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Ferulic acid alleviates the symptoms of diabetes in obese rats

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ABSTRACT

The effect of ferulic acid on biochemical and histological properties, mRNA expression of HO-1 and GST in the liver and heart were investigated in obese, diabetes rats after ferulic acid administration for 16 weeks. The results showed that ferulic acid (60 mg/kg) decreased the activities of ALT, AST, CK, and LDH in the serum, by 53.5, 33.6, 47.8, and 405.5% respectively; and reduced cell apoptosis from 16.55 to 9.11% in the liver, and 11.27 to 5.09% in the heart. Ferulic acid significantly increased the antioxidant activity in the plasma, liver, and heart, and upregulated the mRNA expression of HO-1 and GST in the cells of liver and heart of the diabetes animals. Moreover, ferulic acid maintained the body weight, significantly decreased serum glucose and lipid, and advanced glycation end products in the plasma, liver, and heart. It can be concluded that ferulic acid can alleviate late-stage diabetes in obese rats.

1. Introduction

Diabetes mellitus (DM) is a major public health burden worldwide. In 2011, 365 million people in the world had diabetes, 90% of which were cases with type 2 diabetes mellitus (T2DM) (Scully, 2012). According to recent estimates, more than 20 million people in the United States and 90 million people in China have T2DM (Styskal, Van Remmen, Richardson, & Salmon, 2012). T2DM caused more than 3.5 million deaths in middle-income countries in 2011 (Scully, 2012; Styskal et al., 2012).

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Abbreviations: AGEs, advanced glycation end products; ALT, alanine aminotransferase; AST, aspartate aminotrnasferase; BUN, blood urea nitrogen; CK, creatine kinase; DMBG, dimethylbiguanide; FA, ferulic acid; FINS, fasting insulin; FPG, fasting plasma glucose; GSH, glutathione; GST, glutathione S-transferase; HDL-C, high density lipoprotein-cholesterol; HE, hematoxylin-eosinstaiing; HO-1, heme oxygenase-1; LDH, lactate dehydrogenase; LDL-C, low density lipoprotein-cholesterol; PBS, phosphate buffered saline; SOD, superoxide dismutase; STZ, streptozocin; T2DM, type 2 diabetic mellitus; TBARS, thiobarbituric acid-reactive substances; TC, total cholesterol; TG, triglyceride; Tunel, transferase dUTP nick-end labeling

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The incidence of T2DM is closely linked to obesity, which is a predictor of development of T2DM (Seidell, 2000; Styskal et al., 2012). It has been proposed that oxidative stress is involved in obesity-induced insulin resistance and the pathogenesis and development of DM complications (Matough, Budin, Hamid, Alwahaibi, & Mohamed, 2012; Seidell, 2000). Hyperglycaemia induces the production of free radicals that impair the endogenous antioxidant defense systems by depleting antioxidants, such as glutathione (GSH) and vitamin E in the tissue, and by reducing the activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase (Matough et al., 2012). Thus, antioxidants, especially polyphenols, are regarded as augmentary treatments for various aspects of diabetes mellitus (Avignon, Hokayem, Bisbal, & Lambert, 2012; Bahadoran, Mirmiran, & Azizi, 2013).

Ferulic acid is an active ingredient in the Chinese traditional medicine, *Angelica sinensis*, which elicits protective effects against diabetes, cardiovascular disease, cancer, and Alzheimer's disease (Ou & Kwok, 2004; Shahidi & Chandrasekara, 2013; Zhao & Moghadasian, 2008). Previous studies have investigated the treatment effects of ferulic acid and its combinations with other antioxidants on streptozotocin (STZ)- or alloxan-induced diabetes in animals (rats and mice). Several short-term observations (lasting 3–8 weeks) have revealed that ferulic acid reduces the elevated levels of plasma lipid, blood glucose, urea, creatinine, serum glutamic pyruvic transaminases, and serum glutamic oxaloacetate transaminases, in addition to restoring the levels of low-molecular-weight antioxidants and antioxidant enzymes in tissues in diabetic rats (Choi et al., 2011; Ohnishi et al., 2004; Prabhakar, Prasad, Ali, & Doble, 2013; Ramar et al., 2012; Roy, Metya, Sannigrahi, Rahaman, & Ahmed, 2013). While the results in a long-term research (28 weeks) by Hsieh et al. (2010) showed that ferulic acid could not improve diabetes, it did induce nephrocarcinoma. They suggested that phytoantioxidants, including ferulic acid, are beneficial only at the early-stage diabetes mellitus and will become ineffective once renopathy occurs.

T2DM is closely linked to obesity, and ferulic acid is regarded as a functional food ingredient for the management of obesity (Baboota et al., 2013). However, whether ferulic acid showed treatment effect on diabetes in obese animals has not been reported. In the present research, T2DM was induced by STZ in obese rats to model the most common obesity-linked diabetes in humans. The body weight, biochemical markers for hepatocyte and myocardial injury in the plasma, and histological properties of liver and heart were assessed 16 weeks after treatment with ferulic acid; the mRNA levels of enzymes responsible for protection against oxidative stress, namely haem oxygenase-1 (HO-1) and glutathione S-transferase (GST), were also measured in the liver and heart.

2. Materials and methods

2.1. Materials and chemicals

STZ, ferulic acid, paraformaldehyde, and dimethylbiguanide (DMBG) were purchased from Sigma–Aldrich Company (St. Louis, MO, USA). High-fat feed (5.24 kcal/g) containing 26.2% of protein, 26.3% of carbohydrate, and 34.9% of fat was purchased from the Experimental Animal Center of Guangdong Province (Guangzhou, China).

2.2. Experimental animals and establishment of diabetes model

Sprague–Dawley male rats (NO4405900280, permitted by SCXK 2008-0020 [Guangdong]) weighing 100–120 g (4 week old) were purchased from the Experimental Animal Center of Guangdong Province (Guangzhou, China). The animals were acclimatized for 7 days in an environmentally controlled room maintained at 21 ± 2 °C with 12 h light–dark cycle. Tail blood was collected to determine the content of fasting plasma glucose (FPG) using blood glucose test strips. Animals with FPG lower than 7.0 mmol/L were randomly divided into two groups and each group was fed with either normal feed or high-fat feed for 7 weeks. The animals in the high-fat feed group were fasted for 12 h, and those with FPG lower than 7.0 mmol/L were administrated with low levels of STZ to avoid death. The rats were intraperitoneally injected thrice with STZ (30 mg/kg, freshly dissolved in 5 mM citrate buffer, pH 4.5) on days 1, 3, and 4. Rats with FPG ≥ 7.0 mmol/L at 7 days after the first injection were considered diabetic and used subsequently for experiments.

2.3. Animal groups and experimental design

Non-diabetic animals ($n = 10$) served as the normal control group and were continued to be fed with normal feed. The diabetic animals to be fed with high-fat feed were divided into four groups: group II, diabetic control; group III, 30 mg/kg ferulic acid; group IV, 60 mg/kg ferulic acid; and group V, 300 mg/kg DMBG. The rats were weighed, and the drugs were administered orally every day for 16 weeks.

On the day of tissue collection, the animals were fasted for 12 h (overnight), anesthetized with pelltobarbitalum natricum, and then sacrificed. Blood was collected and centrifuged at 5000 × *g* for 20 min, and the plasma obtained used for various biochemical measurements. The heart and liver were extracted after death. Half of the organs were washed with PBS, fixed with 4% paraformaldehyde for 48 h, and then embedded in paraffin for histological examination (haematoxylin–eosin staining) and transferase dUTP nick-end labeling (TUNEL). The other half of the organs were homogenized in PBS and used for biochemical assessment.

2.4. Biochemical assessment

The serum level of glucose was measured using test strips (PWE005003P) from Roche Group (Shanghai, China). The plasma level of insulin was measured using an ELISA kit (YDS0872) from Beijing North Institute of Biological Technology (Beijing, China). Advanced glycation end products (AGEs) were measured using an ELISA kit (STA-817) from Cell Biolabs, Inc. (San Diego, CA, USA). Test kits for the determination of SOD (A001-1), TBARS (thiobarbituric acid–reactive substances) (A003-2), nitric oxide (NO, A013-2), blood urea nitrogen (BUN; C013-2) and GSH (A006-1) were obtained from the Nanjing Jiancheng Biological Engi-