Therapeutic effects of compound herba Houttuyniae in type 2 diabetic rats

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To the Editor: Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance (IR) and β-cell dysfunction,[1] and the development of microvascular (including nephropathy and retinopathy) and macrovascular complications if not well managed. Diabetic nephropathy (DN) is a form of chronic kidney disease that is caused by diabetes.[2] The incidence of chronic kidney disease in Chinese patients with T2DM is gradually increasing.[3] The early stage of DN is characterized by a rise in urine albumin concentration and renal hyper-filtration.

Diabetes mellitus belongs to the "wasting-thirst" category of traditional Chinese medicine (TCM). *Houttuynia cordata Thunb* is a TCM that has heat-clearing and detoxifying effects, and could; therefore, represent a potential treatment for the glucotoxicity and oxidative stress associated with diabetes. *Fructus arctii* is used to disperse wind-heat, and modern pharmacologic studies have shown that it can prevent and treat DN, but there have been few studies of the therapeutic effects of compound herba *Houttuyniae* (CHH), which is composed of *F. arctii* and *H. cordata Thunb*, in animal models of T2DM.

In the present study, we prepared volatile oil, aqueous, and ethanolic extracts from these herbs, combined them to yield CHH, and determined the effects of CHH on rats with T2DM induced by feeding a high-fat, high-sugar diet and administering low-dose streptozotocin (STZ). We assessed fasting blood glucose and markers of early renal injury, including blood and urine biochemical parameters and renal filtration, the serum concentrations of glucagon-like peptide-1 (GLP-1) and fasting insulin (FINS), and homeostasis model of assessment-insulin resistance (HOMA-IR), to determine the effects on IR, aiming to provide a scientific basis for the development of a potential novel treatment for T2DM and DN. The study protocol was approved by the Laboratory Animal Welfare and Ethics Committee of Shanghai University of Traditional Chinese Medicine (No. PZSHUTCM190712011).

Of the 50 rats, 45 were fed a high-fat, high sugar diet for 4 weeks, fasted for 12 h, and then injected with 1% STZ (30 mg/kg) to induce T2DM. They were then provided with a sugar solution to prevent hypoglycemia developing. After 3 days, they were again fasted for 8 h and their fasting blood glucose (FBG) was measured by the portable blood glucose meter. The FBGs of these rats were significantly higher than normal (≥11.1 mmol/L), and they showed polydipsia, polyphagia, and polyuria, confirming the induction of T2DM. These rats were then allocated to four groups: a vehicle group ($n = 10$), a resveratrol (Res) group ($n = 10$), a rosiglitazone (Rsg) group ($n = 10$), and a CHH group ($n = 15$). The remaining five rats were fed a standard chow diet (the non-diabetic group), while the other groups continued to consume the high-sugar, high-fat diet.

A uniform 1:1 mixture of *H. cordata Thunb* and *F. arctii* was prepared, then five volumes of water and 0.004 volumes of ethyl acetate were added, the suspension was left to stand for 1 h, then the essential oils were extracted using an essential oil extractor. An aqueous extract was prepared by immersion in cold water in a round-bottomed flask and an alcoholic extract was prepared by refluxing in 50% ethanol. Dried powder forms of the aqueous and ethanolic extracts were obtained by vacuum evaporation, concentration, and drying. The volatile oils, and aqueous and alcoholic extracts were then mixed to yield CHH. With reference to the human and mouse doses, an appropriate daily oral dose for rats was calculated to be 4.5 g/kg.

Clotted blood samples were centrifuged at 12,000 × *g* for 15 min and the serum was collected and used to measure FBG, creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine transaminase (ALT), and uric acid (UA) concentrations using an automated biochemical

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analyzer. FINS, GLP-1, glycated serum protein (GSP), and glutathione concentrations were measured using commercial kits. Urine total protein (TP), albumin (ALB), and creatinine concentrations were also measured in the 24-h urine samples.

SPSS version 21.0 (IBM, Armonk, NY, USA) was used for data analysis. Data were presented as means ± standard deviations. Each dataset was tested for similar variance, then one-way analysis of variance (ANOVA), paired-samples *t*-tests and the least significant difference method was used to compare the groups. $P < 0.05$ (two-sided) was considered to represent statistical significance.

We found that the effects of T2DM on the body mass, and food and water intake of the rats were ameliorated by all the treatments administered. And we determined the effects of CHH on these biochemical indices, and found that it reduced the activities of aspartate transaminase, alanine transaminase, blood urea nitrogen, and serum concentrations of uric acid and glycosylated serum albumin in diabetic rats. The detailed methods and results are shown in Supplementary Data, http://links.lww.com/CM9/A183.

Resveratrol (Res) is an activator of silent information regulator 1 (SIRT1), which could increase the expression of catalase and have antioxidant effects.[4] Interestingly, the glutathione concentration was significantly higher in the Res group than that in the non-diabetic group in the present study, which implies that Res could reduce the cellular damage caused by oxidative stress. The molecular mechanism involved will be investigated in a future study, in which the activation of the SIRT1/Forkhead box class O1, SIRT1/peroxisome proliferator-activated receptor gamma coactivator 1α,[5] and other related pathways will be assessed.

A relative deficiency in both insulin secretion and IR is the major characteristic of T2DM. HOMA-IR is often used to assess IR in studies of diabetes. GLP-1, which circulates in lower concentrations in T2DM, stimulates insulin secretion post-prandially. Rosiglitazone (Rsg) activates peroxisome proliferator activated receptor γ, which increases the sensitivity of peripheral tissues to insulin, enhances the uptake and utilization of glucose, thereby ameliorating the defective glucose metabolism in T2DM. We found that all of Res, Rsg, and CHH had similar beneficial effects on IR, because they all reduced HOMA-IR. A further beneficial effect of CHH was that it increased the concentrations of FINS and GLP-1 in the diabetic rats.

Glomerular filtration rate is the most important indicator of glomerular function, and 24-h endogenous creatinine clearance (Ccr, contains 24-h urine total protein and albumin) is widely used clinically to assess this. Furthermore, we found that CHH greatly reduced the concentrations of total protein and albumin in 24-h urine samples, as well as reduced 24 h-Ccr and the renal index. At the same time, enlarged glomeruli, mesangial proliferation, and inflammatory cell infiltration into the renal interstitium were all present in the vehicle-treated group. These early pathologic changes were ameliorated by all of the treatments as shown in Supplementary Data, http://links.lww.com/CM9/A183.

Taking all our findings together, we have shown that a high-sugar, high-fat diet in combination with low-dose STZ administration induces early renal injury and metabolic disorders in rats with T2DM, and this can be prevented and/or treated by the administration of CHH.

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Conflicts of interest

None.

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