

Hypoglycemic and hypolipidemic effects of flavonoids from tatar buckwheat in type 2 diabetic rats.

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Abstract

Present study was designed to evaluate hypoglycemic and hypolipidemic effects of flavonoids from tatar buckwheat (TBF) in type 2 diabetic rats induced by combination of high-fat diet and streptozotocin injection. After induction of type 2 diabetes, diabetic rats were randomly divided into five groups: diabetic control group, low-dose TBF treated group, middle-dose TBF treated group, high -dose TBF treated group, and glibenclamide treated group, with normal rats used as the control group. After treatment for 28 days, body weight, fasting blood glucose (FBG), serum insulin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were measured and oral glucose tolerance test (OGTT) was performed. The results showed that TBF significantly decreased FBG and serum insulin levels, increased body weights and improved glucose intolerance in diabetic rats. Furthermore, it decreased TC, TG, and LDL-C levels and increased HDL-C levels in these rats. These evidences indicated that TBF possesses hypoglycemic and hypolipidemic effects in type 2 diabetic rats and suggested that TBF has the potential to be a candidate for investigation as an anti-diabetic agent in humans.

Keywords: Hypoglycemic, Hypolipidemic, Type 2 diabetes, Flavonoids from tatar buckwheat, Rats.

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Introduction

Diabetes mellitus is a hereditary, chronic disorder in the endocrine system that constitutes a major public health problem throughout the world [1]. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism [2,3]. As a consequence of the metabolic derangements in diabetes, many complications develop including hyperlipidemia, hyperinsulinemia, hypertension, and atherosclerosis [4]. Diabetes mellitus is classified into two major categories: type 1 diabetes (formerly known as insulin dependent diabetes mellitus or IDDM) and type 2 diabetes (formerly known as non-insulin dependent diabetes mellitus or NIDDM) [5]. A worldwide survey has reported that 143 million people in the world live with diabetes and this number will probably double by the year 2030 [6]. Over 90% percent of diabetic patients are diagnosed with type 2 diabetes [7]. Type 2 diabetes, often associated with obesity, high blood glucose, blood lipid abnormalities, mainly increase levels of TC, TG, LDL-C, serum insulin and decrease levels of HDL-C, which lead to a series of complications. Different types of oral hypoglycaemic

agents such as biguanides and sulphonylurea are available along with insulin for the treatment of diabetes mellitus but have side effects associated with their uses [8]. Therefore, there is an urgent need to search for the drugs of a natural origin with fewer side effects. Flavonoids, a class of natural drugs with high biological activity are abundant in plants. They are reported to have protective effects against the development of diabetes as well as a mitigation effect of diabetes consequences [9].

Buckwheat, also called triangle wheat, belongs to the family Polygonaceae, genus *Fagopyrum* Meisn [10]. There are 15 kinds of species in the *Fagopyrum* family and only common buckwheat (*Fagopyrum esculentum*) and tartary buckwheat (*Fagopyrum tataricum*) are cultured species. Tartary buckwheat originated in eastern Tibet or northwestern Yunnan in China and is grown only in Asia, Europe and North America [11]. As an important functional food material, tartary buckwheat grain contains proteins with high biological value and balanced amino acid composition, relatively high crude fiber and vitamins B₁, B₂, and B₆ and more flavonoids than common buckwheat [12]. The flavonoids content was 40 mg/g in tartary buckwheat seeds while it was 10

mg/g in common buckwheat seeds [13]. Flavonoids from tatar buckwheat (TBF) mainly include rutin, quercetin, orienin, vitexin, isovitexin, isoorientin, protocathechuic acid, and hyperin [14]. It has been reported that TBF exhibit multiple pharmacological activities such as anti-hypertensive, antioxidant, anti-hypercholesterolemia, anti-cancer and neuroprotection functions [10]. However, few studies have examined the therapeutic effects of TBF on diabetes mellitus. The present investigation was aimed at evaluating the hypoglycemic and hypolipidemic effects of TBF in diabetic rats induced by combination of high-fat diet and streptozotocin injection.

Materials and Methods

Plant Material

The air-dried tartary buckwheat grains were purchased from Liangshan agricultural institution (Sichuan, China) and identified by Professor Zhong Zhang, Xichang College (XiChang, China). Voucher specimens were deposited at the herbarium of Xichang College. The plant materials were ground into a coarse powder with the help of a suitable grinder. The powder was stored in an airtight container and kept in a cool, dark and dry place before experiment.

Chemicals and Reagents

Streptozotocin (STZ) was purchased from Sigma Chemical Co. (St. Louis, Mo, USA). Glibenclamide was purchased from Shandong Boshan Pharmaceutical Co., Ltd. (Zibo, China). The kits for triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were purchased from the Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Insulin ELISA kits were purchased from Pumai Biotechnology Co., Ltd. (Shanghai, China). Glucose analyzer and strips were purchased from Roche Diagnostics (Shanghai) Co., Ltd. (Shanghai, China). All of the other chemicals and reagents were standard commercially available biochemical quality. Triple distilled water was used in all experiments.

Animals and Breeding Conditions

Male Sprague Dawley rats, weighing 180-220 g were obtained from the Experimental Animal Center of Sichuan University (Chengdu, China). The animals were housed in a room kept under controlled conditions with temperature maintained at 22°C to 25°C on a 12 h light: 12-h dark cycle, diet and water were supplied *ad libitum*. All experiments and protocols described in present study were approved by the Institutional Animal Ethics Committee of XiChang College.

Preparations of Flavonoids from Tatar Buckwheat

The flavonoids from tatar buckwheat (TBF) were prepared as previously described [10, 15] with a few modifications. Briefly about 10.0 g of the ground powder was mixed with 400 ml ethanol-water (60:40, v/v) in a

sealed vessel and then placed in a microwave extraction apparatus (WF-4000C, PreeKem Scientific Instruments Co., Ltd., Shanghai, China). The extraction temperature was 70°C, extraction time was 20 min and microwave power was 600 W. After that, the extract was centrifuged at $1,509 \times g$ for 10 min to remove the insoluble and the supernatant was filtrated through 0.45 mm of filter membrane to obtain a clarified solution. The filtrate was collected and evaporated with a rotary evaporator at 40°C until the sediment was formed. After being collected and vacuum-dried at 40°C, the sediment was rightly the solid-state product of TBF. The flavonoids contents were determined using the aluminium nitrate methods of colorimetry with rutin as a standard and the content of total flavonoids was 27.97 mg/g.

Establishment of Type 2 Diabetes Model

After adaptation to a new environment for 7 days, the rats were fed with high-fat diet (45% fat, 35% carbohydrate, and 20% protein) for 4 weeks. After the animals overnight fasting (deprived of food for 16 hours but allowed free access to water), diabetes was induced through intraperitoneal (ip) administration of STZ at a dose of 60 mg/kg body weight. STZ was freshly prepared in an ice-cold citrate buffer (0.1M citric acid, pH 4.5) and immediately injected into the animals (within 5 min) [16]. After 72 h of injection, the blood samples were collected for measurement of blood glucose from the tail vein. The blood glucose level of over 11.1 mmol/L was defined as type 2 diabetes model.

Experimental Design and Treatment

After confirmation of the diabetic state, the diabetic rats were randomly divided into five groups (12 rats per group) and normal rats were used as the control group.

Normal control group (NC): normal rats were allowed to free access to a normal diet (12% fat, 60% carbohydrate, and 28% protein) and treated with distilled water (2.5 ml) for 28 days.

Diabetic control group (DC): diabetic rats were allowed to free access to a high-fat diet and treated with distilled water (2.5 ml) for 28 days.

Low-dose TBF treated group (LTT): diabetic rats were allowed to free access to a high-fat diet and treated with TBF solution (100 mg/kg) for 28 days.

Middle -dose TBF treated group (MTT): diabetic rats were allowed to free access to a high-fat diet and treated with TBF solution (200 mg/kg) for 28 days.

High-dose TBF treated group (HTT): diabetic rats were allowed to free access to a high-fat diet and treated with TBF solution (400 mg/kg) for 28 days.

Glibenclamide treated group (GT): diabetic rats were allowed to free access to a high-fat diet and treated with glibenclamide solution (4 mg/kg) for 28 days.

Treatments were administered by oral gavage. TBF and glibenclamide solution were prepared through dissolving it in 2.5 ml distilled water. The dose selected in this study based on the preliminary experiment.

Biochemical Assays

During experiments, the body weight and fasting blood glucose (FBG) levels were measured for once every week. Blood was collected from the tail vein (starting from 9:00 a.m.) after a 12-14 h overnight fast. On the last day of experiment, oral glucose tolerance test (OGTT) was performed after overnight fasting. Blood was collected at 0, 30, 60 and 120 min after an oral glucose load of 3.0 g/kg of body weight [17]. Following completion of the experiment, the rats were sacrificed by cervical decapitation under anesthesia with sodium pentobarbital (40 mg/kg, ip). Blood was collected in polystyrene tubes without the anticoagulant. Serum was immediately separated by centrifugation at $1,509 \times g$ at room temperature for 10 min. Samples were stored at -20°C for the assay of TC, TG, HDL-C, LDL-C and serum insulin. TC level was determined using cholesterol oxidase phenol 4-aminoantipyrine peroxidase method. TG level was measured using glycerol-3-phosphate oxidase p-aminophenol method. LDL-C level was determined using polyvinyl sulfate method. HDL-C level was measured using phospho-wolframic acid magnesium precipitation method. Insulin level was measured using enzyme-linked immunosorbent assay method.

Statistical Analysis

All Data are presented as mean \pm SD and assessed with one-way analysis of variance (ANOVA) followed by Fisher's least-significant difference (LSD). Differences with a value of $P < 0.05$ were considered to indicate a statistically significant difference. Data were analyzed by SPSS for Windows, version 13.0 (SPSS Inc, Chicago).

Results

Effect of TBF on Body Weights of Rats

As shown in Figure 1, prior to the experiment (0 days), the body weights were not significantly different among diabetic groups ($P > 0.05$). Compared with the NC group, body weights in the DC group were significantly higher ($P < 0.05$). After 28 days of administration, body weights showed increasing trend in the LTT, MTT, HTT and GT groups and compared with the DC group, body weights in the MTT, HTT, and GT groups were significantly higher ($P < 0.05$), the increase ratios were 11.46%, 13.44% and 10.48%, respectively. So, a clear dose-dependent increase in body weights after TBF treatment was observed.

Effect of TBF on FBG Levels of Rats

As shown in Figure 2, prior to the experiment (0 days), there was no significant difference in the FBG levels among diabetic groups ($P > 0.05$). They were consistently at similar levels throughout the course of the experiment

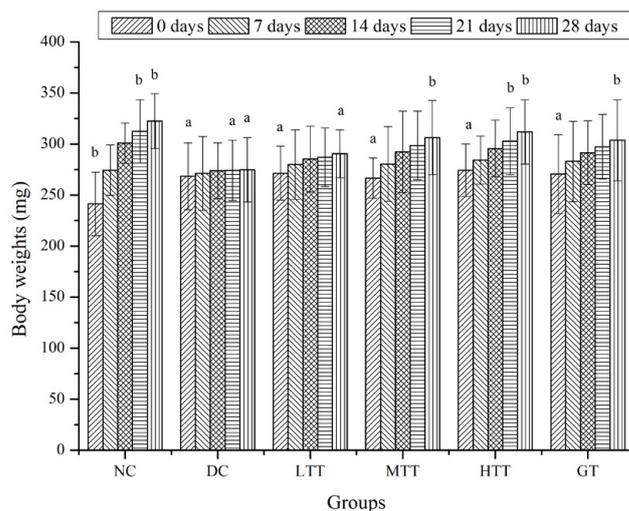


Figure 1. Effect of TBF on body weights of rats

Data is presented as mean \pm SD. NC group: normal control group, DC group: diabetic control group, LTT group: low-dose TBF (100 mg/kg) treated group, MTT group: middle-dose TBF (200 mg/kg) treated group, HTT group: high-dose TBF (400 mg/kg) treated group, GT group: glibenclamide (4 mg/kg) treated group. ^a $P < 0.05$ as compared with normal control (NC) group. ^b $P < 0.05$ as compared with the diabetic control (DC) group.

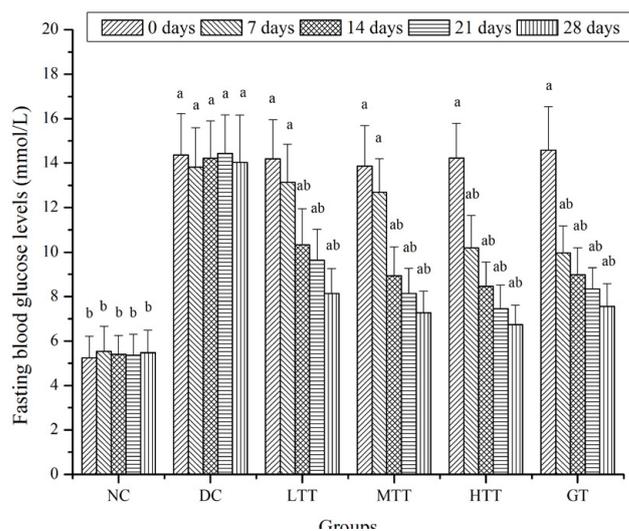


Figure 2. Effect of TBF on FBG levels of rats

Data are presented as mean \pm SD. NC group: normal control group, DC group: diabetic control group, LTT group: low-dose TBF (100 mg/kg) treated group, MTT group: middle-dose TBF (200 mg/kg) treated group, HTT group: high-dose TBF (400 mg/kg) treated group, GT group: glibenclamide (4 mg/kg) treated group. ^a $P < 0.05$ as compared with normal control (NC) group. ^b $P < 0.05$ as compared with the diabetic control (DC) group.

in the NC and DC groups. After 7 days of administration, FBG levels were found to be significantly lower in the HTT and GT groups than the DC group ($P < 0.05$) and the decrease ratios were 35.62% and 38.76% respectively. After 14 days of administration, FBG levels were found to be significantly lower in the LTT, MTT, HTT, and GT

groups than the DC group ($P < 0.05$) and the decrease ratios were 37.69%, 65.96%, 67.97% and 58.27% respectively. After 28 days of administration, FBG levels showed a decreasing trend in the LTT, MTT, HTT, and GT groups and the decrease ratios were 72.36%, 92.72%, 108.16% and 85.58%, respectively. So, a clear dose-dependent decrease in FBG levels after TBF treatment was observed. However, after 28 days of administration, FBG levels remained significantly increased when compared with the NC group ($P < 0.05$).

Effect of TBF on Glucose Tolerance of Rats

As shown in Figure 3, in all groups, blood glucose levels reached peak at 30 min after glucose administration and then the glucose levels started to decline. Blood glucose levels in the LTT, MTT, HTT and GT groups were significantly lower than those of the DC group at 30 min ($P < 0.05$) and the decrease ratios were 28.81%, 43.07%, 52.58% and 60.99% respectively. Blood glucose levels in the LTT, MTT, HTT and GT groups were significantly lower than those of the DC group at 60 min ($P < 0.05$) and the decrease ratios were 54.45%, 58.62%, 91.48% and 78.01% respectively. Blood glucose levels in the LTT, MTT, HTT and GT groups were significantly lower ($P < 0.05$) than those of the DC group at 120 min and the decrease ratios were 71.16%, 101.44%, 123.08% and 93.92%, respectively. So, a clear dose-dependent decrease in blood glucose levels at different time intervals (0, 30, 60 and 120 min) after TBF treatment was observed.

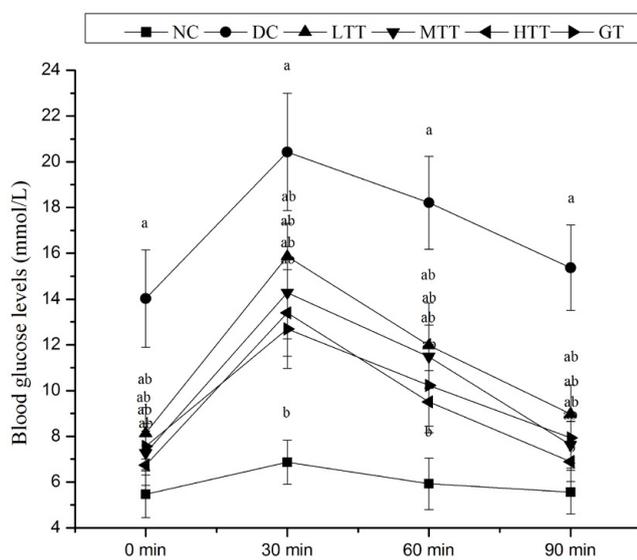


Figure 3. Effect of TBF on glucose tolerance of rats
The glucose tolerance was measured at 28 days. Data are presented as mean \pm SD NC group: normal control group, DC group: diabetic control group, LTT group: low-dose TBF (100 mg/kg) treated group, MTT group: middle-dose TBF (200 mg/kg) treated group group, HTT group: high-dose TBF (400 mg/kg) treated group group, GT group: glibenclamide (4 mg/kg) treated group. ^a $P < 0.05$ as compared with normal control (NC) group. ^b $P < 0.05$ as compared with the diabetic control (DC) group.

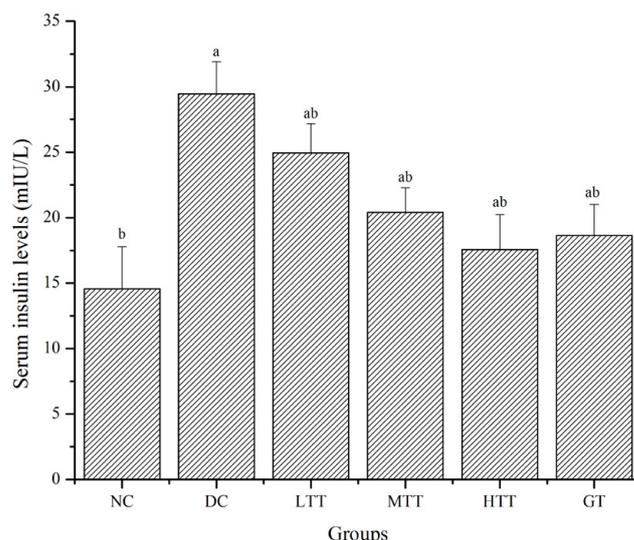


Figure 4. Effect of TBF on serum insulin levels of rats
The serum insulin level was measured at 28 days. Data are presented as mean \pm SD. NC group: normal control group, DC group: diabetic control group, LTT group: low-dose TBF (100 mg/kg) treated group, MTT group: middle-dose TBF (200 mg/kg) treated group group, HTT group: high-dose TBF (400 mg/kg) treated group, GT group: glibenclamide (4 mg/kg) treated group. ^a $P < 0.05$ as compared with normal control (NC) group. ^b $P < 0.05$ as compared with the diabetic control (DC) group.

However, blood glucose levels in the LTT, MTT, HTT and GT groups were significantly higher than those of the NC group at different time intervals ($P < 0.05$).

Effect of TBF on Serum Insulin Levels of Rats

As shown in Figure 4, serum insulin levels in the LTT, MTT, HTT and GT groups were significantly decreased when compared with the DC groups ($P < 0.05$) and the decrease ratios were 18.08%, 44.43%, 67.62% and 58.08%, respectively. So, a clear dose-dependent decrease in FBG levels after TBF treatment was observed. However, serum insulin levels in the LTT, MTT, HTT and GT groups were significantly increased when compared with the NC groups ($P < 0.05$).

Effects of TBF on Serum Lipids Levels in Rats

As shown in Figure 5, TC levels in the LTT, MTT, HTT and GT groups were significantly decreased when compared with the DC groups ($P < 0.05$) and the decrease ratios were 30.47%, 51.54%, 89.32% and 56.37% respectively. TG levels in the LTT, MTT, HTT and GT groups were significantly decreased when compared with the DC groups ($P < 0.05$) and the decrease ratios were 58.02%, 91.04%, 118.80% and 141.51% respectively. LDL-C levels in the MTT, HTT and GT groups were significantly decreased when compared with the DC groups ($P < 0.05$) and the decrease ratios were 24.29%, 59.73% and 77.39% respectively. So, a clear dose-dependent decrease in TC, TG and LDL-C levels after TBF treatment was observed. However, TC, TG and LDL-C levels in the LTT, MTT, HTT and GT groups were significantly increased when compared with the NC groups ($P < 0.05$). HDL-C levels

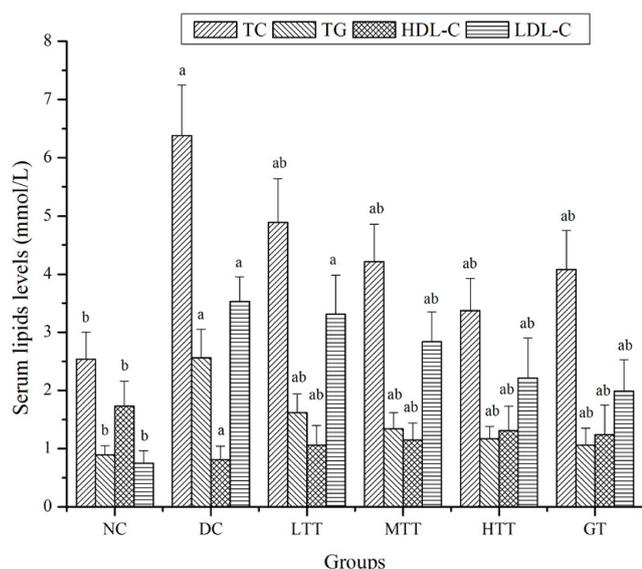


Figure 5. Effects of TBF on serum lipids levels in rats. The serum lipids levels was measured at 28 days. Data are presented as mean \pm SD. NC group: normal control group, DC group: diabetic control group, LTT group: low-dose TBF (100 mg/kg) treated group, MTT group: middle-dose TBF (200 mg/kg) treated group, HTT group: high-dose TBF (400 mg/kg) treated group, GT group: glibenclamide (4 mg/kg) treated group. ^a $P < 0.05$ as compared with normal control (NC) group. ^b $P < 0.05$ as compared with the diabetic control (DC) group.

in the LTT, MTT, HTT and GT groups were significantly increased when compared with the DC groups ($P < 0.05$), and the increase ratios were 30.86%, 41.96%, 61.73% and 53.07% respectively. So, a clear dose-dependent increase in HDL-C levels after TBF treatment was observed. However, HDL-C levels in the LTT, MTT, HTT and GT groups were significantly decreased when compared with the NC groups ($P < 0.05$).

Discussion

Type 2 diabetes is a heterogeneous disorder characterized by hyperglycemia and insulin resistance [18]. Previous studies have shown that insulin resistance may be caused by an excess nutrient supply and low-dose STZ injection leads to the partial destruction of pancreatic beta cells and a high-fat diet induces insulin resistance in rats [19]. In this study, high-fat diet-fed and low-dose STZ-injected rat were used as an animal model for type 2 diabetes and high FBG and serum insulin levels in the animal model were observed, showing that the type 2 diabetes model had been induced.

STZ-induced diabetes was characterized by a severe loss in body weight, and this reduction in body weight is due to the loss or degradation of structural proteins, since structural proteins are known to contribute to the body weight [20]. In this study, TBF increased the body weights in diabetic rats. These results indicate that TBF can attenuate the toxicity of STZ, which might be as a result of its ability to reduce hyperglycemia. Effective control of the blood glucose level is important in preventing or reversing

diabetes complications and improving the quality of life in type 2 diabetes patients [21]. In this study, the data show that TBF decreased the FBG levels in diabetic rats. These results indicate that TBF possesses hypoglycemic effects in diabetic rats. In addition, improved blood glucose homeostasis was also observed by oral glucose tolerance test in the TBF treated groups. It has been previously reported that insulin resistance is a prominent feature of type 2 diabetes, and insulin resistance in peripheral tissues leads to compensatory hyperinsulinemia followed by β -cell failure [22]. Diabetic rats with high insulin and hyperglycemia may reflect a compensated stage of diabetes with pancreatic β -cells producing increased insulin in response to insulin resistance [23]. Serum insulin measurement has been considered as the most practical and accurate approach for insulin sensitivity [24]. In this study, the data show that TBF decreased the serum insulin levels in diabetic rats. These results indicate that TBF increases insulin sensitivity by decreasing blood glucose and insulin levels. Dyslipidemia is a common characteristic of type 2 diabetes and is the primary cause of cardiovascular disease in people with diabetes [25]. The abnormal concentration of serum lipids in diabetic subjects is mainly due to the increased fatty acid mobilization from adipose tissue. Since insulin has an inhibitory action on HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase), the key enzyme in cholesterol biosynthesis, insulin deficiency or insulin resistance may therefore be responsible for dyslipidemia [26]. In this study, the data show that TBF not only lowered the TC, TG, and LDL-C levels, but also enhanced the HDL-C levels. These results indicate that TBF possesses hypolipidemic effects in diabetic rats and thus may lead to a decrease in the risk of cardiovascular disease and related complications. The improvement of lipid profile might be directly or indirectly related to the reducing of FBG levels in diabetic rats [27].

Conclusion

This study demonstrated the hypoglycemic and hypolipidemic effects of TBF, which significantly decreased FBG and serum insulin levels, increased body weights, and improved glucose intolerance in type 2 diabetic rats. Furthermore, it decreased TC, TG, and LDL-C levels, and increased HDL-C levels in these rats. These results suggest that TBF has the potential to be a candidate for investigation as an anti-diabetic agent in humans. Further studies needs to be carried out to elucidate precise mechanisms of these effects.

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