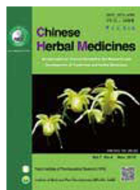

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Original article

Hypoglycemic and Hypolipidemic Effects of *Lycium barbarum* Polysaccharide in Diabetic Rats

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ABSTRACT

Objective To study the antidiabetic effects and the underlying molecular mechanisms of *Lycium barbarum* polysaccharide (LBP) and its DEAE cellulose elution fraction LBP-IV in diabetic rats induced by high fat diet (HFD) and streptozotocin (STZ). **Methods** After ig administration of LBP-IV [50, 100, and 200 mg/(kg·d)] and LBP [100 mg/(kg·d)] once daily for consecutive 4 weeks to diabetic rats, the glucose and lipids in blood, mRNA expression of phosphoenolpyruvate carboxykinase (PEPCK), sterol regulatory element binding-protein-1c (SREBP-1c), and fatty acid synthase (FAS) in liver were determined. **Results** Ig administration of LBP and LBP-IV significantly decreased the levels of blood glucose, HbA1c, TC, TG, and LDL-C, as well as the hepatic mRNA expression of PEPCK, SREBP-1c, and FAS, whereas significantly increased the oral glucose tolerance of diabetic rats. **Conclusion** The findings suggest that the antidiabetic effects of LBP and LBP-IV are associated with the decreased hepatic mRNA expression of PEPCK, SREBP-1c, and FAS in HFD-STZ induced diabetic rats.

Key words

antidiabetic effect; diabetic rat model; *Lycium barbarum* polysaccharides

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1. Introduction

Fruit of *Lycium barbarum* L. is an important Chinese materia medica (CMM) and nowadays has been widely used as a popular functional food with vital biological activities. The main chemical components were *L. barbarum* polysaccharides (LBP), zeaxanthin, and other constituents with small molecules, such as betaine, cerebroside, β-sitosterol, *p*-coumaric acid, and various vitamins. LBP possesses a range of biological activities, including anti-fatigue/endurance, glucose control in diabetics, anti-oxidant property, immunomodulation, and antitumor activity (Jin et al, 2013; Zhang et al, 2012). Recently, many studies have focused on the isolation, preparation, and structural characterization of LBP and its purified constituents (Shan et al, 2010; Wang et al, 2010; Liang et al, 2011; Ke et al, 2011; Peng et al, 2012; Zhu et al, 2013), as well as their anti-oxidant activity (Luo et al, 2004; Li et al, 2007; Ma et al, 2009; Wang et al, 2010; Liang et al, 2011; Jia et al, 2012) and antidiabetic effects (Luo et al, 2004; Ma et al, 2009; Rui et al, 2009; Shan et al, 2010; Jing et al, 2013). The results demonstrated that LBP and its purified constituents not only have anti-oxidant activity *in vitro* (Wang et al, 2010; Liang et al, 2011; Ke et al, 2011) and *in vivo* (Luo et al, 2004; Ma et al, 2009; Liang et al,

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2011; Jia et al, 2012), but also have the ability to alleviate the insulin resistance of liver cells *in vitro* (Shan et al, 2010; Jing et al, 2013), decrease the blood glucose and lipid levels of alloxan-induced diabetic rabbits (Luo et al, 2004) and mice fed by high fat diet (HFD) (Ma et al, 2009), and protect kidney from STZ-induced damage in diabetic rats (Rui et al, 2009).

It is known that the reactive oxygen species (ROS) produced by cytochrome P450 2E1 (CYP2E1) is an important causative factor for insulin resistance in diabetes and related conditions (Bloch et al, 2005; Kathirvel et al, 2009). LBP can alleviate CCl_4-induced acute hepatic damage by down-regulation of nuclear factor kappa-B and CYP2E1 activity in mice liver (Jia et al, 2012), increase insulin sensitivity by up-regulation of myocyte glucose transporter four of diabetic rats (Zhao et al, 2005). LBP-4 (the major active component of LBP) can significantly increase the activities of anti-oxidant enzymes such as SOD, CAT, and GSH-Px, inhibit protein kinase C over-activation in kidneys of STZ-induced diabetic rats. And the antidiabetic mechanism of LBP-4 was demonstrated to be associated with the decreased phosphorylation of ERK1/2 signal transduction pathway (Rui et al, 2009). Although numerous studies have been published on humans and animals examining the health aspects of LBP, to the best of our knowledge, there are little report about the antidiabetic mechanism of LBP and its purified constituents in experimental type 2 diabetic rats *in vivo*. In this work, we investigated the therapeutic effects of LBP and its DEAE cellulose elution fraction LBP-IV in diabetic rats induced by HFD and STZ and the underlying molecular mechanism.

2. Materials and methods

2.1 Reagents

Fruits of *Lycium barbarum* L. were purchased from Yinchuan City Herb Market (Ningxia, China). Streptozotocin (STZ) was purchased from Sigma (USA). Trizol and PCR primers were purchased from Invitrogen (USA). ReverTra Ace qPCR RT Kit and TransStart Green qPCR Super Mix were purchased from Toyobo (Japan). The test kits of glucose, total cholesterol (TC), triglyceride (TG), glycosylated hemoglobin (HbA1c), high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) were purchased from Nanjing Jiancheng Bioengineering Institute (China). Cellulose DE-52 and SephadexG-100 were purchased from GE Healthcare Bio Sciences AB (Sweden). The other chemicals used were of reagent grade from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

2.2 Preparation for LBP and LBP-IV

Lycium barbarum polysaccharide (LBP) was extracted with hot distilled water (1:10) at 100 ^{o}C for 2 h under constant stirring. The extract was filtered, evaporated under vacuum, and precipitated by adding 3-fold volume of ethanol. The precipitate was washed with acetone and alcohol, and then dried under vacuum to give crude LBP. The contents of carbohydrate and protein in LBP extract were determined by phenol-sulfuric acid method using *D*-glucose as standard sample and by Bradford method using BSA as standard sample, respectively.

The decoloration and deproteinization of LBP were performed by continuous stirring 1% crude LBP aqueous solution with D101-I nonpolar macroporous resin (7:1) at room temperature for 3 h followed by filtration and lyophilization. Then LBP (5 g dissolved in 50 mL water) was dialyzed (MWCO8000) against distilled water for 48 h and separated by DEAE cellulose-52 column (40 cm × 8 cm) with the step gradient elution of water, 0.05, 0.10, and 0.50 mol/L NaCl in turn at a flow rate of 5 mL/min. There were four eluted fractions designated as LBP-I, LBP-II, LBP-III, and LBP-IV, respectively. LBP-IV was dialyzed in distilled water for 24 h, and dried by lyophilization. The purity and molecular weight of LBP-IV were determined by Sephadex G-100 gel-filtration column (50 cm × 0.5 cm) at a flow rate of 0.5 mL/min eluent (deionized water). Column calibration was performed using standard dextrans with different molecular weights (10 000, 40 000, 70 000, 100 000, 500 000, and 2 000 000, respectively). The standard curve represented the linear relationship of the retention time and the logarithm of their respective molecular weights. The molecular weight of LBP-IV was calculated by comparing with the standard dextrans with different molecular weights.

2.3 Diabetic rats induced by HFD and STZ

Male Wistar rats [weighing (200 ± 20) g, purchased from Provincial Disease Prevention and Control Center of Hubei] were maintained in SPF animal room at temperature of (22 ± 2) ^{o}C, with humidity of (60 ± 5)% and 12 h/12 h day/night cycle. All procedures were approved by Ethic Committee of Hubei University, and complied with health guidelines for the care and use of laboratory animals. The diabetic rat model was built by HFD and STZ as follows (Reed et al, 2000). Rats in diabetic group were fed with HFD diet (composed of 10% lard oil, 10% white sugar, 5% yolk power, 1% cholesterol, and 74% regular diet) for continuous 6 weeks, and then the rats were ip injected with 40 mg/kg STZ (dissolved in citrate buffer, pH 4.4). Rats in normal control group were fed with regular diet and injected with same volume of citrate buffer. One week after STZ injection, the diabetic rats with blood glucose level ≥ 16.7 mmol/L were selected for the further study. Animals were kept on their respective diet till the end of the study.

The diabetic rats were randomly divided into five groups (n = 8) as follows: diabetic control group (treated with saline alone), LBP group (treated with 100 mg/kg body weight of LBP), LBP-IV 50, 100, and 200 groups (treated with 50, 100, and 200 mg/kg body weight of LBP-IV, respectively). The rats were ig administered with LBP and LBP-IV (dissolved in saline) respectively once daily for continuous 4 weeks. The blood samples collected from orbit and HbA1C were determined in EDTA-blood samples using commercial assay kit (Nanjing Jiancheng Bioengineering Institute, China). Blood samples were centrifuged at 7000 r/min for 10 min at 4 ^{o}C to

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