Huangyusang decoction for Type 2 diabetes
A protocol for systematic review and meta analysis

Peiyu He, MD, Junyin Zhang, MD, Tianyu Gao, MD, Yingxiang Wang, MD, Teng Peng, MD*

Abstract
Background: Diabetes is a chronic metabolic disease characterized by elevated blood glucose levels due to insulin resistance and β-cell dysfunction. In China, Huangyusang decoction (HYS) has been widely used to treat Type 2 diabetes. However, there is no systematic review found. In order to evaluate the efficacy and safety of HYS in the treatment of Type 2 diabetes, we need to conduct a meta-analysis and systematic evaluation.

Methods: We will enroll the randomized controlled trials (RCTs) evaluating the effectiveness and safety of HYS in the treatment of Type 2 diabetes. Data come mainly from 4 Chinese databases (CNKI, Wanfang, CBM, and VIP Database) and 4 English databases (PubMed, Embase, Cochrane Library, and Web of science). The enrollment of RCTs is from the starting date of database establishment till January 30, 2021. Fasting blood glucose is considered as the main indicator of the dyslipidemia, while the body mass index, glycated hemoglobin, fasting insulin, triglycerides, and cholesterol are regarded as the secondary indicators. There are safety indicators including liver enzyme and kidney function. The work such as selection of literature, data collection, quality evaluation of included literature, and assessment of publication bias will be conducted by 2 independent researchers. Meta-analysis will be performed by RevMan 5.0 software.

Results: This study will provide high-quality evidence for the effectiveness and safety of HYS in the treatment of type 2 diabetes.

Conclusion: The results of this study will help us determine whether HYS can effectively treat type 2 diabetes.

Ethics and dissemination: This study does not require ethical approval. We will disseminate our findings by publishing results in a peer-reviewed journal.

OSF registration number: DOI 10.17605/OSF.IO/AXBRV.

Abbreviations: BMI = Body mass index, CBM = Chinese biomedical literature database, CNKI = China national knowledge infrastructure, EMBASE = excerpt medica database, FBG = Fasting blood glucose, FINS = fasting insulin, HYS =Huangyusang decoction, OSF= Open Science Framework, PRISMAP = preferred reporting items for systematic review and meta-analysis protocols, RCTs = randomized controlled trials, RR = rate ratio, TC = total cholesterol, TG = triglycerides.

Keywords: β-cell dysfunction, Huangyusang decoction, protocol, systematic review, type 2 diabetes

1. Introduction
Type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance, β-cell failure and low-grade inflammation, is a major health risk worldwide.[1] Data have shown that the world population is facing a surge in T2DM and prediabetes due to rapid changes in lifestyle, including a growing availability of food high in calories and a decline in physical activity.[2] Approximately 5% of the population worldwide has been diagnosed as suffering from T2DM, and this level is projected to increase to 9.9% by 2030.[3] For patients whose diabetic duration is less than 5 years, DR morbidity is approximately 38% to 39%, and for those whose duration is 5 to 10 years, the morbidity is approximately 50% to 56.7%, whereas for patients whose diabetic duration is more than 10 years, the morbidity is approximately 69% to 90%.[4] Insulin, Sulfonylureas, and Biguanides are traditional hypoglycemic drugs. The key to the treatment of diabetes is to reduce blood glucose and fasting blood glucose. The use of conventional drugs also produces side effects, including hypoglycemia, gastrointestinal discomfort, nausea, liver failure and heart failure, and diarrhea.[5–8] These drugs are effective in lowering the glucose level of blood, but they also have
some side effects and body dependence can develop.\textsuperscript{[9]} In this case, the hypoglycemic treatment with alternative drugs has attracted more and more attention. Many studies have shown that the HYS prescription represented by Polygonatum sibiricum, Rhizoma Polygonati Odorati, and Folium Mori has a commendable hypoglycemic effect.\textsuperscript{[10–12]} However, we have found no systematic study on the efficacy and safety of HYS lipid-lowering therapy. So, we will systematically evaluate the efficacy and safety of HYS in treating type 2 diabetes by a meta-analysis method, which provide strong evidence-based medicine support for its clinical applications.

2. Methods

2.1. Protocol and registration

The protocol has been registered on the Open Science Framework (OSF) platform (https://osf.io/axbrv/), registration number: DOI 10.17605/OSF.IO/AXBRV. This protocol was drafted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.\textsuperscript{[13]} The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Meta-analyses of Healthcare Interventions.\textsuperscript{[14]}

2.2. Ethics

We will not need individual data of each patient in the research, as this is a systematic review. Therefore, institutional review board approval and ethics committee is not needed. Our purpose is to publish the results in a peer-reviewed journal. The final results of the review will provide information about the safety and efficacy of HYS and its modified forms in the treatment of type 2 diabetes to help clinicians make decisions on clinical practice.

2.3. Eligibility criteria

The participant (P), intervention (I), comparator (C), outcome (O), and study design (S) are the 5 main factors determining the inclusion and exclusion criteria of this research.

2.3.1. Type of study design. We will exclude quasi-randomized controlled trial (RCT), non-RCT, observation group combination other drugs, animal experiments, control groups not match, and full texts not available by reading the title, abstract, and related quotations information screening. Then, we can eliminate incomplete experimental data and experimental design schemes not rigorous, no clear diagnostic criteria by reading and understanding the full paper, and finally RCTs were included this research.

2.3.2. Type of participant. Adult participants (older than 18 years) with type 2 diabetes and no other illness will be enrolled. The diagnosis of type 2 diabetes can be established if the patient FBG remain high 2 to 4 weeks later after his initial visit.\textsuperscript{[15,16]} No gender, race, nationality, and comorbidity are limited.

2.3.3. Type of interventions. The patients in the treatment groups will be given HYS or modified HYS as a monotherapy or in combination with conventional therapy. HYS consisting of 3 herbs: Polygonatum sibiricum, Rhizoma Polygonati Odorati, Folium Mori. According to “Jun-Chen-Zuo-Shi” principle of Chinese herbal formula, Polygonatum sibiricum is “Jun” herb, and Rhizoma Polygonati Odorati and Folium Mori are “Chen” herb, both of which are the core of HYS. Therefore, modified HYS should include Polygonatum sibiricum, Rhizoma Polygonati Odorati, Folium Mori basically. The number of modified herbs will not exceed 3 (n ≤ 3). Patients of control group will be treated with conventional therapy with placebo, stains, and Biguanides. In addition, the 2 groups have not taken any drugs that possibly interfered with the outcome indicators. The follow-up time was ≥4 weeks.

2.3.4. Type of outcomes

2.3.4.1. Primary outcomes. According to the “Clinical Research Guidelines for New Chinese Medicines” and the new AACE/ACE guidelines, FBG is determined as the main indicator. If FBG decreases by ≥20%, it is considered to have a significant effect;\textsuperscript{[15,17]} if FBG decreases by 10% to 20%, it is considered to be effective; invalid, if the level of FBG decline does not meet the above criteria.

2.3.4.2. Secondary outcomes. According to the “Clinical Research Guidelines for New Chinese Medicines,”\textsuperscript{[15]} the secondary indicators include BMI, TG, TC, FINS.

2.3.4.3. Safety outcomes. Safety indicators consist of liver enzyme, kidney function.

2.4. Literature retrieval strategy

Computer search of PubMed, the Cochrane Library, EMBase, China National Knowledge Infrastructure (CNKI), China Biomedicine (CBM), Chinese Scientific Journals Database (VIP), Wanfang Database for published information about RCTs of HYS for the treatment of type 2 diabetes. The time limit for literature search is from the establishment of each database to January 30, 2021. The language is limited to English and Chinese. In addition, the World Health Organization International Clinical Trials Registration Platform and Clinical Trials website (Clinical Trials.gov) will be searched for ongoing trials related to the disease and RCTs in China. The search method uses a combination of free words and medical subject terms, including “type 2 diabetes,” “pathoglycemia,” “spleen and stomach,” “Chinese medicine,” “huangyusangdecotion,” etc. Chinese database search will use the following terms: “erxingtangniaobei,” “jiangtang,” “xuetangyichang,” “piwei,” “zhongyao,” “huangyusangtang,” etc. Taking PubMed as an example, the initial search strategy is summarized in Table 1, which will be adjusted according to the specific database.

2.5. Data collection and analysis

2.5.1. Literature selection and data extraction. As shown in Fig. 1, 2 researchers (Peiyu He and Junyi Zhang) will screen the documents according to the inclusion and exclusion criteria: Import the retrieved documents into Endnote X9 software for review, then remove duplicate references; By preliminary screening abstract, we exclude documents, which obviously do not meet the inclusion criteria; Download and read the full paper for follow-up examination; After the final inclusion, we will use the pre-designed data extraction table for data extraction and cross-check the results; If there is any objection, the third
researchers (Yingxiang Wang) will be asked to assist in the judgment. The main content of data extraction includes basic information of literature (title, journal, author, publication date), basic information of the research object (sample size, gender, average age, intervention, and course of treatment), and result data (numbers of response events, nonresponse events, dropouts, time points, mean, SD, follow-up time, and adverse events). If the required information is missing or incomplete, we will contact the relevant email address of the corresponding author or first author of the original document. If the relevant data cannot be obtained, the record is excluded. At the same time, the key factors of bias risk assessment are extracted.

2.5.2. **Risk of bias assessment.** The method quality of systematic review reflects the risk of deviation or validity in its process and results. The quality of the method will be evaluated according to Cochrane Manual 5.2.0.18 Two well-trained researchers (Peiyu He and Junyin Zhang) independently assessed the risk of bias in the study. The evaluation content includes generation of random sequences, randomization concealment, the implementation of blinded subjects and researchers, the implementation of blind methods for outcome evaluators, the implementation of blinded subjects and researchers, the generation of random sequences, randomization concealment, and the risk of bias in the study. The evaluation content includes basic information of literature (title, journal, author, publication date), basic information of the research object (sample size, gender, average age, intervention, and course of treatment), and result data (numbers of response events, nonresponse events, dropouts, time points, mean, SD, follow-up time, and adverse events). If the required information is missing or incomplete, we will contact the relevant email address of the corresponding author or first author of the original document. If the relevant data cannot be obtained, the record is excluded. At the same time, the key factors of bias risk assessment are extracted.

2.5.3. **Data synthesis.** Meta-analysis will be performed by RevMan 5.0 software (Version 5.3, Copenhagen: The Nordic Cochrane Center, 2014) provided by the Cochrane Collaboration. Although there is statistical homogeneity between each study ($I^2 < 50\%$), the fixed effect model is used. When the heterogeneity is significant ($I^2 \geq 50\%$) between the results of each study, the sublayer analysis is performed to find the source of heterogeneity. A fixed effect model is used for meta-analysis when there is sufficient similarity between the results of the subgroups ($I^2 < 50\%$). However, a random effect model is used for meta-analysis if the heterogeneity between the results of the subgroups is significant ($I^2 \geq 50\%$). Qualitative heterogeneity is used when heterogeneity is too large or the source of heterogeneity is unknown. Meta-regression analysis can be performed if there are many influencing factors and it is not appropriate to use the stratification method.

2.5.4. **Assessment of heterogeneity.** Before the combination of effect size, the heterogeneity of the included literature is tested using Stata 13.0. When inter-study heterogeneity exists, the random effect model will be used. For comparison of each pair, heterogeneity is determined by heterogeneity test and expressed by $I^2$ value. When $I^2 \geq 50\%$, the heterogeneity is large. When $25\% < I^2 < 50\%$, we think it is moderate. When $I^2 < 25\%$, the heterogeneity is considered small.

2.5.5. **Sensitivity analysis.** Sensitivity analysis is based on sample size, missing data results, and methodological quality. Sensitivity analysis will be put into effect to examine the robustness of the pooled results in case of sufficient data by determining the effects of excluding studies with high risks of bias or with missing data, and outliers.

2.5.6. **Subgroup analysis.** Subgroup analysis is to explore the source of heterogeneity. When more than 10 studies are included, subgroup analyses will be performed based on different participants, gender, duration of disease, interventions, and dose. We can better explore the source of heterogeneity as investigator by this method.

2.5.7. **Assessment of reporting bias.** If 10 or more papers are conducted, a comparison-adjusted funnel plot is developed to using Stata to evaluate the presence of small sample effects or publication bias in the intervention. Descriptive analysis will be carried out by the method of the symmetry of funnel plot. If there is asymmetric or no inverted funnel in the plot, it is deemed that there may be publication bias. It is possibly connected with the difficulty in the publication of the literature with negative results and the low quality of the inclusion methods.

2.5.8. **Grading the quality of the evidence.** To grade evidence quality and understand the actual situation of evidence rating thereby analyzing possible questions, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to evaluate the quality of evidence.19 On account of the risk of bias, imprecision, inconsistency, indirectness, and publication bias, GRADE grades evidence quality into 4 levels: high, medium, low, and very low.

3. Discussion

Diabetes is a metabolic disease characterized by chronic hyperglycemia, which is induced by genetic or environmental factors, accompanied by insufficient or relatively insufficient insulin secretion, causing glucolipid metabolism disorders.20 Insulin, sulfonylureas, and biguanides are traditional hypoglycemic drugs, these drugs are effective in lowering the glucose level of blood, but they also have some side effects and body dependence can develop.21 More studies have shown that HYS not only can control blood glucose levels, but also can effectively alleviate the symptoms of patients with type 2 diabetes. However, there has been no systematic review or meta-analysis to evaluate its efficacy and safety. Therefore, it is necessary to provide convincing evidence for the superiority of HYS in hyperlipidemia through
high-quality systematic review and meta-analysis. In addition, the study may have potential drawbacks. First, the Chinese-English research format is likely to increase the research bias. Second, age, gender, ethnicity, drug formulation, dose, and duration of treatment led to the risk of heterogeneity. Finally, this study may involve a small number of clinical trials, leading to a high risk of bias.

Author contributions
Peiyu He and Junyin Zhang made the same contribution to the research and design, and wrote the original draft of the protocol. Peiyu He has developed a search strategy. Peiyu He, Junyin Zhang, and Yingxiang Wang will conduct literature retrieval and collation. Peiyu He, Junyin Zhang, and Teng Peng will evaluate the risk of bias in the literature. Data analysis and article writing will be done by Peiyu He, Tianyu Gao. Teng Peng, as the corresponding author, will be responsible for overseeing every process of the audit review to control the quality of the study. All the authors have approved the publication of the protocol.

Data curation: Teng Peng.
Methodology: Yingxiang Wang.
Project administration: Tianyu Gao.
Writing – review & editing: Peiyu He, Junyin Zhang.

References
[1] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793–801.
[2] Friedman JM. Modern science versus the stigma of obesity. Nat Med 2004;10:563–9.
[3] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14.
Santiago JG, Walia S, Sun JK, et al. Influence of diabetes and diabetes type on anatomic and visual outcomes following central retinal vein occlusion. Eye (Lond) 2014;28:259–68.

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–36.

Chiriaco M, Pateras K, Virdis A, et al. Association between blood pressure variability, cardiovascular disease and mortality in type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2019;21:2587–98.

Yisahak SF, Beagley J, Hambleton IR, et al. Diabetes in North America and the Caribbean: an update. Diabetes Res Clin Pract 2014;103:223–30.

Chen X, Qian L, Wang BJ, et al. Synergistic hypoglycemic effects of pumpkin polysaccharides and puerarin on type II diabetes mellitus mice. Molecules 2019;24:955.

Betonico CC, Titan SMO, Lira A, et al. Insulin glargine U100 improved glycemic control and reduced nocturnal hypoglycemia in patients with type 2 diabetes mellitus and chronic kidney disease stages 3 and 4. Clin Ther 2019;41:2008–20.

Hung HY, Qian K, Morris-Natschke SL, et al. Recent discovery of plant-derived anti-diabetic natural products. Nat Prod Rep 2012;29:580–606.

Li You-yuan, Deng Hong-bo, Zhang Ping, et al. Effect of polygonati polysaccharide on glucose metabolism in diabetic mice. Chin J Clin Rehabil 2005;9:90–1.

Wang Y, Lan CJ, Liao X, et al. Polygonatum sibiricum polysaccharide potentially attenuates diabetic retinal injury in a diabetic rat model. J Diabetes Invest 2019;10:915–24.

Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.

Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.

Jellinger PS, H.ltman NO, Rosenblit PD, et al. American College of Clinical Endocrinology and American College of Endocrinology guideline for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23:1–87.

Joint Committee for the Revision of Guidelines for Prevention and Treatment of Diabetes in Adults in China Guidelines for the prevention and treatment of adult dyslipidemia in China (2016 revised, edition). China Circulation Magazine 2016;31:937–53.

Pharmaceutical Affairs Bureau of the Ministry of Health of the People’s Republic of China Compilation of Guidelines for Preclinical Research on New Drugs (Western Medicine), (Pharmacy, Pharmacology, Toxicology). China: Pharmaceutical Affairs Bureau of the Ministry of Health of the People’s Republic of China; 1993.

Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0. USA: The Cochrane Collaboration; 2017.

Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

Weyer C, Bogardus C, Mott DM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787–94.