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Efficacy of integrative medicine in deficiency of both *qi* and yin in the rat model of type 2 diabetes

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KEYWORDS
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Abstract *Objective:* To establish a rat model of type 2 diabetes (T2DM) manifesting the Chinese medicine syndrome pattern of both *qi* and yin deficiency for evaluating the efficacy of a Chinese herbal formula (CHF), integrative medicine (IM), and pioglitazone (PIO) on T2DM indicators in the animal model.
Methods: The rat model was induced by a high-fat diet (HFD) and streptozotocin (STZ, 30 mg/kg). CHF (3.4 g/kg), PIO (2.7 mg/kg), and IM (3.4 g CHF + 2.7 mg PIO) were administered to rats once daily for 14 days. Related laboratory parameters were observed.
Results: Diabetic rats showed unsmooth fur, alopecia, reduced activity, huddling, somnolence, depression, pale or reddened tongue, damp/dark red tail, and high levels of water and food intake, urine volume, and stool weight, but weakened grip strength. Low levels of serum SOD, Na^+-K^+-ATPase, cAMP/cGMP, and a high level of iNOS were observed. Hyperglycemia, hyperinsulinemia, insulin resistance, high levels of serum glucagon/IDE and pancreatic amylin, and low serum and pancreatic SS levels were evident as well.
Conclusions: A rat model of T2DM with both *qi* and yin deficiency was successfully replicated. CHF appeared to be more efficacious than IM and PIO in the rat model of *qi* and yin deficiency pattern of T2DM, though IM and PIO were each found to have their merits and drawbacks in attenuating T2DM indicators in the rat model.

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Introduction

Integrative medicine (IM) is defined as the combination of traditional Chinese medicine (TCM) and western medicine (WM). In China, TCM, WM, and IM are all treatment methods in the clinics. IM is especially popular in China and Asia in general.[1–3] It is thought that IM's advantage is that it is efficacious with few side effects.[4] A large number of clinical pharmacology studies on IM, most of which give priority to WM and few to TCM, have been reported and the main evaluation system is based on indicators of WM.[5–8] To date, there has been no systematic evaluation that includes both disease indicators of WM and syndrome patterns of TCM.

Given that TCM and WM have their own merits and characteristics,[9,10] there are many explanations for the curative effects of IM, such as a synergistic effect, an antagonistic effect, and no significant effect but to mitigate side-effects. Moreover, research is limited by many factors that make it impossible for IM to be studied in a clinical environment. It is also impossible to prohibit IM in unconfirmed clinical research. Therefore, establishing an experimental IM design that uses a pharmacologic evaluation is important for guidance of medication safety.

Type 2 diabetes (T2DM), formerly called non-insulin-dependent diabetes mellitus and commonly caused by insulin resistance, accounts for about 90% of diabetes.[11] In TCM theory, T2DM is known as wasting and thirsting disorder, and the disease progresses in a set way.[12,13] In the early stages, yin deficiency or deficiency of both *qi* and yin is the main pattern. In subsequent stages, the pattern turns into one of stasis of phlegm and blood.

Liu et al. established a rat T2DM model of the TCM pattern of deficiency of both *qi* and yin with a high-fat diet and low dose streptozocin.[13] In our study, we replicated this animal model. Subsequently, a system of laboratory indicators based on disease indicators of T2DM and a TCM pattern of deficiency of both *qi* and yin was established. A Chinese herbal formula (CHF) was then used to validate the rat model and assess its efficacy in treating T2DM in rats. The CHF was based on an extensive literature search for effective traditional medicinal used empirically to treat T2DM and on the TCM treatment strategy of reinforcing *qi* and replenishing yin. Pioglitazone hydrochloride (PIO), a widely-prescribed agent for T2DM,[14] was used as the WM control. CHF and PIO comprised the IM. We also evaluated the efficacies of IM, CHF, and PIO.

Materials and methods

Preparation of CHF

CHF was composed of five herbal medicines (Table 1). The raw herbs were purchased from Beijing Tong Ren Tang Herbal Pharmacy (Beijing, China) and authenticated by Professor Chunsheng Liu at Beijing University of Chinese Medicine. For the preparation of the aqueous extract of CHF, all herbs except dioscorea rhizome (*Dioscorea oppositifolia L.*) were soaked in 8 volumes of water for 2 h, and decocted (extracted) three times for 1 h each. The pooled aqueous extract was filtered through gauze and concentrated and dried under vacuum at 70°C. The extraction rate was 65.76%; soft material was made by adding dioscorea rhizome (*Dioscorea oppositifolia L.*) flour and 95% ethanol, then dried at 70°C and pelletized by micro-mesh sieve (1.58 g of herbs for every 1 g of granule).

Table 1 Composition of Chinese herbal formula (CHF).

Herb	Plant part	Amount used (%)
Astragalus *Astragalus membranaceus* (Fisch.) Bunge	Root	25.4
Cooked rehmannia *Rehmannia glutinosa* (Gaertn.) DC.	Root	20.3
Dioscorea *Dioscorea oppositifolia* L.	Root	20.3
Cornus *Cornus officinalis* Sieb.et Zucc.	Fruit	16.9
Ophiopogon *Ophiopogon japonicas* (Thunb.) Ker Gawl.	Tuber	16.9

Chemicals and reagents

Pioglitazone hydrochloride (PIO) was purchased from Takeda Pharmaceutical (Tianjin, China); streptozotocin (STZ) was purchased from Sigma-Aldrich (St. Louis, MO, USA); sodium citrate and citric acid were purchased from West Long-Chemical (Guangdong, China); 0.01 M PBS (pH = 7.4–7.6) was purchased from Fuzhou Maixin Biotech (Fuzhou, China); blood glucose test strips were purchased from Johnson and Johnson Medical (Shanghai, China); diethyl ether was purchased from Beijing Chemical Factory (Beijing, China); vacuum blood collection tubes were Hunan Liuyang Medical Instruments (Liuyang, Hunan, China). Assay kits and reagents were purchased from RGB&CHN (Beijing, China).

Animals

Male Sprague-Dawley (SD) rats (specific pathogen free), weighing 180–200 g, were purchased from the Vital River Laboratory (Beijing, China). Rats were housed in the animal center of Beijing University of Chinese Medicine under standard conditions at 21–23°C, with a relative humidity of 50–60%. High-fat diet (HFD) consisting of 75% basal diet, 10% lard, 5% sugar, 5% egg yolk powder, 2% cholesterol, and 0.5% ox-gall acid sodium, were provided by the Beijing branch of Australia Together to Feed Co, Ltd (Beijing, China).

All experimental procedures were approved by the University Committee on Research Practice, Beijing University of Chinese Medicine.

Establishing rat model of T2DM

The rat model of T2DM was established as described by Mansor, et al.[15] Briefly, after adaptive breeding for 5 days, 65 rats were assigned randomly and divided into 2 groups: