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Hypoglycemic effect of extract of *Hericium erinaceus*

Jinn Chyi Wang,[1]* Shu Hui Hu,[2] Jih Terng Wang,[1] Ker Shaw Chen[1] and Yi Chen Chia[1]

[1]Department of Food Science and Technology, Tajen Institute of Technology, Ping Tung, Taiwan
[2]Department of Technology for Medical Science, Kaohsiung Medical University, Kaohsiung, Taiwan

Abstract: Recent studies have determined that many types of mushroom (eg *Hericium* spp), may have important physiological functions in humans, including antioxidant activities, the regulation of blood lipid levels and reduction of blood glucose levels. In this study, a methanol extract of the fruiting bodies of *Hericium erinaceus* was adsorbed on silica gel columns and eluted using polarity gradients of chloroform/ethyl acetate/acetone/methanol. The major components of the extract were D-threitol, D-arabinitol and palmitic acid identified by their chromatographic profiles and spectroscopic characteristics. The methanol extract of *H erinaceus* was concentrated to remove solvent yielding a residue (referred to as HEM) which was added to the diet. The hypoglycemic effects of feeding HEM to streptozotocin-induced diabetic rats were studied. Polydipsia was stronger in induced diabetic rats not fed HEM than in those receiving HEM. Rats fed with HEM had significantly lower elevation rates of blood glucose level than those not fed with HEM. The effects on blood glucose, serum triglyceride and total cholesterol levels were more significant in the rats fed daily with HEM at doses of 100 mg kg^{-1} body weight (bw) rather than 20 mg kg^{-1} bw ($p < 0.05$).

Keywords: hypoglycemic effect; induced-diabetic; extracts; *Hericium erinaceus*

INTRODUCTION

The treatment of diabetes often involves medication to control blood glucose levels; some of these medications have undesirable side-effects. Thus, much effort has been devoted to finding a natural ingredient with hypoglycemic effects that can be safely used in the management of diabetes. Several vegetables have been found to have therapeutic or ameliorating effects in lowering blood glucose levels by reducing insulin resistance and improving glucose tolerance.[1–5] Research on certain fungi has shown promising results. The fruiting bodies and mycelium obtained from solid-state and liquid cultures of *Agaricus* spp and *Cordyceps* spp can play an important role in mediating insulin production and regulating blood glucose.[6–10] Data from bulk fungal material, extracts obtained by using different solvents[11–13] and animal model experiments, verified that terpenoids,[12] polysaccharides,[14] glycosides,[15–17] polypeptides,[18] aldehydes, acids and alcohol,[19,20] can actively lower blood glucose levels.

In addition to these hypoglycemic effects, many edible mushrooms have antitumor and antioxidative effects and can affect the physiology of the gastrointestinal, cardiovascular and immune systems in humans and animals. Therefore, they can serve as potential health products or medicinal aids.[21] *Hericium* spp: are widely accepted as edible mushrooms. The physiological potency of the fruiting bodies and mycelium has been established by both *in vivo* and *in vitro* testing.[22–24]

The present study evaluated the influence of the extract from the fruiting bodies of *Hericium erinaceus* on blood glucose levels in a diabetic rat model. Residues from the fruiting bodies were resolved by gradient chloroform/ethyl acetate/acetone/methanol elution from a silica gel column, the constituents were separated and purified by further silica gel chromatography in order to identify the structure of their influential components spectroscopically.

MATERIALS AND METHODS

Cultivation of Hericium erinaceus

Hericium erinaceus (ATCC 56457) was cultivated on a medium containing (g kg^{-1}): sawdust 700, miller's offal 50, rice bran 150, sucrose 30, $(NH4)_2SO_4$ 50, and $CaCO_3$ 20, in polyethylene bags at 23 ± 2 °C,

* Correspondence to: Jinn Chyi Wang, Department of Food Science and Technology, Tajen Institute of Technology, 20, Wei-Shin Rd, Shin-Erh Village, Yen-Pu Shiang, Ping Tung, Taiwan 90703
E-mail: jicy.wang@msa.hinet.net
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humidity 92 ± 2% for 25 days. The fruiting bodies were harvested and dried by lyophilization.

Preparation of the extracts and isolation of compounds

The powdered fruiting bodies of *H erinaceus* (6 kg) were extracted three times with MeOH (10 l) at room temperature and the combined MeOH extracts (1985 g) evaporated under reduced pressure. Part of the residue, referred to as HEM, was used to assay the hypoglycemic effects, and the remainder (250 g) was chromatographed over silica gel (Merck, Darmstadt, Germany, Kiesegel 60, 230–400 mesh, 1400 g) and eluted with mixtures of $CHCl_3$/EtOAc/Me_2CO/MeOH of increasing polarity (1:0:0:0 to 0:0:0:1, v/v) to yield 66 fractions (120 ml each). Fractions (1.2 g) eluted by $CHCl_3$/EtOAc (10:1, v/v), were further purified by silica gel column chromatography (5 cm × 40 cm) with $CHCl_3$/MeOH (25:1, v/v) to give compound 1 (48.9 mg kg^1 dry wt of raw material). Fractions (2.68 g) eluted by EtOAc/Me_2CO (300:1, v/v), were further purified by silica gel column chromatography and preparative TLC (Merck, Kiesegel 60 F-254, 0.50 mm) with $CHCl_3$/MeOH (23:1, v/v) (R_f 0.45–0.53) to give compound 2 (350.7 mg kg^1 dry wt of raw material). Fractions (2.16 g) eluted by Me_2CO/MeOH (100:1, v/v) were further purified by silica gel column chromatography (5 cm × 40 cm) with $CHCl_3$/MeOH (21:1, v/v) to give compound 3 (300.4 mg kg^1 dry wt of raw material). Compound 1 was identified as palmitic acid by direct comparison with the authentic compound. Compounds 2 and 3 were identified as D-threitol and D-arabinitol, respectively, (Fig 1) by polarimetry (JASCO DIP-370) (JASCO Inc, Easton, MD, USA), ^{1}H NMR, and/or ^{13}C NMR (Varian Gemini NMR spectrometer) (Varian Inc, CA, USA) data as well as by comparison with reports from related literature.[25]

Effects of extract of *Hericium erinaceus* on induced-diabetic rat[19,26]

Male Wistar rats (average body weight 210 ± 20 g, 6 weeks old, purchased from National Laboratory Animal Center, Taiwan) were housed in stainless-steel wire cages and had free access to water and a semi-purified diet (AIN-76, ICN Biochemical Inc, CA, USA) for 7 days at 24 ± 1 °C, humidity 55 ± 5%, 12:12 h light-dark cycle; they were then randomly divided into five groups of 12 rats each. One group designated as normal rats and used as a control, was fed a regular diet. The other groups were injected intraperitoneally with streptozotocin (STZ, Sigma, St Louis, MO, USA) dissolved in 0.1 M acetate buffer (pH 4.5) at a dose rate of 55 mg kg^{-1} bw and then transferred to metabolic cages. The rats with fasting blood glucose levels over 230 mg dl^{-1} were included in the diabetic groups. One group of diabetic rats received a HEM-free regular diet and was used as a negative control group(non-HEM fed group), while the other groups of diabetic rats were fed orally a regular AIN-76 diet with 1 ml of aqueous HEM each day at dose rates of 20, 100 and 200 mg kg^{-1} bw, respectively, for 20 successive days (HEM-fed groups). Food intake, water intake and urine excretion were recorded daily. Body weight, serum triglyceride and total cholesterol levels were measured 2 days before the start of the experiments (day −2) and at the end of 20 days. Fasting blood glucose was determined every five days following 18 h of food deprivation. Blood samples were collected, without anesthesia, from the tail vein into heparinized tubes, and were then immediately analyzed. Blood glucose, serum triglyceride and total cholesterol levels were determined with kits (Randox Laboratories Ltd, Antrim, UK).

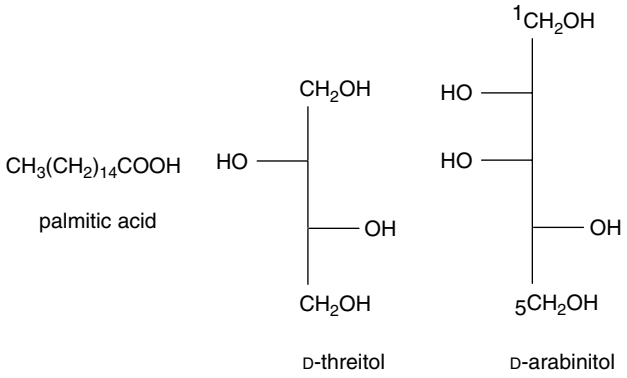

Figure 1. The structures of pure compounds identified in the *Hericium erinaceus* extract.

Statistical analysis

The data are shown as means ± SD. Data from each treatment were subjected to SAS (Version 6.08) for analysis of variance, and Duncan's multiple range test was used to determine significant differences ($p < 0.05$) among treatments.

RESULTS AND DISCUSSION

Identification of compounds

The spectroscopic data for the tested ingredients were as follows:

Palmitic acid

$[\alpha]_D^{25}$ + 2.5 °C, 0.42, MeOH; ^{1}H NMR: (400 MHz, CD3OD, δ in ppm) 2.27 (2 H, t, $\mathcal{J}$ = 7.6 Hz, H-2), 1.60 (2 H, t, $\mathcal{J}$ = 7.2 Hz, H-3), 1.29–1.33 (24 H, m, H-4 ~ H-15), 0.90 (3 H, t, $\mathcal{J}$ = 6.8 Hz, H-16); ^{13}C NMR: (100 MHz, CD3OD, δ in ppm) 177.68 (s, COOH), 35.00 (t, C-2), 33.10 (t, C-3), 30.26 ~ 30.81 (t, C-4 ~ C-13), 26.11 (t, C-14), 23.75 (t, C-15), 14.48 (q, C-16).

D-Threitol

$[\alpha]_D^{25}$ + 54.1 °C, 0.12, MeOH. ^{1}H NMR: (400 MHz, pyridine-*d*5, δ in ppm) 4.49 (2 H, d, $\mathcal{J}$ = 11.0, H-2, H-3), 4.43 (2 H, dd, $\mathcal{J}$ = 7.2, 11.0 Hz, H-1, H-4), 4.36 (2 H, dd, $\mathcal{J}$ = 5.2, 11.0 Hz, H-1, H-4); ^{13}C NMR:

(100 MHz, pyridine-*d*5, δ in ppm) 74.25 (d, C-2), 74.25 (d, C-3), 65.15 (t, C-1), 65.15 (t, C-4). The structure is shown in Fig 1.

D-Arabinitol

^{1}H NMR: (400 MHz, pyridine-*d*5, δ in ppm) 4.84 (1 H, ddd, $\mathcal{J} = 2.0, 6.0, 6.0$ Hz, H-2), 4.62 (1 H, m, H-4), 4.53 (2 H, m, H-1, H-5), 4.39 (1 H, d, $\mathcal{J} = 6.0$, H-3), 4.37 (2 H, d, $\mathcal{J} = 6.0$, H-1, H-5); ^{13}C NMR: (100 MHz, pyridine-*d*5, δ in ppm) 73.38 (d, C-3), 73.01 (d, C-2), 72.25 (d, C-4), 65.37 (t, C-5), 65.00 (t, C-1). The structure is shown in Fig 1.

Effects of extract of *Hericium erinaceus* on the induced-diabetic rats

Food and water intake and urine excretion by the HEM-fed group at a dose rate of 200 mg kg^1 bw were significantly lower than those of the non-HEM-fed group. On day 20, the food intake of the HEM-fed group at a dose rate of 100 mg kg^{-1} bw was 6% less than that for rats in the non-HEM-fed group, but was 4% more than for those in the control group(Fig 2). The food intake of the non-HEM-fed induced-diabetic rats was 11% higher than that of the control group on day 20. On day 20, the water intake of the induced-diabetic rats fed with HEM at a dose rate of 100 mg kg^1 bw was 12% less than that of rats fed with HEM at a dose rate of 20 mg kg^{-1} bw and 20% less than that for rats in the non-HEM-fed group (Fig 3). There was no significant difference ($p > 0.05$) in water intake between the rats fed with HEM (100 mg kg^{-1} bw) and HEM (200 mg kg^{-1} bw). The measurement of urine excretion demonstrated similar results(Fig 4). The differences in both urine excretion and water intake between the non-HEM-fed group and the HEM-fed group were statistically significant ($p < 0.05$). Collectively, these observations were consistent with the role of HEM in improving polydipsia in induced-diabetic rats.[11]

The weight of the rats in the control group increased normally (an average of 1.12 ± 0.07 g daily), while the weight of the induced-diabetic rats not fed HEM decreased by 11.5% after receiving an injection of STZ (Table 1). No significant difference ($p > 0.05$) of body weight was evident between the non-HEM-fed and HEM-fed induced-diabetic rats, at a dose rate of 20 mg kg^{-1} bw. There were, however, significant differences between the groups of non-HEM-fed and HEM-fed at dose rates of 100 and 200 mg kg^{-1} bw ($p < 0.05$). This loss of body weight phenomenon is commonly seen in insulin-independent diabetes.[27] When the HEM dosage given to the STZ-induced rats was increased from 20 to 200 mg kg^{-1} bw, the levels of serum triglycerides were significantly reduced ($p < 0.05$). The doses of 100 and 200 mg kg^{-1} bw could alleviate the incremental increases of serum triglycerides in the induced-diabetic rats. Comparable observations have been documented in other studies.[13,26,28] The HEM-fed group had a significantly lower increase in serum total cholesterol levels than the non-HEM-fed group ($p < 0.05$) and when the dosage of HEM was increased, the difference in serum total cholesterol levels became more significant. A similar pattern was shown in other studies where the serum total cholesterol levels of insulin-dependent rats increased less after they received a diet containing 40 g kg^{-1} *Pleurotus ostreatus* (oyster fungus) and a methanol extract of *Prunus davidiana* stem.[17,29] The primary objective in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) is to achieve normoglycemia, without aggravating coexisting abnormalities. Some measures have been taken to treat NIDDM, such as using fatty acid oxidation inhibitors, lipid-lowering agents and sorbitol inhibitors.[30] The changes in

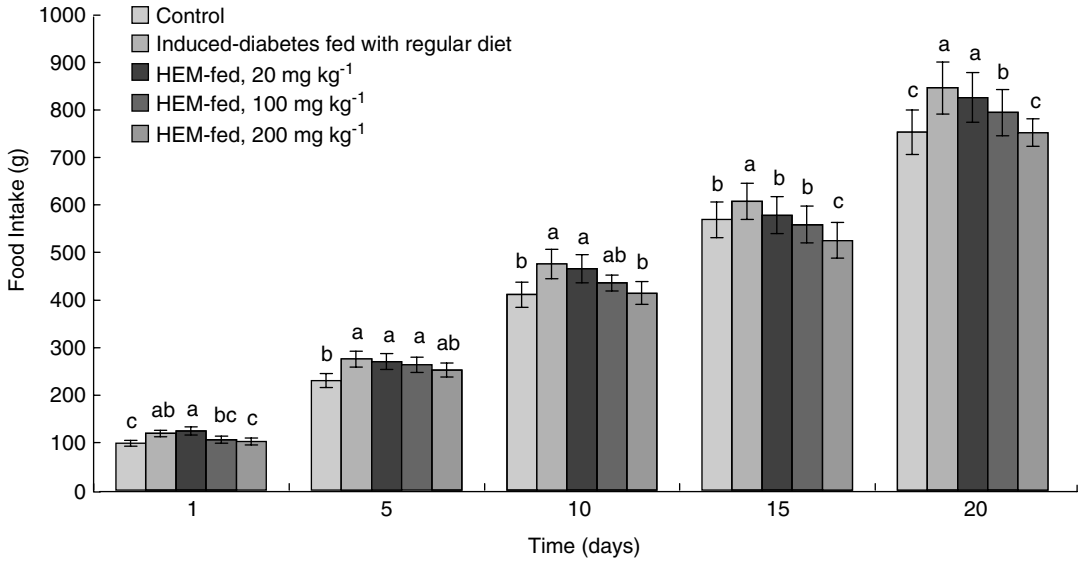

Figure 2. Effect of HEM on food intake in induced-diabetic rats. The normal rats were fed with regular diet as control group. The induced-diabetic rats fed with HEM-free regular diet, and with regular diet containing 20, 100 or 200 mg kg^{-1} HEM daily, respectively. Values with different letters in the same experimental period are significantly different at $p < 0.05$. There were 12 rats in each group.

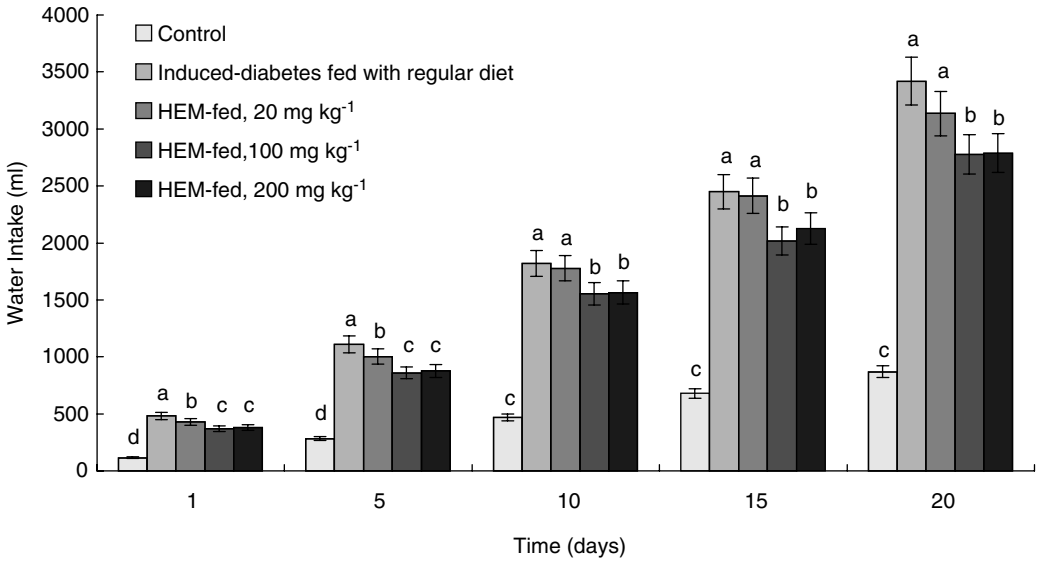

Figure 3. Effect of HEM on water intake in induced-diabetic rats. Experimental mice were fed as described in the legend of Fig 2.

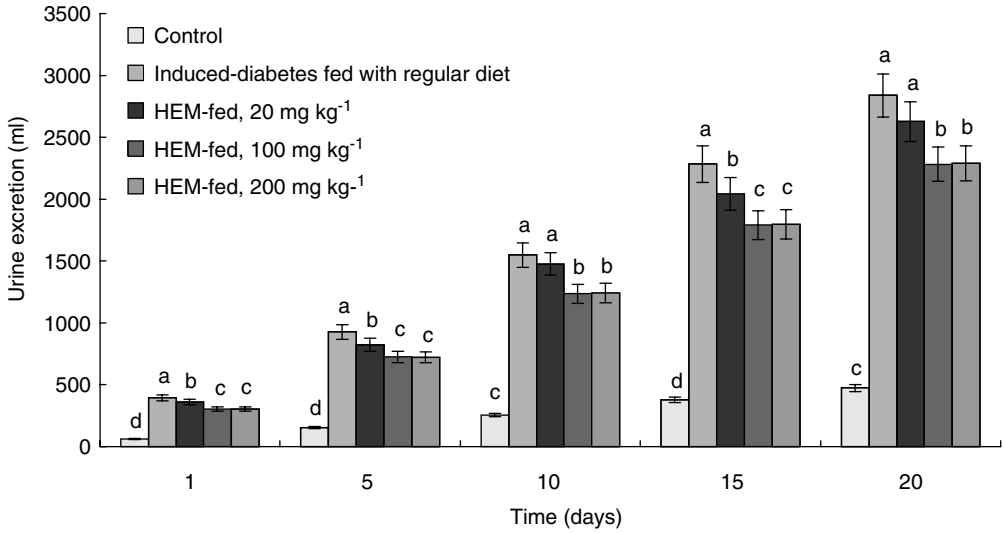

Figure 4. Effect of HEM on urine excretion in induced-diabetic rats. Experimental mice were fed as described in the legend of Fig 2.

Table 1. The changes of body weight, triglyceride and total cholesterol level on day 20 and two days before (day −2) for feeding HEM

	Body weight (g)		Triglyceride (mg dl^{-1})		Total cholesterol (mg dl^{-1})	
	Day −2	Day 20	Day −2	Day 20	Day −2	Day 20
HEM-fed group						
20 mg kg^{-1}	216.2 ± 14.1A[a]	190.3 ± 11.9AB	121.2 ± 8.1A	134.1 ± 8.1A	110.1 ± 6.6A	133.5 ± 8.1A
100 mg kg^{-1}	214.7 ± 12.6A	194.5 ± 12.1BC	120.5 ± 7.2A	127.8 ± 8.1B	108.3 ± 6.8A	123.1 ± 7.7B
200 mg kg^{-1}	215.6 ± 12.3A	197.4 ± 11.8C	122.7 ± 7.3A	125.9 ± 7.8B	107.6 ± 6.7A	120.4 ± 7.5B
Control (–)[b]	216.2 ± 13.1A	187.3 ± 11.4A	123.4 ± 7.7A	156.6 ± 9.8C	107.2 ± 6.3A	134.9 ± 8.4A
Control[c]	228.4 ± 13.5B	252.1 ± 13.9D	60.5 ± 3.7B	61.5 ± 3.8D	67.8 ± 3.9B	70.2 ± 4.2C

[a] The values in a column with different capital letters are significantly different at $p < 0.05$. There were 12 rats in each group.
[b] The control (–) was a induced-diabetic group fed with HEM-free regular diet.
[c] This control was a group of normal rats fed with regular diet.

serum triglyceride and total cholesterol levels were reported in previous studies and also in our study; this phenomenon could be explained by postulating that certain HEM components may affect the regulation of lipid metabolism in induced-diabetic rats.

The changes in blood glucose levels of induced-diabetic rats during administration of HEM are shown in Fig 5. On day 1, blood glucose levels were more than 230 mg dl^{-1}, which was significantly different from the control group ($p < 0.05$). Non-HEM-fed

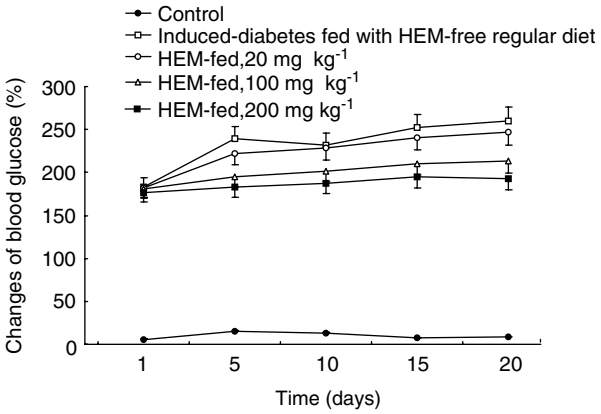

Figure 5. The changes in fasting blood glucose levels of induced-diabetic rats. The changes of blood glucose are indicated as percentage differences from the two days earlier.

induced-diabetic rats had 2.4 times higher blood glucose levels on day 5 than on day −2 and 2.6 times more on day 20. The rates of increase of blood glucose in the HEM-fed rats were significantly lower than those in the non-HEM-fed group ($p < 0.05$). Both the HEM-fed group at a dose rate of 20 mg kg^{-1} bw and the non-HEM-fed induced-diabetic group had increased blood glucose during the experimental period. However, the rates of increase of blood glucose of the HEM-fed group at dose rates of 100 and 200 mg kg^{-1} bw were about 13–18% and 19–26% lower, respectively, than that of the non-HEM-fed group during days 5 through day 20. The rate of increase of blood glucose showed no significant differences ($p > 0.05$) between the HEM-fed rats at dose rates of 100 and 200 mg kg^{-1} bw. Therefore, a dosage of 100 mg kg^{-1} bw would seem to be favorable in reducing the elevation of blood glucose level in induced-diabetic rats. Administration of aqueous extracts of yacon tea (*Smallamtus sonchifolius*) to STZ-induced diabetic rats has reduced the level of blood glucose in rats significantly after 30 days, while increasing the level of insulin in the blood plasma.[31] Similar blood glucose reductions have been shown in diabetic rats while being fed aqueous extracts of *Pandanus odorus*[32] and *Suaeda fruticosa*.[26] Such effects were attributed to extra-pancreatic action,[26] with some activity from enzymes involved in sugar metabolism[33,34] and elevation of insulin levels.[1,35–39] The major components of the HEM used in the present study were D-threitol and D-arabinitol, well-known polyhydroxy alcohols.[25] Some polyols, such as erythritol, threitol, ribitol, arabitol and galactitol are found in mammalian tissue, and these compounds may influence the blood glucose regulation mechanism.[40] Water-soluble polysaccharides (excluding the acidic portion) from the fruiting bodies of *Auricularia auricula-judae* Quel had a significant effect in lowering blood glucose when given to KK-A^y mice.[13,14] However, the use of methanol-extracted polysaccharides from *Psacalium decompositum* in alloxan-diabetic mice produced significant hypoglycemic activities in mildly dlyiabetic mice.[41] A tetrasaccharide from the root of *Amorphophallus konjac* had a hypoglycemic effect on STZ-induced diabetes.[42] Water-soluble mixtures from *H erinaceus* have been found to enhance the immune system and display antitumor activities.[24] A mixture of chemical compounds may be capable of regulating blood glucose, while individual components within the mixture may not be effective.[12] Furthermore, animal model experiments using natural ingredients did not find significant hypoglycemic effects in severely diabetic rats, while more significant effects have been observed in mildly diabetic rats.[1,36,40]

CONCLUSIONS

Previous studies indicated that methanol extracts of *H erinaceus* have the ability to affect physiological activity. In this study, the methanol extract was found not only to have a hypoglycemic effect but also to reduce the elevation rates of serum triglyceride and total cholesterol levels when administered to STZ-induced diabetic rats.

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