



SCHOOL OF CHINESE MEDICINE THE CHINESE UNIVERSITY OF HONG KONG

MPhil Degree Oral Presentation

by

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Investigation on the Anti-diabetic Effects of Selected Natural Products/Chinese Herbs by Inhibiting the Activity of Sodium-glucose Cotransporter 2 (SGLT2)

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☞ ☞ ALL ARE WELCOME ☞ ☞

Abstract

Diabetes Mellitus (DM) is a chronic disorder of glucose metabolism characterized by abnormally high blood glucose level. Type 2 DM is the common form of diabetes which accounts for more than 90% of all DM cases. All causes of diabetes ultimately lead to hyperglycemia, and it can cause the late complications involving the eyes, kidneys, nerves and blood vessels, which are harmful to health. DM is now affecting about 6% population of the world, and the prevalence is still increasing quickly year by year. In Hong Kong, more and more elderly and youth are suffering from diabetes because of lacking of exercise and high energy diet. DM is not a fatal disease, but if no good action is taken, it can finally cause some kinds of complications, which can lead the patients to the end of their lives. Hyperglycemia is the major characteristics of diabetes, and it is also an important factor which induce all kinds of diabetic complications. In the therapy of type 2 diabetes, a lot of western medicine have been developed in the market according to various pathological causes. However, they have limitations such as existence of side effects. Therefore, combination therapy and development of new agents with novel mechanisms should be required to control the glycemic level and protect the patients from the long-term complications. Nowadays, the significance of the kidney's role in glucose homeostasis is well recognized. Glucose excretion with urine by reducing the renal glucose reabsorption to attenuate the glycemic level has been considered as a new mechanism to treat diabetes since the past two decades. Inhibitors on sodium glucose cotransporters 2 (SGLT 2) which are responsible for the glucose reabsorption in kidney are considered as a kind of new agents that have a potential on the treatment of diabetes. However, there is still no such kind of drug developed in the market, since the most potential one, dapagliflozin, is still on Phase III clinical trial. So far, only few information is found on natural products/traditional Chinese medicines (TCMs) that possess SGLT inhibitory action. Regarding the protection of patients from long-term complications, Chinese medicine which consider the body as a whole, may have advantages over western drugs.

Therefore, the aim of this study is to search for anti-diabetic TCM/natural products which specifically inhibit the activity of SGLT2 *in vitro* and attenuate plasma glucose level *in vivo* via increasing glucose excretion through urination. From literature review, 11 TCMs and 2 natural products frequently used in treating DM were selected for screening.

Using hSGLT 1 and hSGLT 2-expressed COS-7 cell lines as a model, *in vitro* study demonstrated that Fructus Schisandrae chinensis (ethanolic extract) and paeonol possess the most potent inhibitory effect on SGLT 2 in the *in vitro* ¹⁴C- α -methyl-D-glucopyranoside (¹⁴C-AMG) uptake assay.

The purification of active fraction(s) in ethanolic extract of Schisandrae chinensis fructus was carried out using the bioassay-guided fractionation assay. The ethyl acetate-methanol (4:6) fraction (F8) was selected with significant specific inhibitory effect on SGLT 2. UPLC and LC/MS-MS profiles of F8 were also given in this study. The concentrations of three common compounds of Fructus Schisandrae chinensis: deoxyschisandrin, schisandrin B (γ -schisandrin) and schisandrin were shown very low concentration in F8, the results of uptake assay showed none of these three compounds have inhibitory effects on SGLT 2. It is concluded that these three common compounds in Schisandrae chinensis fructus are not the effective ingredients in F8 which can specifically inhibit SGLT 2.

The anti-diabetic effects of paeonol in treating type 2 DM was investigated in animal study. Paeonol (200 and 300 mg/mL) was given to the type 2 diabetic rat model - Zucker Diabetic Fatty (ZDF) rats for three weeks, the results showed no positive effects on the basal glycaemia test and urinary glucose excretion test.