Journal of Ethnopharmacology 151 (2014) 675–685

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

A refined-JinQi-JiangTang tablet ameliorates prediabetes by reducing insulin resistance and improving beta cell function in mice

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ARTICLE INFO

Article history:
Received 19 April 2013
Received in revised form
11 November 2013
Accepted 13 November 2013
Available online 25 November 2013

Keywords:
Insulin resistance
Beta cell function
Herbal effective fractions
High fat diet
Prediabetes

ABSTRACT

Ethnopharmacological relevance: Refined-JQ (JQ-R) is a mixture of refined extracts from three major herbal components of JinQi-JiangTang tablet: *Coptis chinensis* (Ranunculaceae), *Astragalus membranaceus* (Leguminosae), and *Lonicera japonica* (Caprifoliaceae). Our previous studies have indicated that JQ-R could decrease fasting blood glucose levels in diabetic mice and insulin resistance mice. Investigating the hypoglycemic effect of JQ-R on prediabetes has practical application value for preventing or delaying insulin resistance, impaired glucose tolerance and possibly the development of clinical diabetes.

Materials and methods: The anti-diabetic potential of JQ-R was investigated using a high fat-diet (HFD)-induced obesity mouse model. C57BL/6J mice (HFD-C57 mice) were fed with high-fat diet for 4 months. HFD-C57 mice were treated with either JQ-R (administered intragastrically once daily for 4 weeks) or metformin (as positive control), and the effects of JQ-R on body weight, blood lipids, glucose metabolism, insulin sensitivity, and beta cell function were monitored.

Results: The body weight, serum cholesterol, and the Homeostasis Model Assessment ratio (insulin resistance index) were significantly reduced in JQ-R or metformin-treated mice, and the glucose tolerance was enhanced and insulin response was improved simultaneously. Moreover, both JQ-R and metformin could activate liver glycogen syntheses even under a relatively high glucose loading. Although glyconeogenesis was inhibited in the metformin treated mice, it was not observed in JQ-R treated mice. Similar to metformin, JQ-R could also improve the glucose infusion rate (GIR) in hyperglycemic clamp test. JQ-R was also shown to increase the levels of phosphorylated AMPKα and phosphorylated acetyl CoA carboxylase (ACC), similar to metformin.

Conclusion: JQ-R could reduce HFD-induced insulin resistance by regulating glucose and lipid metabolism, increasing insulin sensitivity through activating the AMPK signaling pathway, and subsequently improving β cell function. Therefore, JQ-R may offer an alternative in treating disorders associated with insulin resistance, such as prediabetes and T2DM.

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1. Introduction

Prediabetes is a condition in which the blood glucose concentrations are higher than normal, but lower than the levels for the diagnosis of diabetes. It is a high-risk state for diabetes development especially in patients who remain prediabetic despite intensive lifestyle intervention (Chiolero and Paccaud, 2012; Deedwania and Ahmed, 2012; McMurray et al., 2012; Tabak et al., 2012). Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are considered prediabetic state. Individuals with IGT or IFG are at a high risk for developing type 2 diabetes (T2DM) and cardiovascular diseases. The transition from prediabetes to diabetes may take many years but may also be rapid. It is currently estimated that most individuals (up to 70%) with prediabetes eventually develop diabetes (Tabak et al., 2012), and the average risk of developing diabetes is about 5–10% per year in individuals with IFG or IGT compared with approximately 0.7% per year in normoglycemic individuals. Not surprisingly, prediabetes has been a research focus among clinical investigators over the past several decades.

Abbreviations: ACC, acetyl CoA carboxylase; AMPK, adenosine monophosphate-activated protein kinase; AUC, area under the curves; CON, untreated control group; ELSD, Evaporative Light Scattering Detector; GIR, glucose infusion rate; GLUT2, Glucose transporter 2; HFD, high fat-diet; HOMA-IR, Homeostasis Model Assessment ratio of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IOD, integrated optical density; IR, insulin resistance; ITT, insulin tolerance test; JQ-R, Refined-JinQi-JiangTang tablet; MET, group treated with metformin; NOR, normal control; OGTT, oral glucose tolerance test; S.E.M, standard error of mean; T2DM, Type 2 Diabetes Mellitus; TC, total cholesterol; TG, total triglyceride

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0378-8741/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jep.2013.11.024

Insulin resistance (IR) is one of the major pathophysiological characteristics of prediabetes. The most common cause of IR is obesity. Obesity in humans is generally attributable to the interactions of multiple genes and environmental factors. Dietary fats have been identified as one of the detrimental factors in the pathogenesis of obesity. In recent years, the sharply-increased obesity incidence is largely due to the over-intake of calorie-rich diet and exercise-lacking lifestyles in the developed and developing countries (Caballero, 2007; Kearney, 2010; Matsui et al., 2010). Progressive deterioration of beta-cell function in response to a glucose challenge has been demonstrated in individuals with prediabetes (DeFronzo and Abdul-Ghani, 2011). Declined insulin secretion is characteristic of both IGT and IFG, and accounts for the progressive rise in blood glucose level. Insulin resistance and beta cell dysfunction are the central pathophysiologic defects responsible for the development of diabetes. Therefore, preservation of insulin sensitivity and beta-cell function in the prediabetic state are critical to prevent future development of diabetes.

For thousands of years, traditional herbal medicines have played an important role in health maintenance for peoples throughout the world. Many reports have confirmed that traditional herbal medicines are an effective strategy for ameliorating insulin resistance syndrome (Ghaisas et al., 2010; Hu et al., 2010; Jadeja et al., 2010; Nammi et al., 2009; Park et al., 2008; Zhao et al., 2005). Refined-JQ (JQ-R) is a refined form of a traditional Chinese patent medicine, namely JinQi-JiangTang tablet (approved by the State Food and Drug Administration of China for the treatment of type 2 diabetes, state medical license No. Z10920027), consisting of extracts from three herbal plants: *Coptis chinensis* (rhizome of Ranunculaceae *Coptis chinensis* Franch.), *Astragalus membranaceus* (root of Leguminosae *Astragalus membranaceus* Moench), and *Lonicera japonica* (flower buds of Caprifoliaceae *Lonicera japonica* Thunb.). It has been used clinically for the treatment of T2DM (Chao et al., 2009; Cui, 2000; Lin, 2006; Vray and Attali, 1995), and has also been used to improve abnormal glucose and lipid metabolism in patients with IGT and IFG (Cao et al., 2010; Zhou, 2002). Nevertheless, as a compounded crude extract from Chinese medicine, it leaves something to be desired. To improve the potency and quality of the medicine, a lot of orthogonal pharmacodynamics experiments have been conducted. Three active components of this Chinese herbal medicine were extracted and identified. They are total alkaloids, total saponins, and sugar alcohols in *Coptis chinensis*, *Astragalus membranaceus*, and *Lonicera japonica*, respectively (Shen et al., 2007). In previous studies, we have found that only the total alkaloids of *Coptis chinensis* have hypoglycemic effect. Total saponins of *Astragalus membranaceus* have been shown to improve insulin resistance. Total saponins have also been shown to be synergistic with total alkaloids of *Coptis chinensis* to reduce blood sugar. Sugar alcohols (but not other gradients) in *Lonicera japonica* could inhibit blood glucose increase in oral glucose tolerance test in a dose-dependent manner. Based on these observations, we have decided to use the combination of these three active gradients from JinQi-JiangTang tablet to re-formulate JQ-R used in the current study.

Our previous studies have shown that JQ-R could decrease fasting blood glucose levels, increase insulin sensitivity index, and ameliorate pathological changes of pancreas in mice with monosodium L-glutamate induced insulin resistance (Tian et al., 2009). However, there have been inadequate pharmacological studies of JQ-R on dietary fats induced prediabetes. C57BL/6J mice develop prediabetes with insulin resistance, obesity and dyslipidemia after being fed with a high-fat diet (HFD) for an extended period of time (Cong et al., 2008). However, the underlying mechanisms are still unclear. In this manuscript, we studied the potential mechanisms that JQ-R ameliorates prediabetes in C57BL/6J mice induced by HFD.

2. Materials and methods

2.1. Preparation of JQ-R

JQ-R is composed of total alkaloids from the stems of *Coptis chinensis*, total saponins from the roots of *Astragalus membranaceus*, and sugar alcohols from the flower buds of *Lonicera japonica.* The preparation of the effective components of these herbs was performed as previously described and supplied by the Laboratory of Chemistry of Natural Products, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC) (Shen et al., 2007). Ethanol extraction and hydrochloric acid precipitation were used to prepare the alkaloids of *Coptis chinensis*, in which the content of total alkaloids was over 70%. Total saponins of *Astragalus membranaceus* were prepared with ethanol extraction and macroporous resin absorption, in which the content of total saponins was more than 50%. *Lonicera japonica* granular powders were extracted by water circumfluence and alcohol precipitation. After purification with macroporous resin, sugar alcohol extracts with more than 50% of the total sugar alcohols content was obtained. A total of 230 kg of *Coptis chinensis* were used for extraction and the total alkaloids yield was 18.6 kg with a recovery rate of 8.1%. A total of 200 kg of *Astragalus membranaceus* were used and 4.6 kg of total saponins were obtained with a recover rate of 2.3%, and 5.58 kg of sugar alcohols were extracted from 40 kg of *Lonicera japonica* (14.2% recovery rate). All extractions were homogenously mixed by the following weight ratio: alkaloids/saponins/sugar alcohols = 15/10/5. In our prior experiments, we have determined empirically that the optimal hypoglycemic effect was achieved at this ratio (Shen et al., 2007, and data not shown).

2.2. Quantity control of JQ-R

The representative components from alkaloids, saponins and sugar alcohols were individually analyzed for quality control. The berberine hydrochloride content of the *Coptis* alkaloid extract was determined by HPLC using an octadecylsilane bonded silica column. The mobile phase was CH3CN/0.1 M sodium dihydrogen phosphate (28:72, v/v); and flow rate was 1.0 ml/min. The analysis was performed at 35 °C and the absorbance at 350 nm was measured. The content of berberine hydrochloride was 65.89% when compared with standards.

The astragaloside IV content of the *Astragalus* saponin extract was determined by HPLC using an amino-bonded silica column and detected using Evaporative Light scattering Detector (ELSD) with drift tube temperature at 100 °C. The mobile phase was CH3CN/H_2O (37:63, v/v); the gas flow rate was 2.7 L/min. The content of astragaloside IV was 2.08% as compared with standard.

The meso-inositol content of the *Lonicera japonica* polyol extract was determined by HPLC analysis under the following conditions: HPLC column, amino-bonded silica; detection, ELSD; drift tube temperature, 100 °C; mobile phase, CH3CN/H_2O (70:30, v/v); the gas flow rate, 2.7 L/min. The content of meso-inositol was 7.09% as compared with the standard.

Based on the results, the total alkaloids, saponins and sugar alcohols were mixed at a 15/10/5 ratio. The composition of the mixture was further verified by comparing the representatives of each gradients using TLC (data not shown).

2.3. Animals and treatments

Eight weeks old male C57BL/6J mice (weighing 17–19 g) were purchased from the Animal Center of the Institute of Laboratory Animal Sciences, CAMS & PUMC. Male, but not female mice were used because the female periodic hormonal changes could

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