# The Efficacy and Safety of Chinese Herbal Medicine YH1 as Add-On Medication in Poorly Controlled Type 2 Diabetes Patients

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# Study Protocol and Statistical Analysis Plan

## Trial design

This study was a randomized, double-blind, placebo-controlled trial. All eligible subjects were 1:1 randomly assigned to receive either YH1 or placebo for 12 consecutive weeks, and all subjects continuously received their OHAs without any dose or medicine change. The primary objective was *to evaluate whether* YH1 enhances glycemic control and is safe as an add-on medication in the study population. The Committee on Research Ethics of the Chang Gung Memorial Hospital in Taiwan approved the study (No: 104-7934A3, 105-7009C, 106-0917C). Because of difficulties in enrolling participants, we expanded the eligibility criteria once, such as $HbA_{1c}$ (from ≧ 9 % to > 7 %), BMI (from ≧ 24 kg/$m^2$ to ≧ 23 kg/$m^2$), and added an additional branch of hospital for recruiting subjects. All participants provided their informed consents prior to participation.

## Participants

Patients who met the following inclusion criteria were referred from endocrinology and metabolism clinics to Chinese medicine clinics to join this study: 1) diagnosed as type 2 diabetes and treated with ≥ 3 classes of OHAs with persistent (> 6 months) poorly glycemic controlled ($HbA_{1c}$ >7.0 % or 53 mmol/mol); 2) 20–75 years of age; 3) BMI ≥ 23 kg/$m^2$.

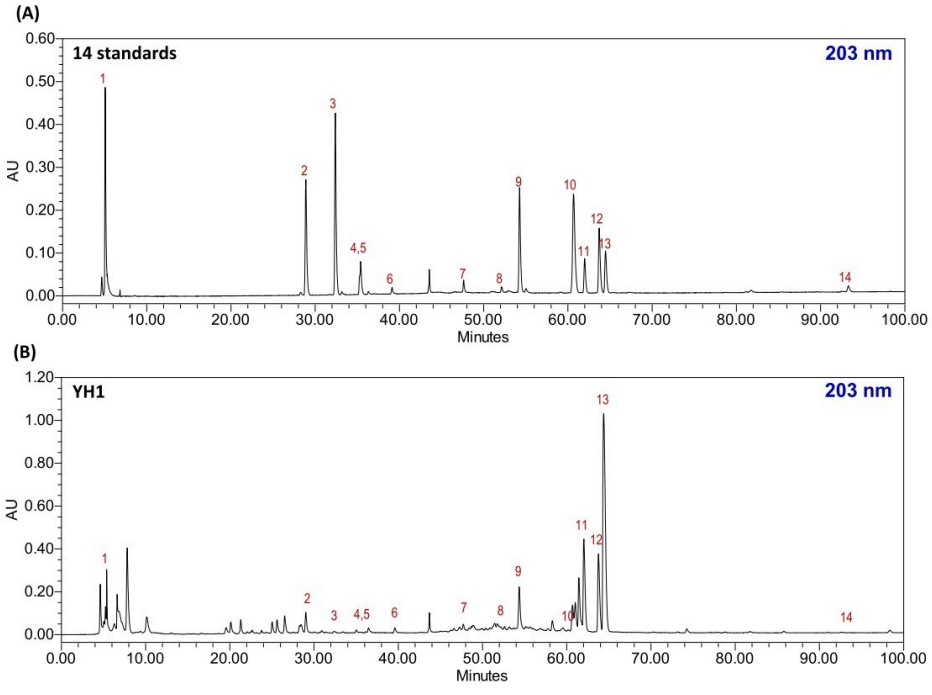
The exclusion criteria were as follows: 1) type 1, gestational, or other specific types of diabetes; 2) received insulin therapy in the past three months; 3) serious gastrointestinal (GI) tract diseases, such as peptic ulcers or GI tract bleeding; 4) experienced stressful situations, including diabetic ketoacidosis, nonketotic hyperosmolar diabetic coma, severe infection, or surgery in the previous month; 5) suffered from hepatic insufficiency with alanine aminotransferase (ALT) two times the upper limit of normal or renal insufficiency with estimated glomerular filtration rate (eGFR) < 60; 6) uncontrolled hypertension (blood pressure ≥ 160/100 mmHg); 7) mental illness, abused or addicted to alcohol, psychoactive substances or other drugs; 8) pregnant, lactating, or planning to become pregnant; 9) hemoglobin disease or chronic anemia; 10) underlying conditions that could lead to poor compliance; 11) history of cerebrovascular disease or myocardial infarction; 12) undergone Chinese medicine treatment in the past two weeks.

## Study medication

The YH1 in one batch number was used, manufactured by Sun Ten Pharmaceutical Co., LTD., a renowned GMP manufacturer of concentrated herbal extract granules conforming to international standards. The YH1 was prepared in small granules and packed in aluminum foil packages. The placebo was also prepared as

granules by Sun Ten Pharmaceutical Co., LTD., and the packaging of the placebo was identical to that of YH1. The chemical composition of YH1 was analyzed and profiled by using a high performance liquid chromatography (HPLC) with photodiode array (PDA) detection (Fig 1). Fourteen components, allantoin, atractylenolide III, berberine, coptisine, ginsenoside Rb1, ginsenoside Re, ginsenoside Rg1, glycyrrhizin, liquiritin, pachymic acid, palmatine, platycodin D, magnoflorin and quercitrin, were simultaneously used in the qualitative analysis under the developed HPLC-PDA method. As for the quantitative detection, each gram of YH1 contained 20.05 mg berberine.

**Fig 1. 2D-HPLC fingerprint of YH1. (A) HPLC of 14 standards (B) HPLC of YH1**




## Interventions

The subjects who provided their informed consents were randomly and equally

assigned to receive either YH1 or the placebo for 12 consecutive weeks. Subjects in the two groups were orally administered two packages of granules (3 g / package) three times daily with warm water after a meal. The dose of the OHAs was stable for at least three months before enrollment and remained unchanged throughout the study. Education for lifestyle management of type 2 diabetes on the use of medications was provided to both groups.

During the 12-week period, patients were assessed at 0, 2, 4, 8 and 12 weeks. In each session, all subjects received symptom assessment and a physical examination including body weight, BMI and waist circumference. In addition, drug compliance and any side effects were also recorded. The $HbA_{1c}$, FPG, and 2hPG were measured at 0, 4 and 12 weeks. Insulin resistance index, β-cell function index, lipid profile, hepatic and renal function were assessed at 0 and 12 weeks.

## Outcomes

The primary efficacy endpoint was the percentage of change in $HbA_{1c}$ levels from the baseline at 12 weeks. The $HbA_{1c}$ was measured in the laboratory medicine department of Chang Gung Memorial Hospital by high-performance liquid chromatography. The secondary efficacy endpoints were the percentage of changes of several parameters from baseline, including fasting and postprandial glycemic level,

homeostatic model assessment (HOMA) of insulin resistance (IR) and HOMA-β, lipid profile, body weight and waist circumference, and clinical symptoms.

The safety endpoints were the incidence rates of adverse events, such as any undesirable or unintended symptoms, and laboratory test abnormalities of alanine aminotransferase (ALT) and serum creatinine, regardless of the causal relationship with the study drug. Adverse events were recorded throughout this trial by direct questioning.

## Randomization and blinding

Randomization codes were generated with a computer program (SAS version 9.2, Cary, NC) by an independent statistician. Study drugs prepared by Sun Ten Pharmaceutical Co., LTD. were packed and numbered according to the random coding form, which was concealed in an opaque envelope after randomization. The envelope was not decoded until the end of the trial. Study drugs were provided based on the assigned numbers according to the visit sequence and study drug number sequence. During the trial, both the clinicians and patients were unaware of the grouping.

## Statistical analysis

The comparison of clinical characteristics between the two groups was based on Wilcoxon rank-sum test for continuous variables, and Fisher's exact test was used to evaluate the associations between categorical variables. Longitudinal analysis of $HbA_{1c}$ change between groups was based on repeated measure ANOVA using SPSS 21.0 software (SPSS Inc., Chicago, IL). Other statistical analyses were performed in R V.3.4.3 (http://www.r -project.org). A two-tailed $p < 0.05$ was considered statistically significant.