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Hypoglycemic and hypolipidemic effects of oxymatrine in high-fat diet and streptozotocin-induced diabetic rats

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ABSTRACT

Oxymatrine, a quinolizidine alkaloid, has been widely used for the treatment of hepatitis. In this study, we investigated the hypoglycemic and hypolipidemic effects and new pharmacological activities of oxymatrine, in a high-fat diet and streptozotocin (STZ)-induced diabetic rats. The results demonstrated that oxymatrine could significantly decrease fasting blood glucose, glycosylated hemoglobin (GHb), food and water intake, non-esterified fatty acid (NEFA), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol levels (LDL-c), and increase serum insulin, liver and muscle glycogen, high density lipoprotein cholesterol (HDL-c), glucagon-like peptide-1 (GLP-1) and muscle glucose transporter-4 (GLUT-4) content in diabetic rats. The results of the histological examinations of the pancreas and liver show that oxymatrine protected the islet architecture and prevented disordered structure of the liver. This study displays that oxymatrine can alleviate hyperglycemia and hyperlipemia in a high-fat diet and STZ-induced diabetic rats might by improving insulin secretion and sensitivity.

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Introduction

Diabetes mellitus (DM) is a complex metabolic disease characterized by high blood glucose levels and a disorder of carbohydrate, fat and protein metabolism. The number of people with diabetes worldwide will rise from over 366 million in 2011–552 million by the year of 2030 and the major part of this increase will occur in developing countries (International Diabetes Federation, 2011). The abnormal increase of blood glucose in diabetes will result in long-term damage and dysfunction of various organs including the eyes, kidneys, nerves and blood vessels (American Diabetes

Association, 2010). Consequently, people with diabetes are more likely to have retina damage, nephropathy, amputation and stroke (Prabhakar et al., 2013). Currently, diabetes mellitus is one of the ten leading causes of death and one of the most costly chronic diseases worldwide (American Diabetes Association, 2010). Therefore, it is attractive and urgent to search for more effective and safer antidiabetic drugs.

Various drugs, including biguanide, thiazolidinedione, sulfonylurea, α -glycosidase inhibitors and insulin were used for treatment of diabetes for many years, however, the usage of these agents were restricted due to several considerable side effects (Prabhakar et al., 2013). A large number of medicinal plants and their bioactive constituents have been used to treat diabetes and its complications for hundreds of years throughout the world, especially in Asian countries (Xie and Du, 2011). Oxymatrine (Fig. 1A, OMT), the major quinolizidine alkaloid in *Sophora flavescens* (Kushen in Chinese), has various kinds of pharmacological effects, such as antihepatitis, analgesia, antiinflammatory, antioxidation, neuroprotection and antitumor in modern pharmacological research (Hong-Li et al., 2008; Wang et al., 2011a,b). However, up to the present, few reports have confirmed in detail the effect of oxymatrine on diabetes. In order to obtain more knowledge about oxymatrine, this study was carried out to examine the antidiabetic property of oxymatrine in a high-fat diet combined with a low-dose of streptozotocin (STZ)-induced diabetic rats. In this work, we tested the effect of

Abbreviations: AUC, area under glucose concentration-time curve; DC, diabetic control; DM, diabetes mellitus; GHb, glycosylated hemoglobin; GLP-1, glucagon-like peptide-1; GLUT-4, glucose transporter-4; HDL-c, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; LDL-c, low density lipoprotein cholesterol; Met, metformin hydrochloride; NC, normal control; NEFA, non-esterified fatty acid; OGTT, oral glucose tolerance test; OMT, oxymatrine; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

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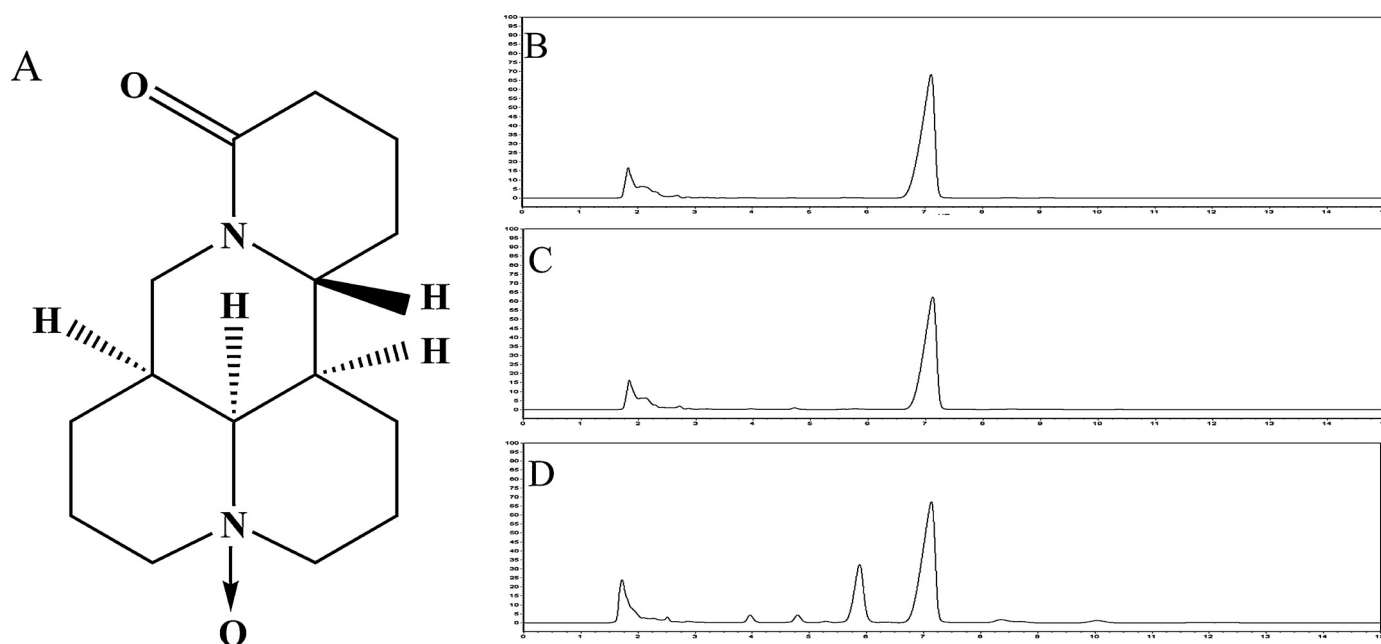


Fig. 1. Structure of oxymatrine (A). HPLC chromatogram of oxymatrine standard (B), oxymatrine sample (C) and *Sophorae flavescentis radix* (D).

oxymatrine on blood glucose, lipid profiles, insulin secretion, and insulin sensitivity in diabetic rats.

Materials and methods

Reagents

STZ was purchased from Sigma–Aldrich Inc., Saint Louis, USA. ELISA kits of insulin and glucagon-like peptide-1 (GLP-1) were obtained from Merck Millipore Inc., Billerica, USA. ELISA kits of glucose transporter 4 (GLUT-4) were obtained from Cusabio Inc., Wuhan, China. The kits of blood glucose, non-esterified fatty acid (NEFA), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), glycogen, hemoglobin and glycosylated hemoglobin (GHb) were purchased from Nanjing Jiancheng Bioengineering Institute. Oxymatrine (purity > 98%) was supplied by Nanjing Qingze Pharmaceutical Co. Ltd., which was isolated from the *Sophorae flavescentis radix*. Oxymatrine standards and *Sophorae flavescentis radix* were purchased from National Institutes for Food and Drug Control, Beijing, China. Metformin hydrochloride (Met) was obtained from Beijing Jingfeng pharmaceutical Co. Ltd.

Analysis of oxymatrine by high-performance liquid chromatography (HPLC)

The oxymatrine in the *Sophorae flavescentis radix* was characterized by HPLC, according to the [Chinese Pharmacopoeia Committee \(2010\)](#). The samples were analyzed using Hederarose NH₂ column (150 mm × 5 mm, 4.6 μm) with the detector wavelength set at 220 nm, and the mobile phase consisted of acetonitrile–ethanol–3% phosphoric acid solution (80:10:10, v/v).

Animals

Adult male Sprague–Dawley rats (200–220 g, animal quality certificate number SCKX2008-0010) were purchased from Nantong University laboratory animal center, Jiangsu province, China, and maintained at a constant temperature (23 ± 2 °C) on a 12 h light/dark cycle with free access to normal laboratory chow and

water. All procedures were carried out in accordance with the Principles of Laboratory Animal Care ([World Health Organization, 1985](#)).

Experimental induction of diabetes in rats

After 1 week of adaptive feeding, animals were randomly divided into the control and experimental group. The control group rats were given regular diet and the experimental group rats were fed with a high-fat diet (consisting of 70% standard laboratory chow, 15% carbohydrate, 10% lard and 5% yolk powder) ([Wu et al., 2012](#)). After 4 weeks of high-fat diet feeding, the experimental group rats were injected with STZ (30 mg/kg, dissolved in 0.01 M sodium citrate buffer, pH 4.4) intraperitoneally, while the control group rats were injected with the vehicle citrate buffer. Fasting blood glucose was measured 1 week after the injection. The rats with blood glucose above 11.1 mmol/l were considered diabetic and selected for further pharmacological studies. The animals were fed their respective diets until the end of the study ([Tahara et al., 2011](#); [Veerapur et al., 2012](#); [Wang et al., 2011a,b](#); [Wu et al., 2012](#)).

Experimental design

The rats (40 diabetic surviving and 8 normal) were randomly divided into 6 groups of 8 rats in each. Normal control (NC) group: normal rats treated with saline in a matched volume; diabetic control (DC) group: diabetic rats treated with saline in a matched volume; Metformin (Met) group: diabetic rats administered with metformin hydrochloride 200 mg/kg/day; oxymatrine-50 (OMT-50) group: diabetic rats administered with oxymatrine 50 mg/kg/day; oxymatrine-100 (OMT-100) group: diabetic rats administered with oxymatrine 100 mg/kg/day; oxymatrine-150 (OMT-150) group: diabetic rats administered with oxymatrine 150 mg/kg. All the drugs were administered orally via an orogastric cannula, continuously for 11 weeks. Body weight, food and water intake were measured every 2 weeks, and fasting blood glucose was monitored periodically. A schematic diagram of the induction and treatment schedule is shown in [Fig. 2](#).

At the end of study, urine samples were collected from the rats housed in individual metabolic cages for 24 h to measure urine

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