International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2017.457.464

Research Article

Vitis thunbergii var. *taiwaniana* Leaf Extract Reduces Blood Glucose Levels in Mice with Streptozotocin-induced Diabetes

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Abstract

Background and Objective: *Vitis thunbergii* var. *taiwaniana* (VTT) is a native folk medicinal plant in Taiwan used to treat hepatitis, jaundice, stomachaches, diarrhea and arthritis. This study aimed to investigate the antidiabetic activity of VTT extracts using a mice model of streptozotocin (STZ)-induced diabetes. **Materials and Methods:** The ICR male mice were received a single i.p., injection of 100 mg kg^{-1} of STZ to induce type 2-like diabetes. Diabetic mice were orally administered with 100 mg kg^{-1} of VTT-leaf alcohol extracts, VTT-stem alcohol extracts, VTT-leaf hot water extracts or VTT-stem hot water extracts five times per week for 4 weeks. In short-term experiments, the mice were orally received with 100 mg kg^{-1} of VTT-leaf or stem hot water extracts once for 180 min. The fasting blood was collected for determining the glucose level and lipid profile. The one-way analysis of variance (ANOVA) was used to determine whether there were any statistically significant differences ($p<0.05$) between the means of three or four independent groups. **Results:** The alcohol extracts of VTT-stem and leaf were used to examine the hypoglycemic activity in STZ-induced diabetic mice. However, these two kinds of VTT alcohol extracts did not have any effects on blood glucose level of diabetic mice. Second, the hot water extracts of VTT-stem and leaf were orally administered to the STZ-induced diabetic mice for 4 weeks. Interestingly, only hot water extracts of VTT-leaf significantly ($p<0.05$) decreased blood glucose level, but the stem extracts did not. In the short-term experiments, the blood glucose level of diabetic mice could be quickly decreased after feeding with hot water extracts of VTT-leaf for 2-3 h. In addition, hot water extracts of VTT-leaf could protect pancreatic β-cells from STZ-induced damage by immunohistochemistry staining. On the other hand, only hot water extracts of VTT-stem could decrease triglyceride level in STZ-induced diabetic mice. **Conclusion:** It is concluded that hot water extracts of VTT-leaf exhibited antidiabetic activity and might be developed as functional food to treat diabetes mellitus in the future.

Key words: *Vitis thunbergii* var. *taiwaniana*, streptozotocin, glucose, pancreatic β-cells, diabetes mellitus

Received: February 06, 2017 Accepted: April 26, 2017 Published: June 15, 2017

Citation: Wan Leung, Feng-Ming Ho, Wen-Pin Li and Yu-Chih Liang, 2017. *Vitis thunbergii* var. *taiwaniana* leaf extract reduces blood glucose levels in mice with streptozotocin-induced diabetes. Int. J. Pharmacol., 13: 457-464.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes Mellitus (DM) is common in many developing and developed countries, a kind of metabolic disorder resulting from defects in insulin secretion, insulin action or both[1]. The main characterization of diabetes is chronic hyperglycemia which is caused by disturbances of carbohydrate, fat and protein metabolism. Type 1 and type 2 diabetes are the main types of diabetes, while other categories of diabetes include gestational diabetes and other rarer causes[1]. Type 1 diabetes is prevalent in childhood and the patients with type 1 diabetes lack insulin secretion and require lifelong insulin therapy for survival[2]. In contrast, type 2 diabetes is prevalent in adults who are usually obese and have unhealthy diets; these patients have detectable insulin secretion but with abnormal action (insulin resistance). Approximately 90% of diabetes worldwide is type 2 diabetes that can be improved by changing one's lifestyle, reducing one's body weight and taking oral medications and insulin injections[3].

High blood glucose levels in type 2 diabetes can be improved by many treatments, including injectable agents, insulin and non-insulin injectable and oral agents, secretagogues, sensitizers and dipeptidyl peptidase IV inhibitors[4,5]. Secretagogues stimulate insulin secretion by cells, decrease hepatic glucose production and ameliorate glucose uptake by skeletal muscles[6]. There are three kinds of sensitizers, including biguanides, thiazolidinediones and α-glucosidase inhibitors[7,8]. The biguanides (e.g., metformin) reduce glucose levels by inhibiting gluconeogenesis and glycogen breakdown and increasing insulin sensitivity. The thiazolidinediones are Peroxisome Proliferator Activated Receptor (PPAR) agonists that increase insulin sensitivity and result in increased glucose uptake by tissues[9]. The α-glucosidase inhibitors decrease the absorption of glucose by inhibiting carbohydrate breakdown in the intestinal tract[10].

Vitis thunbergii var. *taiwaniana* (VTT) is a wild grape originally grown in Taiwan, which has long been used as a folk medicine for treating hepatitis, jaundice, stomachaches, diarrhea and arthritis[11]. *Vitis* species, including VTT are rich in polyphenols, among which oligo stilbenes, quercetin and resveratrol are major components and other minor components are miyabenol C, cis-miyabenol C, α-viniferine, (+)-ϵ-viniferine, ampelopsin C, 3,5-dimethoxy-4-hydroxy-phenyl propanol-9-O-D-glucopyranoside, catechin, dihydrosyringin, resveratrol-3-O-D-glucopyranoside, O-hydroxybenzylglycoside and syringin[11,12]. These polyphenols were found to have various kinds of biological activities, including inhibition of platelet aggregation[13,14], antioxidant activity, scavenging of free radicals[15,16], anti-inflammatory activity[17], antitumor activity[18], antibacterial activity[19], protection of neurons and the cardiovascular system[20], antihypertensive activity[21] and inhibition of adipocyte differentiation[22].

Natural products can improve hyperglycemia in different experimental models through various kinds of molecular mechanisms[23]. The VTT is rich in quercetin and resveratrol, which were found to have beneficial antidiabetic actions. Resveratrol can protect β-cells from damage, improve insulin sensitivity, enhance glucose transporter 4 (GLUT4) translocation, reduce oxidative stress and activate sirtuin1 (SIRT1) and AMP-activated protein kinase (AMPK)[24], while quercetin can improve glucose uptake and insulin resistance[25,26]. While it was unclear whether the VTT extracts have hypoglycemic activity. This study aimed to examine the potential role of VTT in antidiabetic activity and investigate which portions of VTT can potentially be developed as antidiabetic drugs.

MATERIALS AND METHODS

Preparation of VTT extracts: The VTT was kindly obtained from the Taiwan Seed Improvement and Propagation Station (SIPS, Taichung, Taiwan) and was morphologically authenticated by experts at the SIPS. Stem and leaf portions were collected from air-dried whole plants of VTT, dissected into small pieces, separately extracted with hot water or ethanol and filtered as described by Wang *et al.*[27]. The filtrate was evaporated under vacuum yielding corresponding dried extracts.

Induction of diabetes by streptozotocin (STZ) and investigation of hypoglycemic activities of VTT extracts: Male ICR mice (8 weeks old) were purchased from BioLASCO Taiwan (Taipei, Taiwan) and housed in an air-conditioned animal room. All animal experimental procedures were approved by the Institutional Animal Care and Use Committee of Taipei Medical University (LAC-99-0150).

To investigate STZ's (Sigma Chemical, St. Louis, MO) induction of diabetes in mice, starved mice were divided into three groups and received a single i.p., injection of 100, 150 and 200 mg kg^{-1} of fresh STZ prepared in 0.05 M citrate buffer[28] at pH 4.5.

To investigate VTT extracts regulation of blood glucose levels, diabetes was induced in mice with 100 mg kg^{-1} of STZ and then the mice were divided into five groups (with six mice per group). Normal Control (NC) mice and DM control mice were orally administered the vehicle (0.5% carboxymethylcellulose sodium in water), while the other four groups also orally received 100 mg kg^{-1} of VTT-leaf

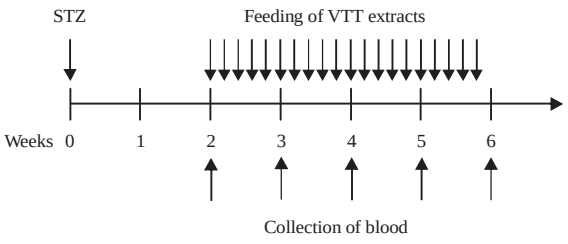

Fig. 1: Experimental schedule of the feeding of VTT extracts and collection of blood in ICR mice with STZ-induced diabetes

alcohol extract, VTT-stem alcohol extract, VTT-leaf hot-water extract or VTT-stem hot-water extract five times per week for 4 weeks (Fig. 1).

Fasting blood (after being starved for 4 h) was collected once per week from the submandibular vein by a cheek pouch technique for 6 weeks, or collected from a tail vein. At the end of the experiment, fasting blood (after being starved for 4 h) was collected via heart puncture under Zoletil 50 (Virbac Taiwan, Taipei, Taiwan) anesthetization. Glucose levels were measured using a GLUCOSE (GLUC-PAP) kit according the manufacturer's manual (RANDOX Laboratories, Antrim, UK), or with an Accu Chek Performa Blood Glucose Meter (Roche Diagnostics, Indianapolis, IN)[29].

Determination of plasma biochemical profiles: Total cholesterol, High Density Lipoprotein Cholesterol (HDLC), Low Density Lipoprotein Cholesterol (LDLC) and tri glycerol (TG) levels were determined by a Hitachi 7600 Automatic Analyzer (Hitachi, Tokyo, Japan)[30].

Immunohistochemical (IHC) staining: Paraffin-embedded mice pancreases were excised and sections were IHC-stained with an anti-insulin antibody (Santa Cruz Biotechnology, Santa Cruz, CA) by a Ultravision Detection System (Thermo Fisher Scientific, Fremont, CA) and counterstained with Mayer's hematoxylin[31].

Statistical analysis: All animal experimental data were analyzed by a one-way analysis of variance (ANOVA) followed by Dunnett's multiple-comparison test[27,29]. Data were expressed as the Mean±Standard Deviation (SD) and differences were considered significant at $p<0.05$.

RESULTS

Induction of type 2-like diabetes by an appropriate concentration of STZ: Eight weeks old male ICR mice were intraperitoneally injected with 100, 150 and 200 mg kg^{-1} of

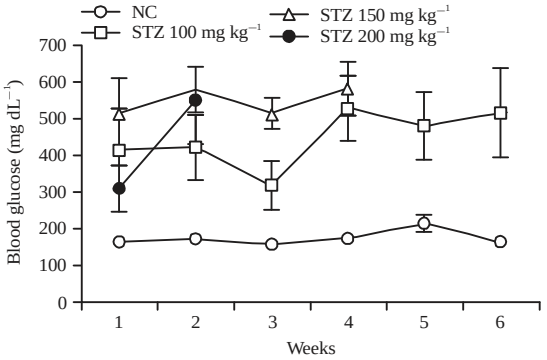

Fig. 2: Effects of different concentrations of STZ on the induction of diabetes in ICR mice
Glucose levels are presented as the Mean±SD

STZ and fasting blood was collected once per week from 2-6 weeks after the STZ injection. Blood glucose levels of control normal mice remained in the range of 160-220 mg dL^{-1}, however, mice treated with various concentrations of STZ had higher blood glucose levels than control normal mice (Fig. 2). Injection of 100 mg kg^{-1} STZ significantly increased blood glucose levels to about 320-531 mg dL^{-1} during the 6 weeks period after the STZ injection. Although, 150 and 200 mg kg^{-1} STZ markedly induced high blood glucose levels, all mice died at weeks 2 and 4 when they were injected with 150 and 200 mg kg^{-1} STZ, respectively. Therefore, this model was used to examine the hypoglycemic activity of VTT extracts in subsequent experiments.

Hot-water extracts of VTT-leaves downregulated blood glucose levels in mice with STZ-induced diabetes: Two weeks after the 100 mg kg^{-1} STZ injection, diabetic mice were orally administered either VTT-leaf or VTT-stem extracts for 3-4 weeks. Average blood glucose levels significantly increased to a range of 558,633.2-661,139.1 mg dL^{-1} in mice with STZ-induced diabetes. Additional alcohol extracts of VTT-leaves and VTT-stems did not alter blood glucose levels in mice with STZ-induced diabetes (Fig. 3a, b). Hot-water extracts of VTT-leaves significantly ($p<0.05$) downregulated blood glucose levels in 1-4 weeks after the STZ injection, while hot-water extracts of VTT-stems reduced blood glucose levels only at 4 week after the STZ injection (Fig. 3c). To examine whether VTT hot-water extracts had short-term effects on regulating blood glucose levels, mice with STZ-induced diabetes were either starved for 4 h or fed normally and then given VTT hot-water extracts for 180 min. Blood glucose levels of starved mice and normally fed mice remained in the range of 489.6±38.5 to 519.6±45.8 and 501.8±28.0 to 573.0±31.2 mg dL^{-1}, respectively, over a period

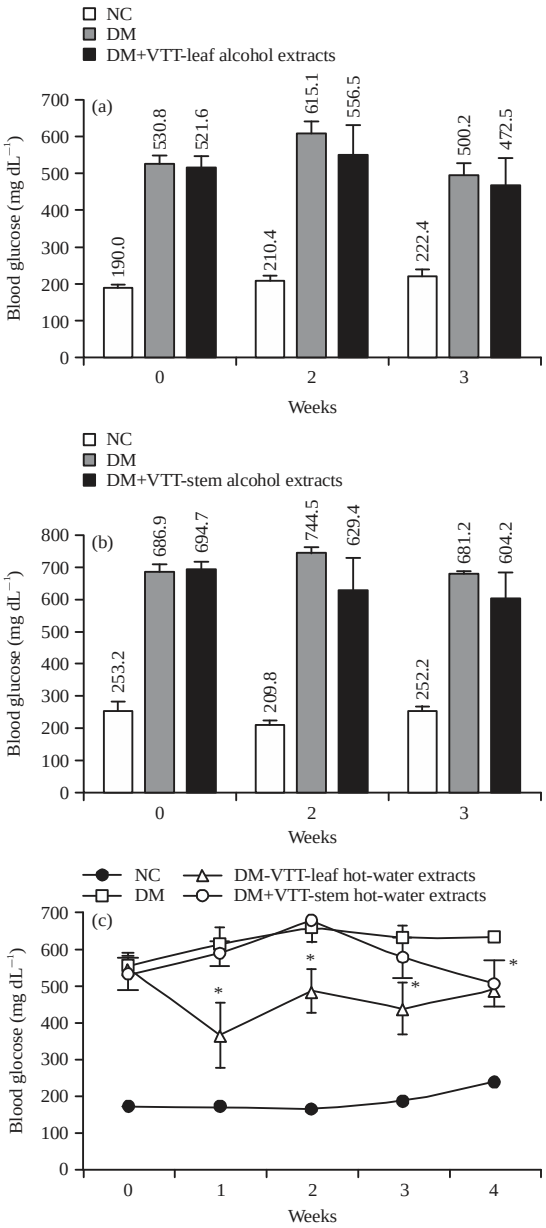

Fig. 3(a-c): Long-term effects of different kinds of VTT extracts on blood glucose levels in mice with STZ-induced diabetes

*p<0.05 vs. mice with STZ-induced diabetes, NC: Normal control mice, DM: Diabetic mice

of 180 min in mice with STZ-induced diabetes (Fig. 4). Additional hot-water extracts of VTT-leaves gradually decreased blood glucose levels to 359.6±43.5 and 426.0±20.6 mg dL^{-1} in starved mice and normally fed mice, respectively, at 180 min after treatment. However, hot-water extracts of VTT-stems had no significant effect on downregulating blood glucose levels. These results suggest that hot-water extracts of VTT-leaves have

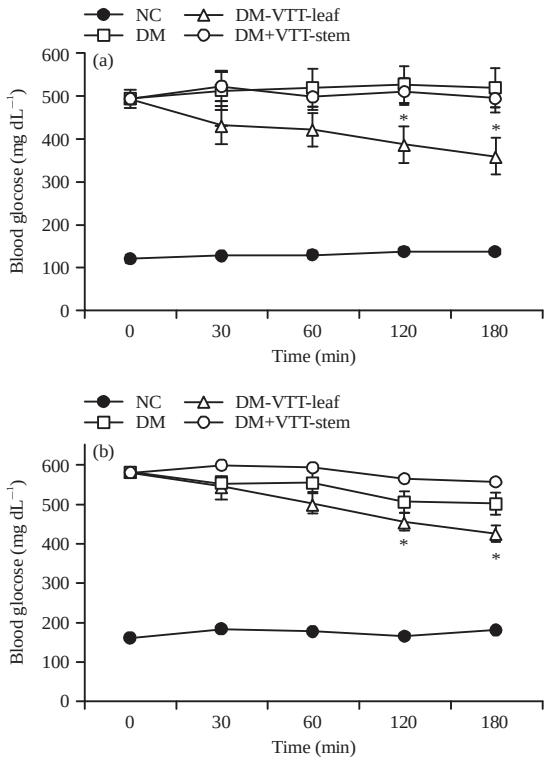

Fig. 4(a-b): Short-term effects of VTT hot-water extracts on blood glucose levels in mice with STZ-induced diabetes

*p<0.05 vs. mice with STZ-induced diabetes, NC: Normal control mice, DM: Diabetic mice

both long and short-term effects on downregulating blood glucose levels in mice with STZ-induced diabetes.

Hot-water extracts of VTT-leaves reversed β-cell declines in mice with STZ-induced diabetes: To examine whether the VTT hot-water extract can improve hyperglycemia through protection of or an increase the number of β-cells, pancreatic tissues were used to perform IHC staining with an anti-insulin antibody. When viewed through a microscope (Olympus CK30, Japan) at 100x magnification, each field contained about 2-3, 0-1, 1-2 and 0-1 islets of Langerhans in control normal mice, mice with STZ-induced diabetes, mice with STZ-induced diabetes and hot-water extracts of VTT-leaves and mice with STZ-induced diabetes and hot-water extracts of VTT-stems, respectively. The STZ at the dose of 100 mg kg^{-1} caused significant declines in β-cell numbers and the β-cells maintain in a reasonable low numbers (Fig. 5), indicating that the mice were considered to have type II-like diabetes. Treatment with hot-water extracts of VTT-leaves increased β-cell numbers and insulin levels by about 2.5-fold compared

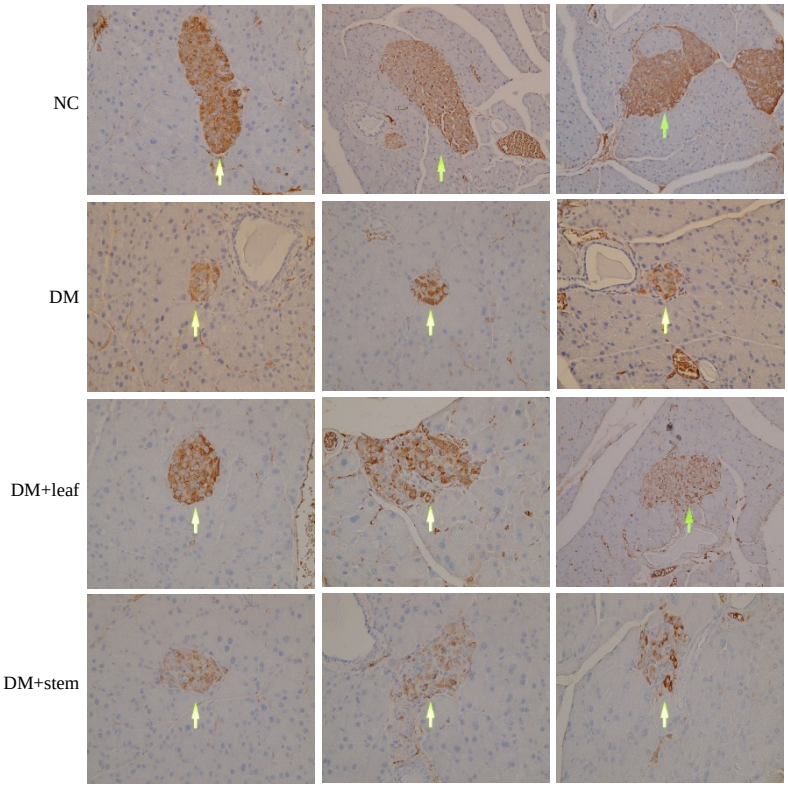

Fig. 5: Long-term effects of VTT hot-water extracts on histopathological changes of pancreatic cells in mice with STZ-induced diabetes

Yellow arrows indicate β-cells, NC: Normal control mice, DM: Diabetic mice

to mice treated with STZ. Treatment with hot-water extracts of VTT-stems only slightly increased β-cell numbers and insulin levels compared to mice treated with STZ (Fig. 5). These results suggested that the decreased blood glucose levels by hot-water extracts of VTT-leaves might be mediated through protecting β-cells from STZ-caused damage.

Hot-water extracts of VTT-stems reduced blood TG levels in mice with STZ-induced diabetes: Besides the blood glucose level, the lipid profiles were determined in STZ-treated mice and STZ-treated mice with VTT hot-water extracts. After orally administering hot-water extracts of VTT-leaves or VTT-stems for 4 weeks, fasting blood samples were collected to determine levels of total cholesterol, tri glycerol (TG), High Density Lipoprotein Cholesterol (HDLC) and Low Density Lipoprotein Cholesterol (LDLC). The mice with STZ-induced diabetes exhibited no changes in levels of total cholesterol or LDLC, but a decrease in the HDLC level and an increase in the TG level (Fig. 6). Compared to STZ-treated mice, the addition of hot-water extracts of VTT-stems decreased levels of total cholesterol and HDLC, but they did not reach a significant level ($p<0.05$) and hot-water extracts of VTT-leaves had no effects on cholesterol levels. Interestingly, mice with STZ-induced diabetes exhibited higher TG levels than control normal mice and the addition of hot-water extracts of VTT-stems decreased TG levels induced by STZ. These results suggested that hot-water extracts of VTT-stems might have the potential to be developed as an anti-TG drug in the future.

DISCUSSION

The VTT is a native plant to Taiwan and has long been used as a folk medicine. In particular, its rhizome is widely used to treat certain types of diseases, such as inflammatory diseases like arthritis and hepatitis. In this study, VTT-stems and leaves were used to examine the hypoglycemic activity in mice with STZ-induced diabetes. Approximately 100 mg kg^{-1} STZ-induced ICR mice were found to develop a condition similar to type 2 diabetes, which is characterized by a lack of sufficient amounts of insulin and/or the occurrence of insulin resistance. Alcohol extracts of three kinds of VTT tissues had no significant effect on reducing blood glucose levels in mice with STZ-induced diabetes. Hot-water extracts of VTT-stems also failed to decrease blood glucose levels. However,

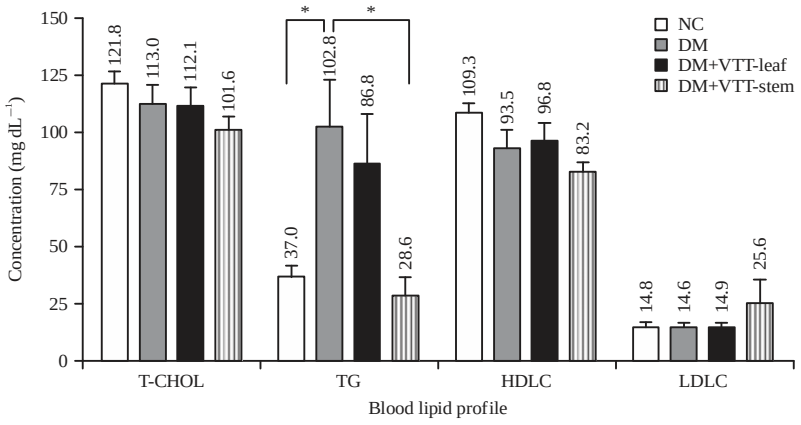

Fig. 6: Long-term effects of VTT hot-water extracts on blood cholesterol and tri glycerol levels in mice with STZ-induced diabetes
*p<0.05, NC group vs. DM group as well as DM group vs. DM+VTT-stem group. T-CHOL: Total cholesterol, TG: Tri glycerol, HDLC: High density lipoprotein cholesterol, LDLC: Low density lipoprotein cholesterol

hot-water extracts of VTT-leaves improved hyperglycemia in both short and long-term experiments in mice with STZ-induced diabetes. These results suggest that VTT-leaves might be developed as an antidiabetic herbal medicine for treating or preventing high glucose levels.

The VTT contains many phenolic compounds which were found to have antidiabetic activities, such as quercetin[25], resveratrol[32], luteolin-7-O-glucoside[30] and cinnamic acid[33]. Resveratrol, in particular, was pointed out to be the most important component for improving hyperglycemia through different molecular mechanisms. Resveratrol can improve hyperglycemia as mediated by its insulin-like effect[34], increasing insulin sensitivity through activation of Akt or the PPAR[35,36], increasing glucose uptake by enhancing GLUT4 translocation to cell membranes[37] and protecting cells from STZ-induced apoptosis[38]. According to Kowalczyk *et al.*[39] phenolic compounds could be extracted more by alcohol than hot water. However, results showed that alcohol extracts of VTT did not improve hyperglycemia, but hot-water extracts of VTT-leaves did. As to the components of VTT extracts, the alcohol and hot-water extracts of VTT have been analyzed by electrospray ionization (ESI) mass spectrometer or High Performance Liquid Chromatography (HPLC) in different laboratories[27,40]. Alcohol extracts of VTT contain more stilbene, quercetin and phenolic acids and no resveratrol in such analysis[27]. On the other hand, resveratrol was found in hot-water extracts of VTT[40]. Therefore, the antidiabetic activity of VTT hot-water extracts might be associated with the presence of resveratrol. However, the possibility that other components in hot-water extracts of VTT contribute to the hypoglycemic activity cannot be ruled out.

In this study, long-term feeding of VTT-leaf hot-water extracts were found to improve hyperglycemia (Fig. 3) and maintained a higher number of β-cells than in STZ-treated mice (Fig. 5). The diabetogenicity of STZ has been linked to free radical generation and breakage of DNA strands by STZ, which consequently causes β-cell toxicity[41]. These hypotheses were confirmed by several *in vivo* studies, which demonstrated that the administration of antioxidants (e.g., superoxide dismutase) and a free radical scavenger (α-phenyl-tert-butylnitrone) ameliorated the severity of STZ-induced diabetes[42,43]. The VTT extracts contain many polyphenolic compounds that are known to be strong free radical scavengers. The protection of VTT-leaf extracts on β-cells might be mediated by decreasing free radical generation by STZ and the survival of small numbers of β-cells contributes to reducing blood glucose levels. On the other hand, hot-water extracts of VTT-leaves was found to have a short-term effect of reducing blood glucose levels in mice with STZ-induced diabetes. These results indicated that hot-water extracts of VTT-leaves might have insulin-like activity to increase glucose uptake by cells. Since several polyphenolic compounds, such as grape seed-derived procyanidins[44], myricetin-3-O-rhamnoside[45], epicatechin[46] and resveratrol[34] were found to have insulin mimetic activity and therefore, had antihyperglycemic activity.

CONCLUSION

In this study, ICR male mice were received a single i.p., injection of 100 mg kg^{-1} of STZ to induce type 2-like diabetes. Long-term and short-term treatments of hot-water extracts of VTT-leaves could improve the hyperglycemia, suggesting hot-water extracts of VTT-leaves might protect β-cells from STZ-induced damage and exhibit insulin-like activity, respectively. Therefore, the hot water extracts of VTT-leaf

might be developed as functional food to lower blood glucose level in the person with early stage of diabetes mellitus or further developed into drug for treatment of patients with diabetes mellitus.

SIGNIFICANCE STATEMENTS

- In this study, hot water extracts of VTT-leaf was found to decrease the blood glucose level in diabetic mice and might be beneficial in the prevention and treatment of DM patients in the future
- Diabetes Mellitus (DM) is an important global health issue and the tight control of blood glucose level will help prevent the complications
- *Vitis thunbergii* var. *taiwaniana* (VTT) has long been used as a folk medicine in Taiwan

ACKNOWLEDGMENTS

The author would like to thank the Ministry of Science and Technology of the Republic of China (MOST 104-2320-B-038-035) and Yuan's General Hospital (104YGH-TMU-03) for funding this study.

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