks treatment with 54 g/kg of ethanol extract of *Momordica charantia*, the body weight and visceral white adipose tissue weight were decreased in HFD mice.

Obesity is a chronic metabolic disorder characterized by increased fat accumulation, such as increases in the cell number and/or cell size in adipose tissue and elevated lipid concentrations in blood[25]. The increased concentrations of TG, CHO and LDL-C and hypertrophic adipocyte in epididymal adipose tissue were observed in HFD mice in our study. Interestingly, treatment with 54 g/kg ethanol extract of *Momordica charantia* could normalize the concentrations of TG and LDL-C and the size of adipocyte in epididymal adipose tissue and significantly decreased the conecetration of CHO. In agreement with our results, decreased serum TG, CHO and LDL-C and increased serum HDL-C were reported after administration of *Momordica charantia* extrat in diabetic rats[26-28]. Furthermore, our results shown that the concentration of HDL-C was decreased in HFD-Control group, and was restored by the treatments of MCE 13.5, 27.0 and 54.0 g/kg, respectively.

Recent advances have shown that adipose tissue not only stores excess energy in the form of fat but also is a critical endocrine organ that is innately involved in regulating obesity and other metabolic processes. For example, resistin was considered to be a mechanistic mediator form adipocytes to insulin resistance[18, 29]. Insulin resistance is the salient feature of type 2 diabetes mellitus. Insulin resistance occurs when normal circulating concentrations of the hormone fail to regulate body glucose homeostasis[30]. Since insulin resistance is a major metabolic abnormality of T2D, there has been considerable interest in insulin-sensitizing agents to counteract insulin resistance for the treatment of this disease[31]. The present study proved that *Momordica charantia* was effective to decrease the serum concentration of glucose and insulin and to improve insulin resistance in a diet-induced obese mice model. A substantial number of reports indicated that *Momordica charantia* was able to exert a hypoglycemic effects in a variety of animal models, such as STZ-induced diabetic mice, KK-Ay mice and alloxan-induced rats, the related mechanisms included protection of β-cells, increase of glycogen content, enhancement of GLUT4 translocation and inhibition of gluconeogenesis[19, 32-34]. The decreased visceral white adipose weight might be another mechanism responsible for amelioration of insulin resistance, for some substance secreted from adipocytes might be reduced, such as leptin or resistin, but this was needed further investigation.

In *Momordica charantia*, there exist many active chemicals including saponins, alkaloids, fixed oils, triterpenoids, steriods, polypeptides, glycosides, carotenoids, flavanoids and polyphenols[35-39]. Quercetin and gallic acid, two kinds of polyphenols contained in *Momordica charantia*, have been demonstrated to inhibit adipogenesis and induce apoptosis in 3T3 - L1 mouse adipocytes[40-41]. The hypoglycemic effects of *Momordica charantia* might result from saponins known as charantin, alkaloids known as glycoalkaloid, and triterpenoids known as momordicoside[39,42]. The polyphenols and flavanoids in *Momordica charantia* beside quercetin and gallic acid have been displayed to inhibit obesity and metalism disorder *in vivo or vitro*[43-46]. Which components are responsible for the anti-obesity and anti-diabetic effects in the present investigation remains unknown.

Some clinical trials about hypoglycemic effects of *Momordica charantia* extract have been carried out in type 2 diabetes[47-51], but the controversial results are reported too[52]. Despite the need for more information in randomised controlled trails, but no serious adverse effects on humans have been reported until now. However, long term studies testing the effects of *Momordica charantia* extract on body weight, glucose and lipid metabolism as well as identifying the pharmacokinetics and effective dose of *Momordica charantia* extract is warranted, before it can be recommended as an effective alternative and/or complementary therapy.

In conclusion, MCE signifcantly decreased body weight and serum lipids, improved insulin resistance and inhibited visceral adipose tissue accumulation and hypertrophy of epididymal adipocyte in HFD mice. All these results suggested that MCE may serve as an alternative therapy for obesity and diabetes.

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