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ARTICLE

Effects of *Lactobacillus plantarum* SCS2 on blood glucose level in hyperglycemia mice model

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Abstract In this study, the hyperglycemia mice model was established with 1-week high sugar and fat diet plus with 70 mg/kg body weight of streptozotocin injection for 3 days. Sixty male Kunming mice of 3 weeks old in a specific-pathogen-free grade were divided into six groups randomly, which includes normal group (NG), prevention group (PG), treatment group for low dose (TGL), middle dose (TGM), high dose (TGH), and model group (MG). NG and MG mice were fed with sterile physiological saline (10 mL/kg body weight). PG mice were fed with the concentration of 6.0×10^9 CFU/mL *L. plantarum* SCS2 suspensions from the second to third week. TGL, TGM, and TGH mice were fed with the concentration of 2.0×10^9, 4.0×10^9, and 6.0×10^9 CFU/mL *L. plantarum* SCS2 suspensions (10 mL/kg body weight), respectively from fourth to tenth week. The results showed that the fasting and postprandial 2 h blood glucose levels of TGH mice were reduced by *L. plantarum* SCS2 significantly ($p < 0.05$) as compared with MG. The body weight of TGH mice came to normal level at tenth week. Content of K^+ in plasma of TGH mice was increased and contents of Na^+ and Cl^- in the plasma of TGH mice were decreased as compared with MG. Meanwhile, content of glycogen in TGH mice was reduced. However, the effect of *L. plantarum* SCS2 on the prevention of hyperglycemia in PG mice was not significant as compared with NG mice during the experiment. These results suggested that *L. plantarum* SCS2 showed a hypoglycemic effect on hyperglycemic mice model.

Keywords Blood glucose · Hyperglycemia · Hypoglycemic effect · *L. plantarum* SCS2 · Prevention

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from the defects in insulin secretion partially or totally, cellular insulin receptor, and decreased receptor sensitivity (Schuster and Duvuuri 2002). Several new medications approved for the treatment of diabetes currently (Li et al. 2014; Guthrie 2015; Seino et al. 2015; Stern and Murphy 2015). However, many untoward effects such as irritability and tolerance for human were caused by these medications, which are also harmful to liver and kidney (Fan et al. 2012). Recently, much effort has been focused on developing traditional medicines of lactic acid bacteria as complementary or an alternative diabetic treatment (Yun et al. 2009). As it's a kind of biological effect regulator, mild and obvious effects, stable properties of lactic acid bacteria without side effects or toxicity (Fan et al. 2012).

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In recent years, it has been reported that lactic acid bacteria have effects relating to the progression of diabetes. Matsuzaki et al. (1997) indicated that blood glucose and insulin levels in type II diabetes mice were reduced by *Lactobacillus casei* intake in 2 months. Yadav et al. (2006) reported that blood glucose, insulin, and total cholesterol in plasma and low density lipoprotein cholesterol of type II diabetes mice were improved by the combination of *Bacillus acidophilus* and *Lactobacillus casei*. Yun et al. (2009) identified that the hypoglycemic activity of *Lactobacillus gasseri* BNR17 was observed in this study. Additionally, Andreasen et al. (2010) found that insulin resistance was improved by adding lactic acid bacteria in diets. Ejtahed et al. (2011, 2012) reported that the fasting blood glucose level of type II diabetes patients were improved by *Bacillus acidophilus* and *bifidobacterium* derived from yogurt products in initial fermented period. Furthermore, Park et al. (2013) suggested that immune system function, hyperglycemia, and enterocinesia of human were improved by *Lactobacillus plantarum*. Calcinaro et al. (2005) demonstrated that morbidity rate of type II diabetes mice were decreased by VSL#3 (a kind of probiotics complexing agent). Yamano et al. (2006) reported that oral administration of *Lactobacillus johnsonii* La1 for 2 weeks reduced the elevation of blood glucose and glucagon levels in streptozotocin-diabetic rats.

In previous study, two lactic acid bacilli (*L. plantarum* SCS1 and *L. plantarum* SCS2) were isolated and identified from fermented sausage of Sichuan. The objectives of this present study were to investigate the effects of *Lactobacillus plantarum* SCS2 (*L. plantarum* SCS2) on body weight, blood glucose level, oral glucose tolerance, content of K^+, Na^+, and Cl^-, pH in plasma, and content of glycogen in hyperglycemia mice model.

Materials and methods

Strain and medium

Lactobacillus plantarum SCS2 (*Cillobacterium*, Lactobacteriaceae) was obtained from the Experiment Center, Public Health College, Chengdu University of Traditional Chinese Medicine (China). MRS broth (Oxoid Ltd., UK) was used as the culture medium for lactic acid bacteria.

Chemicals and reagents

Streptozocin (STZ) of biological reagent grade was purchased from Sigma-Aldrich (USA). All the remaining chemicals were of biological and analytical reagent grades, and were obtained from Kelong Chemical Reagent Factory (China).

Preparation of bacterial suspension

Lactobacillus plantarum SCS2 used in this study was isolated from fermented sausage of Sichuan in our laboratory. *L. plantarum* SCS2 stored at −80 °C was cultured three generation in MRS broth at 37 °C for 18 h. The suspension was centrifuged (3000×*g*, 5 min, 5 °C) and the supernatant was removed. The resultant cell pellets were washed three times and stored at −20 °C as lyophilized bacterial powder. *L. plantarum* SCS2 for administration to animals was prepared by the suspending lyophilized bacterial powder in sterile physiological saline (Srinivasan and Ramarao 2007; Chen et al. 2013).

Animals and experimental study

Sixty 3-week-old male Kunming mice in a specific-pathogen-free grade were obtained from Chengdu darso experimental animal Co. Ltd. (China) and divided into six groups randomly ($n = 10$ per group), which include normal group (NG), prevention group (PG), treatment group for low dose (TGL), treatment group for middle dose (TGM), treatment group for high dose (TGH), and model group (MG). Mice were administered for 10 weeks as shown in Table 1. NG and MG mice were fed with sterile physiological saline (10 mL/kg body weight) respectively. PG mice were fed with concentration of 6.0×10^9 CFU/mL *L. plantarum* SCS2 (10 mL/kg body weight) suspension from the second week to third week (He 2012). TGL, TGM, and TGH mice were fed with concentration of 2.0×10^9, 4.0×10^9, and 6.0×10^9 CFU/mL *L. plantarum* SCS2 (10 mL/kg body weight) suspension, respectively from the fourth week to the end of the experiments. All animals were housed in standard plastic cages (five mice per cage), constant temperature and humidity were controlled to 20 ± 3 °C and 50–70 %, respectively. The hyperglycemia model was established with high sugar and fat diets for 1 week and streptozocin of 70 mg/kg body weight for 3 days (Yang et al. 2006). The fasting and postprandial 2 h blood glucose of mice was higher than 7.0 and 11.1 mmol/L, respectively was the mark of good model (Xiang 2010). Body weight and blood glucose of fasting and postprandial 2 h blood glucose level of mice was measured once a week (Wang et al. 2010).

Body weight measurement

The body weight of mice was measured with an electronic balance once a week (Shenyang Longteng Electronic Co., Ltd., China).

Table 1 Animals Grouping

Groups	NG	PG	TG			MG
			TGL	TGM	TGH	
Time (weeks)						
1	Common diet	Common diet	Common diet	Common diet	Common diet	Common diet
2	Common diet	Common diet + *L.plantarum* SCS2	Common diet	Common diet	Common diet	Common diet
3	Common diet	High sugar and fat diet + STZ	High sugar and fat diet + STZ	High sugar and fat diet + STZ	High sugar and fat diet + STZ	High sugar and fat diet + STZ
4–10	Common diet + sterile physiological saline	Common diet	Common diet + *L.plantarum* SCS2	Common diet + *L.plantarum* SCS2	Common diet + *L.plantarum* SCS2	Common diet + sterile physiological saline

NG and MG mice were fed with sterile physiological saline (10 mL/kg body weight), respectively. PG mice were fed with concentration of 6.0×10^9 CFU/mL *L. plantarum* SCS2 suspensions. TGL, TGM, and TGH mice were fed with concentration of 2.0×10^9, 4.0×10^9, and 6.0×10^9 CFU/mL *L. plantarum* SCS2 (10 mL/kg body weight) suspensions, respectively. Concentration of STZ was 70 mg/kg body weight

Blood glucose measurement

Mice were fasted for 12 h with water intake and the venous blood of tail was collected and analyzed with a glucometer (Roche diagnostic products (Shanghai) Co., Ltd., China) for fasting blood glucose once a week. The postprandial 2 h blood glucose of mice were measured after 2 h of feeding once a week (Wu et al. 2013).

Effect of *L. plantarum* SCS2 on oral glucose tolerance of mice

Oral glucose tolerance tests (OGTT) were studied at the fourth and tenth week. Before each test, MG, NG, PG, and TGH mice were fasted for 12 h, a glucose solution was prepared at a concentration of 2 g/kg body weight. After that, blood glucose level was measured at 0, 15, 30, 60, 90, and 120 min (Quine and Raghu 2005; He 2012).

Effect of *L. plantarum* SCS2 on content of K^+, Na^+, Cl^-, and pH in plasma of mice

Content of K^+, Na^+, Cl^-, and pH in plasma of mice were performed at the tenth week. Before the test, mice were fasted for 12 h, venous blood of tail was collected and centrifuged (3000×*g*, 3 min, 5 °C) (Quine and Raghu 2005; He 2012). The plasma was measured by electrolyte analyzer (Nanjing zhaoshida Electronic Instrument Co., Ltd., China).

Effect of *L. plantarum* SCS2 on content of glycogen in mice

Content of glycogen in mice was performed at the end of the experiment. Before the test, mice were executed by breaking the neck. The livers were washed in iced physiological saline and then dried. The livers and iced physiological saline were mixed according to the proportion of 1:9 (w:w) and grinded. The homogenate was centrifuged (3000×*g*, 10 min, 5 °C) and the supernatant was measured by glycogen kit (Nanjing Institute of biological engineering, Nanjing, China) (Zhang 2013; Bae et al. 2015).

Statistical analysis

All data are expressed as mean ± standard deviation of triplicate assays. Statistical analyses for body weight, blood glucose level, content of K^+, Na^+, Cl^- (mmol/L), and content of glycogen (mg/g) in mice were carried out using PASW statistics (formerly SPSS), version 20.0 (IBM SPSS, Inc., USA).

Results

Effect of *L. plantarum* SCS2 on body weight of mice

The body weight responses of mice are shown in Fig. 1. The body weight of PG, MG, TGL, TGM, and TGH were decreased in 3 weeks. Also the deceleration rate of body weight of PG was lower than MG after 3 weeks. The result suggested that the decreased body weight of PG mice were improved by *L. plantarum* SCS2. However, the significant difference between PG and MG mice was not observed. The body weight of TGM and TGH mice was increased significantly ($p < 0.05$) compared with MG mice after 4 weeks. Moreover, the body weight of TGH mice was close to NG at the end of the experiment. The results showed that decreased body weight of TGH mice was improved by high dose (6.0×10^9 CFU/mL) of *L. plantarum* SCS2 significantly compared with MG mice ($p < 0.05$).

Effect of *L. plantarum* SCS2 on fasting and postprandial 2 h blood glucose of mice

As shown in Fig. 2, the fasting blood glucose level of MG, PG, TGL, TGM, and TGH mice were increased significantly compared with NG mice in 3 weeks and the highest fasting blood glucose level of MG, PG, TGL, TGM, and TGH mice was observed from fifth to sixth week. The fasting blood glucose level of PG mice was increased until the end of the experiment. It means that the prevention effect of *L. plantarum* SCS2 on fasting blood glucose level

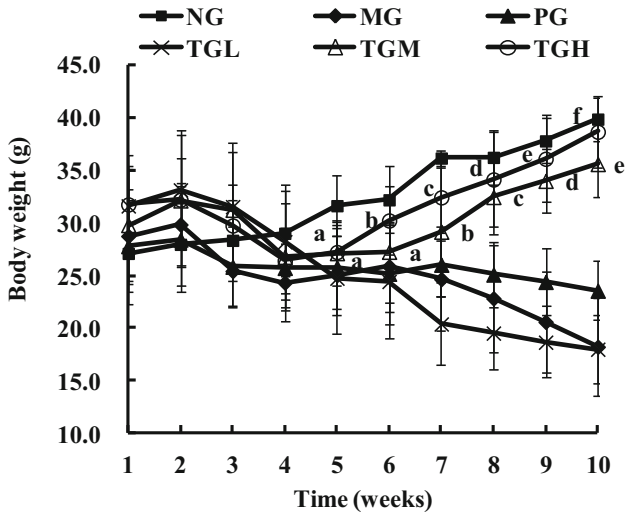

Fig. 1 Effect of *L. plantarum* SCS2 on body weight of mice. *Different symbols* represent different groups. Values are expressed in terms of mean ± SD values of three replicates. Values of TGM and TGH labeled with *different letters* were significantly different ($p < 0.05$)

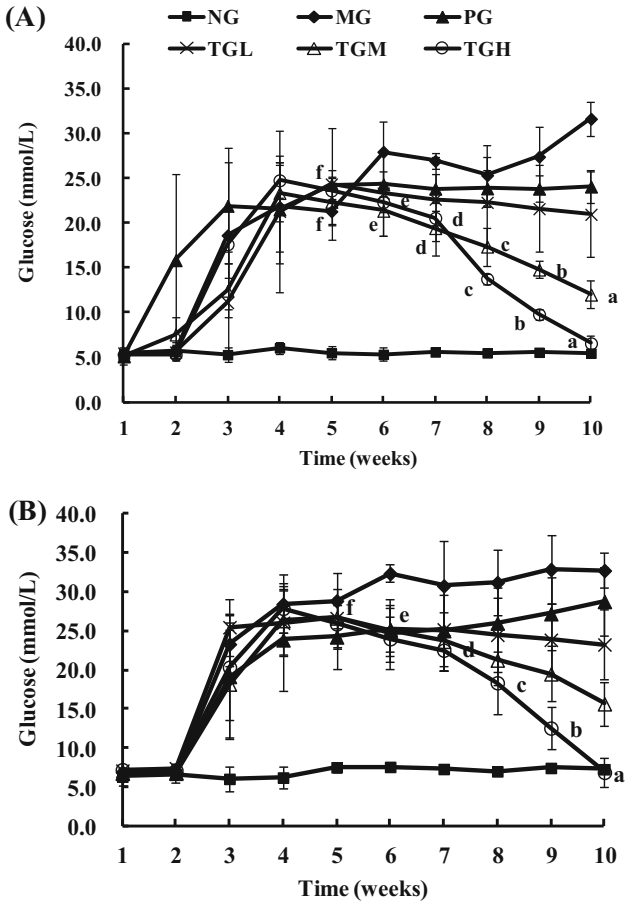

Fig. 2 Effect of *L. plantarum* SCS2 on fasting and postprandial 2 h blood glucose of mice. *Different symbols* represent the different groups. Values are expressed in terms of mean ± SD values of three replicates. The change in fasting blood glucose level of mice was (**A**). The change in postprandial 2 h blood glucose level of mice was (**B**). Values of TGM and TGH labeled with *different letters* were significantly different ($p < 0.05$)

of PG mice was not significant. After the sixth week, the fasting blood glucose level of TGM and TGH mice was reduced significantly as compared with MG mice ($p < 0.05$). At the end of the experiment, the fasting blood glucose level of TGH mice was close to NG. The postprandial 2 h blood glucose level of MG, PG, TGL, TGM, and TGH mice was increased after STZ injection. The postprandial 2 h blood glucose level of PG, TGL, TGM, and TGH mice was the highest at the fifth week. The postprandial 2 h blood glucose level of PG mice was lower than MG. The results suggested that the increased postprandial 2 h blood glucose level of PG mice was improved by *L. plantarum* SCS2. However, the significant difference between PG and MG mice was not observed. Otherwise, the postprandial 2 h blood glucose level of TGL, TGM, and TGH mice was reduced after the fifth week. The significant decrease of postprandial 2 h blood glucose level of

TGH mice was observed as compared with MG mice and the data were close to NG at the end of the experiment. The results indicate that the fasting and postprandial 2 h blood glucose level of TGH mice was decreased by high dose (6.0×10^9 CFU/mL) of *L. plantarum* SCS2 significantly compared with MG mice ($p < 0.05$).

Effect of *L. plantarum* SCS2 on oral glucose tolerance of mice

The results of OGTT are shown in Fig. 3. The blood glucose level of all groups was increased after glucose intake at the fourth week and the highest blood glucose level was observed in 30 min. The blood glucose level of NG mice was decreased to normal values in 120 min. Compared with NG mice, the blood glucose level of MG mice was higher than 26.3 ± 4.0 mmol/L. The results suggested that glucose tolerance of MG mice was impaired. The blood glucose level of TGH mice was reduced after 30 min. However, the change in blood glucose level of TGH mice

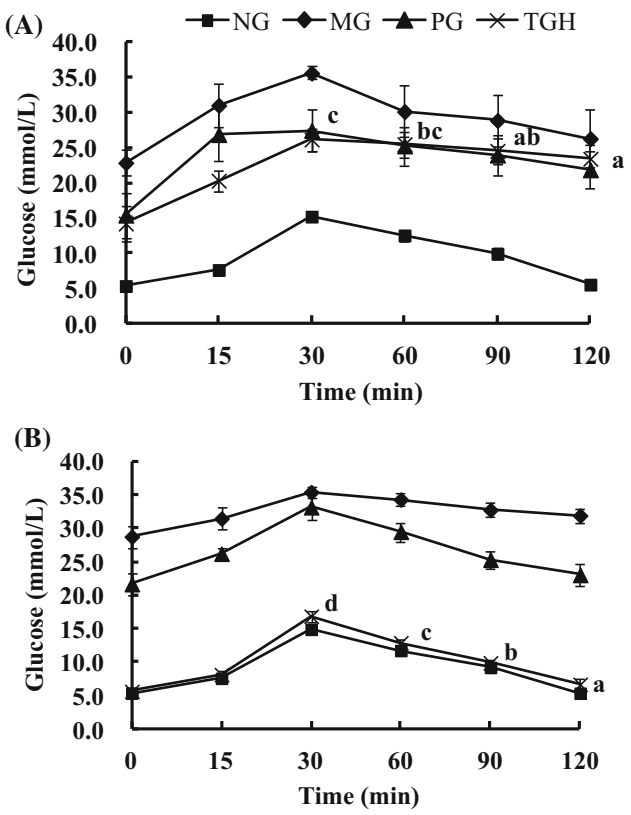

Fig. 3 Effect of *L. plantarum* SCS2 on oral glucose tolerance of mice. *Different symbols* represent the different groups. Values are expressed in terms of mean ± SD values of three replicates. The change in blood glucose level of mice at the fourth week is (**A**). The change in blood glucose levels of mice at the tenth week is (**B**). Values of TGH labeled with *different letters* were significantly different ($p < 0.05$)

was not significant at that time. After 10 weeks, the blood glucose level of TGH mice was reduced to 6.7 ± 0.8 mmol/L, which was a normal level. The result showed that the oral glucose tolerance of TGH mice was improved by high dose (6.0×10^9 CFU/mL) of *L. plantarum* SCS2 significantly compared with MG mice ($p < 0.05$).

Effect of *L. plantarum* SCS2 on content of K^+, Na^+, Cl^-, and pH in plasma of mice

As shown in Fig. 4, at the end of the experiment, the lowest content of K^+ was observed in MG mice, it suggests that K^+ intake was limited by hyperglycemia of mice. Differences between the content of K^+ in plasma of PG and MG mice was not significant, which showed that decreased content of K^+ in the plasma of PG mice was not improved by *L. plantarum* SCS2. However, the content of K^+ in the plasma of TGL, TGM. and TGH mice was higher than in MG mice and the content of K^+ in the plasma of TGH was the highest among all the groups. Differences between TGH and NG mice were not significant. Otherwise, the contents of Na^+ in plasma of TGL, TGM, and TGH mice were increased as compared with MG mice at the end of the experiment. The contents of Na^+ in the plasma of TGH mice was close to NG mice. Differences between PG and MG mice were not significant. The content of Cl^- in the plasma of PG, MG, and TGL mice were higher than the NG mice. The lowest content of Cl^- in plasma was observed in TGH mice among TGL, TGM, and TGH mice, which was close to NG mice. Meanwhile, differences were not significant in pH among NG, MG, PG, TGL, TGM, and TGH mice in 10 weeks.

Effect of *L. plantarum* SCS2 on the content of glycogen in mice

The results are shown in Fig. 5. The contents of glycogen between MG and PG mice does not have a significant difference. Otherwise, the contents of glycogen in TGL, TGM, and TGH mice was lower than MG, difference was observed significantly ($p < 0.05$). However, the contents of glycogen in TGL, TGM, and TGH was higher than NG at the end of the experiments.

Discussion

In this present study, three concentrations (2.0×10^9, 4.0×10^9, and 6.0×10^9 CFU/mL) of *L. plantarum* SCS2 suspensions were used to investigate the hypoglycemic activity in hyperglycemia mice. Reduced body weight of TGH mice was improved by *L. plantarum* SCS2

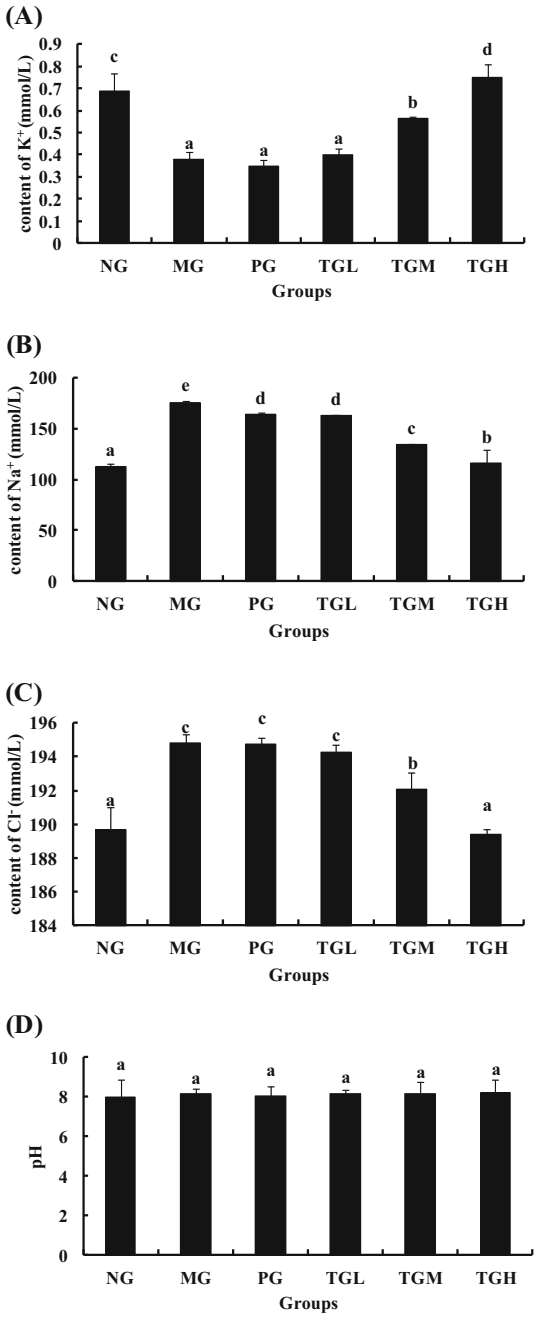

Fig. 4 Effect of *L. plantarum* SCS2 on contents of K^+, Na^+, Cl^-, and pH in plasma of mice. Values are expressed in terms of mean ± SD values of three replicates. Values of columns labeled with *different letters* were significantly different ($p < 0.05$). The change in the content of K^+ is (**A**), the change in content of Na^+ is (**B**), the change in content of Cl^- is (**C**), and the change in pH is (**D**)

suspension with the concentration of 6.0×10^9 CFU/mL significantly ($p < 0.05$) compared with MG mice. The result was higher than some previously investigated microorganisms from other studies regarding the hypoglycemic activity effect. Chen et al. (2013) reported that the body weight of hyperglycemia mice was increased by

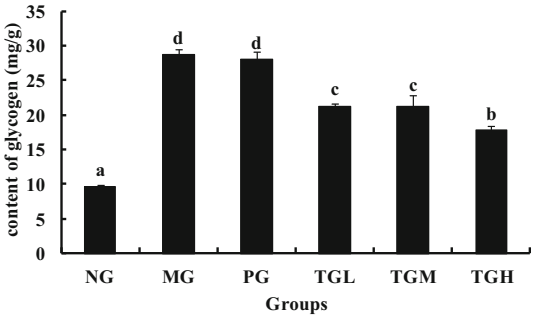

Fig. 5 Effect of *L. plantarum* SCS2 on content of glycogen in mice. Values are expressed in terms of mean ± SD values of three replicates. Values of columns labeled with *different letters* were significantly different ($p < 0.05$)

Lactobacillus rhamnosus suspension with the concentration of 4.0×10^9 CFU/mL. Hsieh et al. (2013) indicated that body weight was improved by *Lactobacillus reuteri* GMNL-263 with a concentration of 10^9 CFU/mL. However, Yun et al. (2009) identified that body weight loss was not seen in the *Lactobacillus gasseri* BNR17 group with concentration of 10^{10} CFU/mL. Wang et al. (2010) suggested that the decreased body weight of hyperglycemia mice was improved by *Lactobacillus acidophilus* ATTC 5220 at a concentration of 1.0×10^{10} CFU/mL. These results were higher than the concentration of *L. plantarum* SCS2 in this study. Moreover, the prevention effect of *L. plantarum* SCS2 on PG mice was not significant in this present study. However, Wang et al. (2010) found that the body weight of prevention group was increased by *Lactobacillus acidophilus* ATTC 5220 at a concentration of 2.0×10^9 CFU/mL in 25 days after STZ injection. The concentration was higher than the result in this study. The different results may be due to the differences among the microorganisms tested.

Furthermore, the effect of *L. plantarum* SCS2 on fasting and postprandial 2 h blood glucose level of hyperglycemia mice was compared with results from previous studies. The results of the present study demonstrated that the concentration of *L. plantarum* SCS2 suspension decreased fasting and postprandial 2 h blood glucose level of TGH mice was 6.0×10^9 CFU/mL significantly ($p < 0.05$) compared with MG mice. The result was lower than Wang et al. (2010), which identified that the fasting blood glucose level of hyperglycemia mice was reduced by 1.0×10^{10} CFU/mL *L. plantarum* SCS2 suspension. Chen et al. (2013) reported that the fasting and postprandial 2 h blood glucose of type II diabetic mice were decreased by *Lactobacillus rhamnosus* with a concentration of 4.0×10^9 CFU/mL. Yun et al. (2009) indicated that the fasting and postprandial 2 h blood glucose level of the *Lactobacillus gasseri* BNR17 groups (10^7 CFU/mL) was lower than the control group over 12 weeks. The results that showed that the

concentration of *L. plantarum* SCS2 suspension decreased the fasting and postprandial 2 h blood glucose level of mice was higher than the result in the study by Chen et al. (2013) and Yun et al. (2009). Additionally, the prevention effect of *L. plantarum* SCS2 on increased fasting and postprandial 2 h blood glucose level of PG mice was not significant during the experiments. The result was not agreed with the study by Wang et al. (2010). The study suggested that the fasting blood glucose level of mice was reduced from 16.7 ± 5.24 to 10.8 ± 0.07 mmol/L in 25 days significantly.

The results of the present study demonstrated that the oral glucose tolerance of TGH mice was not improved by high dose (6.0×10^9 CFU/mL) of *L. plantarum* SCS2 and the blood glucose level was 25.5 ± 1.80 mmol/L in 4 weeks. The result was not agreed with some previous studies of OGTT test. Chen et al. (2013) suggested that the blood glucose level of *Lactobacillus rhamnosus* group mice was reduced to 11.3 mmol/L in 4 weeks. The blood glucose level was higher than the result in the study. The oral glucose tolerance of TGH mice was improved by high dose (6.0×10^9 CFU/mL) of *L. plantarum* SCS2 significantly compared with MG mice at the end of the experiment, which was lower than the result of Yun et al. (2009). The result reported that the glucose tolerances of the *Lactobacillus gasseri* BNR17 group (1.0×10^{10} CFU/mL) improved compared with the control group in 9 weeks. However, Chen et al. (2013) indicated that the blood glucose level of *Lactobacillus rhamnosus* group mice was decreased by a concentration of 4.0×10^9 CFU/mL and achieve to normal values at 12 week during the OGTT test. The result was lower than the concentration of *L. plantarum* SCS2 improved the oral glucose tolerance of hyperglycemia mice in this study.

In this study, administration of *L. plantarum* SCS2 at doses of 6.0×10^9 CFU/mL increases the content of K^+ and decreases the content of Na^+ and Cl^- in plasma. The result was compared with the previous study regarding the effect of microorganisms on the content of K^+, Na^+, and Cl^- in the plasma of mice. He (2012) identified that the content of K^+ was increased and the content of Na^+ was decreased in treatment group. The results were agreed with the variation in the study. However, the content of Cl^- was invariable compared with the beginning of the experiment, which was contrary to the result in the study. In addition, the difference of content of K^+, Na^+, and Cl^- in plasma between PG and NG mice was not significant. The result agreed with the investigation in this study. The different results may be due to differences among experimental animals. Otherwise, pH in plasma was not significant among all groups and the pH was higher than 7.35 in 10 weeks. The results suggested that the oxidosis symptom was not appeared in mice during the experiment (He 2012). Moreover, the content of glycogen in TGH mice was reduced significantly ($p < 0.05$) compared with MG mice at the end of the experiment. The results showed that the damaged islet cells of hyperglycemia mice was repaired by *L. plantarum* SCS2 intake and then the increased content of glycogen was improved along with decreased blood glucose of hyperglycemia mice (Wang et al. 1998; He 2012).

In conclusion, the hypoglycemic effect of *L. plantarum* SCS2 derived from Sichuan fermented sausage was demonstrated in this study. The fasting and postprandial 2 h blood glucose level was reduced significantly compared with MG mice ($p < 0.05$) and symptoms associated with hyperglycemia improved by *L. plantarum* SCS2 with a concentration of 6.0×10^9 CFU/mL. In addition, loss of K^+ and increased Na^+, Cl^-, and glycogen caused by hyperglycemia were improved by *L. plantarum* SCS2. Further investigations were focused on the mechanism of hypoglycemic effect and safety evaluation of *L. plantarum* SCS2. Fan et al. (2012) reported that blood glucose level of organism is regulated by some kind of essential amino acid, vitamin, and mineral elements derived from enzymes, which were produced by lactic acid bacteria. However, no evidence was found up to now. In the next study, we want to find the enzymes of hypoglycemic effect in *L. plantarum* SCS2.

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