INPLASY PROTOCOL

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Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Ginseng-plus-Bai-Hu-Tang combined with western medicine for the treatment of Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

Zhou, M[1]; Yu, R[2]; Liu, X[3]; Lv, X[4]; Xiang, Q[5].

Review question / Objective: **Objective. Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by chronic hyperglycemia, which is also accompanied by changes in blood lipids and protein. According to research reports, Ginseng-plus-Bai-Hu-Tang(GBHT) has significant antihyperglycemic activity. Nevertheless, the evidence of effectiveness is not enough. In order to verify effectiveness and safety of GBHT combined with conventional western medicine (CWM) in the treatment of T2DM, we carried out this meta-analysis. Method. We collected 7 electronic databases from the inception to September 1, 2021, then 12 studies were selected. The data analysis and methodological evaluation were conducted by the software RevMan 5.3.3 and stata 12.0. Results. The meta-analysis revealed that when GBHT was adopted in combination with CWM, the effective rate (OR=2.98, 95%CI=[2.01, 4.43], P<0.00001), the FBG (MD=-0.86, 95%CI=[-1.06,-0.65], P<0.00001), 2hBG (MD=-0.80, 95%CI=[-1.05,-0.55], P<0.00001), and HbA1c (MD=-0.64, 95%CI=[-0.98,-0.30], P= 0.0002) of T2DM patients improved significantly compared with the control group. After GBHT combined with CWM treatment, HOME-RI (MD=-0.75, 95%CI=[-1.38, -0.12], P=0.02) of T2DM patients was superior to CWM alone. In comparison, the benefit from FINS (MD=-1.42, 95%CI=[-4.46, -1.62], P=0.36) was not apparent. In addition, in some of the included literatures, the experimental group mentioned adverse reactions, but no adverse reactions occurred, indicating that it is safe enough. Conclusion. GBHT combined with CWM is an effective and safe as adjunctive treatment for patients with T2DM. Nevertheless, due to the limitation of the quality of the included studies, additional high-quality researches are required to further confirm these results.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 February 2022 and was last updated on 01 February 2022 (registration number INPLASY202220001).

INTRODUCTION

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plus-Bai-Hu-Tang(GBHT) has significant antihyperglycemic activity. Nevertheless, the evidence of effectiveness is not enough. In order to verify effectiveness and safety of GBHT combined with conventional western medicine (CWM) in the treatment of T2DM, we carried out this meta-analysis. Method. We collected 7 electronic databases from the inception to September 1, 2021, then 12 studies were selected. The data analysis and methodological evaluation were conducted by the software RevMan 5.3.3 and stata 12.0. Results. The meta-analysis revealed that when GBHT was adopted in combination with CWM, the effective rate (OR=2.98, 95%CI=[2.01, 4.43], P<0.00001), the FBG (MD=-0.86, 95%CI=[-1.06,-0.65], P<0.00001), 2hBG (MD=-0.80, 95%CI=[-1.05,-0.55], P<0.00001), and HbA1c (MD=-0.64, 95%CI=[-0.98,-0.30], P=0.0002) of T2DM patients improved significantly compared with the control group. After GBHT combined with CWM treatment, HOME-RI (MD=-0.75, 95%CI=[-1.38, -0.12], P=0.02) of T2DM patients was superior to CWM alone. In comparison, the benefit from FINS (MD=-1.42, 95%CI=[-4.46, -1.62], P=0.36) was not apparent. In addition, in some of the included literatures, the experimental group mentioned adverse reactions, but no adverse reactions occurred, indicating that it is safe enough. Conclusion. GBHT combined with CWM is an effective and safe as adjunctive treatment for patients with T2DM. Nevertheless, due to the limitation of the quality of the included studies, additional high-quality researches are required to further confirm these results.

Condition being studied: ①Study type: the included studies were RCTs studying GBHT combined with CWM for treating T2DM. ②Type of patients: the patients were diagnosed with T2DM, regardless of race, nationality, gender, age, or course of disease. ③Types of intervention: the experimental group was treated with GBHT combined with CWM, while the control group was treated with CWM alone (metformin, gliclazide, glipizide, rosiglitazone, etc.). ④Types of outcome measures: the effective rate, fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hBG), glycated hemoglobin (HbA1c). fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOME-RI).

METHODS

Search strategy: We selected all clinical trials of GBHT combined with CWM for the treatment of T2DM. After extensive searches on various websites from their establishment to September 1, 2021, including EMBASE, PubMed, the China Science and Technology Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), the Cochrane Library, the China National Knowledge Infrastructure (CNKI), and the WanFang databases. Then target literatures were picked out. Manual searches would also be performed to track necessary references on related literature. The following were the search keywords and terms we used: “traditional Chinese medicine”, “Chinese medicine”, “ginseng-plus-Bai-Hu-Tang”, “Baihujiarenshentang”, “bai hu jia ren shen tang”, “Diabetes Mellitus”, “Diabetes Mellitus type 2”, “T2DM” OR “Diabetes”, “Xiaoke”, “Xiaodan”, “randomized controlled trial”, “Randomized”, ”clinical research”, and ” placebo”. See Supplemental File 1 for a full description of the search strategy.

Participant or population: The patients were diagnosed with T2DM, regardless of race, nationality, gender, age, or course of disease.

Intervention: The experimental group was treated with GBHT combined with CWM,.

Comparator: While the control group was treated with CWM alone (metformin, gliclazide, glipizide, rosiglitazone, etc.

Study designs to be included: The included studies were RCTs studying GBHT combined with CWM for treating T2DM.

Eligibility criteria: ①Study type: the included studies were RCTs studying GBHT combined with CWM for treating T2DM.②Type of patients: the patients were diagnosed with T2DM, regardless of race, nationality, gender, age, or course of disease.③Types of intervention: the experimental group was treated with GBHT combined with CWM, while the control group was treated with CWM alone (metformin, gliclazide, glipizide, rosiglitazone, etc.).④Types of outcome measures: the effective rate, fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hBG), glycated hemoglobin (HbA1c). fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOME-RI).

Information sources: We selected all clinical trials of GBHT combined with CWM for the treatment of T2DM. After extensive searches on various websites from their establishment to September 1, 2021, including EMBASE, PubMed, the China Science and Technology Journal Database (VIP), the Chinese Biomedical Literature Database (CBM),the Cochrane Library, the China National Knowledge Infrastructure (CNKI), and the WanFang databases.

Main outcome(s): The effective rate, fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hBG), glycated hemoglobin (HbA1c). fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOME-RI). The effective rate was referred to "Guiding Principles for Clinical Research of New Chinese Medicines". Standard of significantly effective: the significant improvement of symptoms and signs, including FBG, 2hBG, and HbA1c dropped ≥40%. Standard of effective: the obvious significant improvement of symptoms and signs, including FBG, 2hBG, and HbA1c decreased by ≥20%. Standard of invalidity: the clinical improvement of symptoms and signs were not reach the above standard.

Additional outcome(s): No.

Data management: Two independent researchers (Min Zhou and Xiu Liu) conducted extensive screening and extracted target-related data for classification and integration. The extracted data included the first author, publication year, baseline characteristics, intervention, outcome indicators, and adverse events. In the process of screening, if we encountered difficulties that were difficult to resolve, we would to discuss and decide in detail with the third researcher(Rong Yu).

Quality assessment / Risk of bias analysis: Based on the Cochrane Systematic Review Manual RCT bias risk assessment tool, we completed the risk assessment of the included studies. The contents include the following: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.

Strategy of data synthesis: "traditional Chinese medicine", "Chinese medicine", "ginseng-plus-Bai-Hu-Tang", "Baihujiarenshentang", "bai hu jia ren shen tang", "Diabetes Mellitus", "Diabetes Mellitus type 2", "T2DM" OR "Diabetes", "Xiaoke", "Xiaodan", "randomized controlled trial", "Randomized", "clinical research", and "placebo". See Supplemental File 1 for a full description of the search strategy.

Subgroup analysis: The random effects model was adopted, and the result indicated that the heterogeneity of interstudy was significant so the reasons for heterogeneity would be analyzed by performing subgroup analysis.no.

Sensitivity analysis: Sensitivity analysis would be conducted on each indicator to evaluate the stability.

Language: English.

Country(ies) involved: China.

Keywords: Ginseng-plus-Bai-Hu-Tang; Type 2 Diabetes Mellitus ; Meta-Analysis.

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