Karolinska Institutet

Institutionen för molekylär medicin och kirurgi

Anti-diabetic effect of Gynostemma pentaphyllum tea in type 2 diabetes

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssalen, Enheten för dermatologi och venereologi, Karolinska Universitetssjukhuset, Solna

Fredagen den 11 november, 2011, kl 09.00

av
Vu Thi Thanh Huyen
MD

Huvudhandledare:
Professor Claes-Göran Östenson
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Bihandledare:
Professor Dao Van Phan
Hanoi Medical University
Department of Pharmacology

Associate Professor Pham Thang
Vietnam National Institute of Gerontology

Fakultetsopponent:
Professor Per-Eric Lins
Karolinska Institutet Danderyds sjukhus
Institutionen för kliniska vetenskaper

Betygsnämnd:
Docent Alexandre Wajngot
Karolinska Institutet
Institutionen för neurobiologi, vårdvetenskap och samhälle

Docent Lisa Juntti-Berggren
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Docent Björn Zethelius
Uppsala Universitet
Institutionen för folkhälso-och vårdvetenskap

Stockholm 2011

ABSTRACT

Type 2 diabetes mellitus (T2D) is a major non-communicable disease and an important health burden worldwide, especially in the developing countries including Vietnam. *Gynostemma pentaphyllum* has been widely used in Vietnam as a herbal medicine for the prevention and treatment of T2D but the mechanism related to its effects is unknown.

This thesis aims to evaluate the anti-diabetic effect and safety of GP extract (tea) in T2D patients and to investigate the major mechanisms of action of GP in T2D patients and in Goto-Kakizaki (GK) rats.

The medication was provided as GP tea (dose 6g/day). The studies were implemented on newly diagnosed T2D patients to investigate the anti-diabetic effect of GP tea (**Paper I**), the effect of GP tea as add-on therapy with sulfonylurea (SU) (**Paper II**), and the effect of GP tea on insulin sensitivity (**Paper III**). Effects of GP tea on glucose tolerance and hepatic glucose output (HGO) were studied in GK rats (**Paper IV**). There was a randomized, placebo-controlled, double blind design for **Papers I, II and IV**, and a cross-over design for **Paper III**.

Significant anti-diabetic effects and improved insulin sensitivity of GP tea were clearly demonstrated in **Paper I**. After 12 weeks of treatment, fasting plasma glucose (FPG) levels decreased 3.0 ± 1.8 mmol/l in the GP group, compared to a decrease of 0.6 ± 2.2 mmol/l in the control group ($p < 0.01$). HbA_{1C} levels decreased approximately 2%-units in the GP group, compared to 0.2%-unit in the controls ($p < 0.001$). Changes in Homeostasis Model Assessment-Insulin Resistance between baseline and the 12th week indicated that insulin resistance decreased significantly in the GP group (-2.1 ± 3.0) compared with that (+1.1 ± 3.3) in the control group ($p < 0.05$). As add-on therapy to SU, GP tea further improved glycemic control and this improvement was sustained over 12 weeks (**Paper II**). After 4 weeks of SU treatment, FPG and HbA_{1C} decreased significantly ($p < 0.001$). FPG was further reduced after add-on therapy by 2.9 ± 1.7 and 0.9 ± 0.6 mmol/l in the GP and control groups, respectively ($p < 0.001$). HbA_{1C} levels decreased approximately 2%-units in the add-on GP group compared to 0.7%-units in the controls ($p < 0.001$). Furthermore, there were potential benefits of maintaining low-dose SU without symptoms of hypoglycemia. The biosecurity of GP tea was suggested clinically, since no hepatotoxicity, nephrotoxicity or other adverse effects were observed in the trials. The GP tea exerted anti-diabetic effects by improving insulin sensitivity, as demonstrated in the placebo-controlled cross-over study using the somatostatin-insulin-glucose infusion test (SIGIT) (**Paper III**). FPG and steady-state plasma glucose (SIGIT mean) were lower after GP treatment, compared to placebo treatment ($p < 0.001$). These glycometabolic improvements were achieved without any major change of circulating insulin levels. Finally, oral administration of GP tea for three weeks to GK rats exerted anti-diabetic effects by reducing plasma glucose (PG) levels and suppressing HGO levels significantly (**Paper IV**). The PG levels decreased from 9.8 ± 0.6 to 6.8 ± 0.4 mmol/L ($p = 0.027$) in GP-treated rats, whereas PG levels were not significantly decreased in the placebo rats. Glucose tolerance, assessed by an intra-peritoneal glucose tolerance test, was significantly improved in GP-treated rats, compared to placebo-treated group (areas under the glucose curves, AUCs, from 0 to 120 min were 1150 ± 200 vs. 1761 ± 87 mmol/L; $p = 0.013$). The glucose response in an intra-peritoneal pyruvate tolerance test was significantly lower in the GP group, indicating suppression of gluconeogenesis by GP treatment. In liver perfusions, the AUCs for HGO during 18 min (0-18 min) were significantly decreased in GP-treated rats, compared with control rats (302.8 ± 36.5 vs. 423.5 ± 44.7 µmol, $p < 0.05$). Three-week GP treatment significantly reduced hepatic glycogen content, but not glycogen synthase activity ($p < 0.007$), compared to the placebo group.

Our studies indicate that GP tea improves glucose tolerance and FPG, most likely by increasing insulin sensitivity and suppressing HGO. GP tea could offer an alternative to the addition of other oral medications in the treatment of T2D patients in Vietnam.

Keywords: Herbal medicine; Type 2 diabetes; *Gynostemma pentaphyllum* tea; Insulin sensitivity; Sulfonylureas; Glucose tolerance.

ISBN 978-91-7457-491-3