P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

File: ■ Chinese Skullcap (*Scutellaria baicalensis, Lamiaceae*)
■ Type 2 Diabetes
■ Glucose Tolerance

HC 062024-659

Date: February 26, 2021

RE: Chinese Skullcap May Improve Glucose Tolerance in People with Diabetes

Shin NR, Gu N, Choi HS, Kim H. Combined effects of *Scutellaria baicalensis* with metformin on glucose tolerance of patients with type 2 diabetes via gut microbiota modulation. *Am J Physiol Endocrinol Metab*. January 1, 2020;318(1):E52-E61. doi: 10.1152/ajpendo.00221.2019.

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that may be influenced by gut microbiota. Several studies have investigated the relationship between the anti-diabetic medication metformin and the composition of the gut microbiota in the treatment of T2DM and obesity. Chinese skullcap (*Scutellaria baicalensis,* Lamiaceae [SB]) root has anti-inflammatory, antiobesity, and antidiabetic effects and may work synergistically with metformin to improve insulin sensitivity. The purpose of this double-blind, randomized clinical study was to investigate whether the combination of SB and metformin influenced intestinal microbiota in patients with T2DM.

The study was conducted at Dongguk University Ilsan Hospital of Goyang-si, South Korea. Patients were recruited from an endocrinology clinic Patients who met the following criteria were eligible for inclusion: 20-75 years of age; diagnosis of diabetes at least 3 months prior; taking ≥ 500 mg of metformin per day; fasting glucose level of 110-180 mg/dL or a glycated hemoglobin level of 8.0-9.0%. Exclusion criteria were as followed: acute or chronic inflammation; taking corticosteroid medications within four weeks before the testing period; cardiovascular disease; stroke; renal or liver failure; history of drug or alcohol abuse; and pregnancy or lactation.

The trial consisted of two treatments, two sequences, a crossover, and a washout period of four weeks. Patients were randomly assigned to one of two sequence groups: SB and metformin in period 1 to placebo and metformin in period 2 (group 1); or placebo and metformin in period 1 to SB and metformin in period 2 (group 2). Patients received four capsules of SB (Nutrex Technology; Seoul, Korea) or placebo based on their sequence group with ≥ 500 mg of metformin 30 minutes after meals three times per day (3.52 grams of SB total) for eight weeks. The placebo capsule contained 1% SB per weight to mimic the flavor of the experimental drug. The SB and placebo capsules had the same appearance. Clinical parameters including serum and urine biochemistry and the oral

glucose tolerance test (OGTT) were measured before and after period 1 and 2. The stool for microbiota analysis and blood for RNA analysis were collected before and after period 1.

Of the 20 patients screened, 17 were eligible for inclusion in the study and randomized into a SB (n = 8) or placebo (n = 9) group. There were no significant differences in patient characteristics, vital signs, biochemical indicators, or metformin intake period and dosage between the groups at baseline. Five patients withdrew for personal or unidentified reasons, and adverse events were reported by three. One patient from the SB group experienced epigastric pain, two from the placebo group reported constipation, and the remaining two withdrew their consent. The remaining 12 patients completed the study.

Serum aspartate aminotransferase (AST) and alanine transaminase (ALT) in the SB and placebo groups increased from 21.4 ± 1.1 to 49.0 ± 19.2 and 21.3 ± 1.4 to 75.1 ± 35.8 IU/L, respectively, with no significant differences between the groups. Four patients (n = 3 SB and n = 1 placebo) experienced AST and ALT levels above the maximum reference range of 40 IU/L. Neither the SB nor placebo demonstrated abnormal levels for markers of renal function. The messenger RNA (mRNA) expression of the inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) decreased following SB treatment compared with placebo. The effect was significant for TNF-α ($P < 0.01$).

Total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol were reduced, and high-density lipoprotein (HDL) cholesterol was increased, albeit not significantly after SB treatment. The relative mRNA expression of cytochrome P450 family 7 subfamily A member 1 (CYP7A1) was reduced following SB treatment compared with placebo. No difference was found between the groups for the 3-hydroxy-3-methylglutaryl-CoA reductase levels. There were also no significant differences in α-diversity indicators of specific microbiota populations for operational taxonomic units (OTUs), angiotensin-converting enzyme (ACE), or Chao1. SB treatment increased levels of *Megamonas*, *Mobilitalea*, *Acetivibrio*_g1, AB606281_g, and AB606237_g, and decreased levels of *Clostridium*_g23, *Oscillibacter*, and *Alloprevotella*. The relative abundance of *Bifidobacterium* was significantly lower in the SB group compared with placebo ($P < 0.01$), whereas *Lactobacillus* ($P < 0.001$) and *Akkermansia* ($P < 0.05$) were significantly higher. There were significant differences in the gut microbiota population between patients who experienced AST and ALT levels above the maximum reference range and those not affected after SB treatment.

A significant correlation between clinical markers and 12 taxa at the phylum level, 32 at the order level, 51 at the class level, and 104 at the family level were found in response to SB treatment. SB treatment altered genes associated with metabolism, genetic and environmental information processing. SB treatment also significantly increased selenocompound metabolism and decreased naphthalene degradation compared with placebo (both $P < 0.05$).

To the authors' knowledge, this is the first double-blind, randomized clinical trial evaluating the combined effects of SB and metformin in patients with T2DM. SB treatment was demonstrated to ameliorate glucose intolerance, in part through the modulation of the gut microbiota composition. However, there were no differences in other clinical markers. The authors cite limitations related to their small sample size and

varying patient dosages of metformin. The authors also recognize the difficulty in exploring the potential mechanisms and interactions between the gut microbiome and treatment effects because of the differences in patients' diets and lifestyles. In either case, the authors call for additional trials with larger sample sizes and multicenter strategies.

The authors declare no conflicts of interest.

–Gavin Van De Walle, MS, RD

The American Botanical Council has chosen not to reprint the original article.