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Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: study protocol for a randomized controlled trial

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Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: study protocol for a randomized controlled trial

Author

Jianrong Chen,[1#] Jiancheng Wang,[1#] Lixia Yuan,[2] Qiuyun Xue,[2] Jieyi Zhou,[2] Xiang Ye,[3] Qihui Fan,[3] Ruting Feng,[3] Chenxi Li,[3] Yan Zhang,[3] Weifeng Zhu[2], Zhengfeng Li,[3*] Xu Zhou[1*]

[#] Jianrong Chen and Jiancheng Wang contributed equally to this work and are co-first authors.

Affiliation

[1] Department of Endocrinology and Metabolism, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi, China

[2] Evidence-based Medicine Research Center, Jiangxi University of Chinese Medicine, Nanchang 330006, Jiangxi, China

[3] Department of Diabetes and Endocrinology, The Affiliated Hospital of Jiangxi University of Chinese Medicine, Nanchang 330006, Jiangxi, China

[*] Corresponding authors:

Xu Zhou (Email: zhouxu_ebm@hotmail.com), Evidence-based Medicine Research Center, Jiangxi University of Chinese Medicine, Mei Ling Avenue No. 1688,

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Nanchang 330004, Jiangxi, China. Phone: +8618870050733, Fax: +86079187118012

Zhengfeng Li (Email: 361127933@qq.com), Department of Diabetes and Endocrinology, The Affiliated Hospital of Jiangxi University of Chinese Medicine, Bayi Avenue No.445, Nanchang 330006, Jiangxi, China

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Abstract

Introduction The current pharmacological management of type 2 diabetes mellitus (T2DM) faces challenges such as low rates of optimal glycemic control, high incidences of adverse drug reactions, and suboptimal treatment compliance. Pueraria lobata radix (PLR), a medicinal and edible herb, has shown hypoglycemic effects in animal models. However, existing clinical studies have only assessed the hypoglycemic effect of PLR-containing herb formulas or PLR extract preparations. The aim of this study is to investigate the efficacy and safety of using PLR solely as an adjuvant therapy for T2DM.

Methods and analysis This study is a multicenter, randomized, double-blind, placebo-controlled trial. Two hundred patients with T2DM will be randomly allocated to either the T2DM group or the placebo group for a consecutive 12-week intervention. Regular visits will be conducted at weeks 4, 8, and 12 following the initiation of the study to evaluate the efficacy and safety of PLR. The primary outcome is the change in hemoglobin A1c (HbA1c) from baseline at week 12. Secondary outcomes include changes in HbA1c from baseline at weeks 4 and 8; the HbA1c response rate (< 7%), changes in fasting blood glucose, two-hour blood glucose, fasting C-peptide, body mass index, severity of diabetes symptoms, quality of life from baseline at weeks 4, 8, and 12; and changes in blood lipid indicators at week 12. Safety outcomes include the incidences of total adverse events (AEs), serious AEs, and PLR-related AEs.

Ethics and dissemination The protocol has been approved by the Ethics Committees of the First Affiliated Hospital of Nanchang University (approval number: IIT[2024]LLS No.303) and the Affiliated Hospital of Jiangxi University of Chinese

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Medicine (approval number: JZFYLL2024006200087). We will disseminate the study findings through publications in peer-reviewed journals and conference presentations.

Trial registration number: ClinicalTrials.gov NCT06494683.

Keywords: Pueraria lobata radix; Type 2 diabetes mellitus; Efficacy; Safety; Randomized controlled trial

Strengths and limitations of this study

- This is the first randomised controlled trial conducted to assess the efficacy and safety of daily pueraria lobata radix as an adjuvant therapy in patients with type 2 diabetes mellitus.
- This trial adopted a multicenter, randomized, double-blind, placebo-controlled design, which could balance the known and unknown confounding factors between groups and overcome the placebo effect. The multiple compliance guarantee measures and reasonable statistical analysis plan will contribute to enhancing the quality of the trial and obtaining accurate evaluation results.
- A total of 200 cases of sample size will be sufficient to ensure the statistical power and the credibility of the pre-specified subgroup analyses.
- A potential limitation of the study is that patients may not adhere to the 12-week pueraria lobata radix or placebo intervention.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with the highest prevalence [1]. Data released by the International Diabetes Federation in 2021 indicated that the number of patients with T2DM among the population aged 20--79 has soared to 537 million, accounting for 10.5% of the total global population, and it is predicted that the number will escalate to 783 million by 2045 [2]. The chronic hyperglycemic state leads to multiple complications, such as cardiovascular diseases, strokes, blindness, renal failure, and foot ulcers [3,4]. These serious consequences are among the chief causes of premature mortality and reduced life expectancy in humans [5,6]. Furthermore, the medical expenditures associated with T2DM impose an immense socioeconomic burden—the total global medical expenses for T2DM in 2021 amount to $966 billion, representing a 27.1% increase from 2019 [7]. This figure, if considered a country's GDP, could secure 18th rank globally [8].

T2DM is conventionally managed through oral hypoglycemic drugs and insulin [9]. These drugs can increase insulin levels, alleviate insulin resistance, and achieve the goal of lowering blood glucose. However, a significant proportion of patients still fail to attain optimal blood glucose control [10,11]. The principal cause of this problem is the limited hypoglycemic ability of existing oral hypoglycemic drugs [12,13]. For example, a network meta-analysis of multiple hypoglycemic drugs revealed that, compared with that of placebo, the reduction in hemoglobin A1c (HbA1c) ranged from -1.48% for the highest semaglutide to only -0.50% for the lowest dipeptidyl peptidase-4 inhibitors [14]. Secondary failure is also a challenging issue. For example, 42% of T2DM patients who

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received metformin, a first-line monotherapy drug, experienced secondary failure during the average follow-up period of 27.6 months, corresponding to a failure rate of 17% per year [15]. The combination of multiple hypoglycemic drugs is a way to solve these issues; however, it considerably increases adverse drug reactions, such as hypoglycemia [16] and gastrointestinal symptoms [17]. Moreover, compliance is a crucial factor affecting the effectiveness of hypoglycemic drugs. A survey has revealed that the proportion of patients with good compliance with hypoglycemic drugs is less than 40% [18]. Adverse drug reactions and complex treatment regimens (combination therapy or the requirement for injection) are the primary reasons for poor patient compliance [19-21]. Therefore, it is imperative to explore complementary therapies that can enhance efficacy, safety, and long-term compliance for the management of T2DM.

Pueraria lobata radix (PLR; Chinese name: Gegen) is the dry root of the leguminous plant *Pueraria lobata* (Willd.) Ohwi. In East Asian countries, particularly in China, PLR has been used as an ingredient in traditional herbal prescriptions for T2DM. For example, Gegen Qinlian Decoction, composed of PLR, Scutellaria baicalensis, Coptis chinensis, and Glycyrrhiza uralensis, has been found to significantly reduce the level of blood glucose and increase the level of serum insulin [22,23]. Isoflavones in PLR, such as daidzein, genistein, and puerarin, have been shown to have hypoglycemic activity. The mechanism of hypoglycemic action may involve multiple signaling pathways, such as the PI3K-Akt, PPAR, and HIF-1 pathways [24-26]. Recent studies have also found that the polysaccharides contained in PLR also have hypoglycemic effects, which improve insulin resistance in mice by regulating the PPAR

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signaling pathway [27].

In China, PLR is a medicinal and edible herb, as stipulated by regulations; that is, based on traditional consumption experience, it is considered to have food-level safety and can be made directly into foods or serve as a food ingredient. The safety evaluation of standardized PLR extracts also reached a conclusion of being favorable safety [28]. These facts provide a prerequisite for its application in the dietotherapy of T2DM. However, to date, all clinical studies regarding the hypoglycemic effect of PLR focused on PLR-containing herbal formulas or preparations of PLR extracts, and there is no evidence from randomized controlled trials (RCTs) for assessing PLR alone for adjunctive hypoglycemic management. Therefore, we plan to conduct an RCT to assess the efficacy and safety of PLR as an adjuvant therapy in the management of T2DM.

METHODS AND ANALYSIS

Study design

This study will be a multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. This protocol has been registered at clinicaltrials.gov (identifier: NCT06494683). Participants will be recruited at the First Affiliated Hospital of Nanchang University and the Affiliated Hospital of Jiangxi University of Chinese Medicine. Eligible patients with T2DM will be randomly assigned to either the PLR group or the placebo group. The reporting of this trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [29]. The study process is

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shown in Figure 1.

Eligibility criteria

The participants will be evaluated by clinicians with professional qualifications in endocrinology to determine whether they meet the following inclusion criteria to participate in this trial:

1) Diagnosed with T2DM according to the criteria of the American Diabetes Association [30], that is, fasting blood glucose (FBG) ≥ 126 mg/dl (7.0 mmol/l) or blood glucose ≥ 200 mg/dl (11.1 mmol/l) 2 hours after oral administration of 75 g glucose or HbA1c ≥ 6.5% (48 mmol/mol).
2) Aged between 18 and 80 years.
3) Treatment-naïve patients or patients who are receiving regular drug hypoglycemic treatment (both oral hypoglycemic drugs and insulin are allowed, regardless of the type and dose).
4) Blood glucose has not been effectively controlled for the past three months, defined as an HbA1c between 6.5% and 10.5%.
5) Agree to the requirements of dietary control during the study period.
6) Voluntarily participate and sign the informed consent form.

Patients with the following conditions will not be eligible to participate:

1) Type 1 diabetes mellitus, gestational diabetes mellitus, or other special types of diabetes mellitus.
2) Experienced acute complications of T2DM, such as ketoacidosis, hyperosmolar coma, and lactic acidosis.

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3) Pregnant or lactating women, or women planning to become pregnant.

4) A history of allergy to PLR.

5) Complicated with severe dysfunction of important organs, such as the heart, liver, and kidney; malignant tumors; or severe mental disorders.

6) Poor expected compliance.

7) Currently participating in other clinical trials.

Interventions and cointerventions

Participants in the PLR group and the placebo group will receive PLR and placebo treatment, respectively, once daily, for 12 weeks, with a dosage of 15 g per dose. PLR and placebo will be made into granules that can be dissolved in warm water for convenient administration. To produce granules, PLR decoction pieces will be fully soaked and then decocted with water three times, and all the decocted liquids will be combined, concentrated, and dried to form granules. The placebo granules will be made by blending lactose, caramel color, sunset yellow, and PLR essence. There will be no or almost no difference in color, smell, taste, appearance, or packaging between the PLR and placebo preparations.

Untreated participants will receive hypoglycemic drug treatment according to the conventional treatment procedure during the study period, and the initial type and dose of hypoglycemic drugs will be maintained unchanged as much as possible. For participants who have been receiving regular treatment with hypoglycemic drugs, the drug type and dose will also be sustained throughout the study period. When clinicians believe that a patient has an uncontrolled blood glucose level (either too high or too

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low), hypoglycemic treatment can be appropriately adjusted. The adjustment might involve increasing the dose of the original hypoglycemic drugs or adding other hypoglycemic drugs (with metformin or glimepiride being preferred), and any adjustments will be recorded. All participants are required to regulate their diet, including restricting the intake of monosaccharides, daily fat intake, and total calories based on body weight, and to adhere to a diet pattern of small and frequent meals, a light diet, and punctual eating. Other herbal remedies will be prohibited. Treatment of comorbidities, such as hypertension and dyslipidemia, as well as adverse reactions during the study period, is permitted. In the event of a violation of the intervention or cointervention protocol, participants should truthfully report the type and dosage of the violation and make detailed records, while subsequent interventions and visits will proceed.

Randomization and Blinding

An independent randomization center will be established to generate and manage random sequences. The "blockrand" function in R 4.1.0 (Ross Ihaka, Robert Gentlemen, New Zealand) will be used to generate random sequences with mixed block lengths of 4, 6, or 8, featuring a 1:1 allocation ratio between the PLR group and the placebo group. One random sequence with a fixed seed will be generated for each research center. Sealed packaging will be adopted to conceal random sequences. First, the central pharmacy will arrange PLR and placebo samples according to the random sequences and then affixes sequential numbers on the packaging. When patients participate in the trial, the samples will be distributed according to the enrollment sequence. Therefore,

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neither the clinicians nor the participants can be aware of the grouping results. Before the completion of data analysis, all participants, clinicians, outcome evaluators, and data analysts will be blinded to the randomized grouping. In the case of serious adverse events (AEs) during the study, emergency unblinding is allowed to provide necessary information for treatment.

Outcomes

Efficacy outcomes

The primary outcome for efficacy assessment is the change in HbA1c at week 12 from baseline. Secondary efficacy outcomes include 1) changes in HbA1c at weeks 4 and 8 from the baseline; 2) the HbA1c response rate at weeks 4, 8, and 12, defined as HbA1c < 7.0%; 3) changes in other blood glucose indicators at weeks 4, 8, and 12, including FBG, 2-hour postprandial blood glucose, and fasting C-peptide; 4) changes in body mass index, systolic blood pressure, and diastolic blood pressure at weeks 4, 8, and 12; 5) changes in levels of blood lipid indicators at week 12, including total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol; 6) changes in the severity of diabetic symptoms at weeks 4, 8, and 12 evaluated by the score of the Diabetic Symptom Severity Grading Scale in the *Clinical Research Guiding Principles for New Drugs of Chinese Medicine* [31]; the scale contains 24 items and assesses the main symptoms of diabetes, such as excessive thirst and desire to drink, excessive eating and easy to be hungry, frequent urination, and frequent nocturia, with each item scoring 0 to 3 (total 0 to 72) and a higher score indicating more severe symptoms (Additional File

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1); 7) changes in the quality of life of patients at weeks 4, 8, and 12 evaluated by the score of the Diabetes-Specific Quality of Life Scale [32]; the scale contains 27 items and assesses the impact of diabetes on the quality of life of patients in four dimensions of physiology, psychology, society, and treatment, with each item scoring 0 to 4 (total 0 to 108) and a higher score indicating a poorer quality of life (Additional File 2); and 8) changes in the dose of hypoglycemic drugs at weeks 4, 8, and 12 from the baseline.

Safety outcomes

Safety outcomes include the incidences of any AEs), serious AEs, and PLR-related AEs within 12 weeks. An AE is defined as any adverse symptom or event that is not related to the natural progression of the patient's original disease. The data sources for safety evaluation include tests of blood, urine, and stool routine, stool occult blood, FBG, liver function (including alanine aminotransferase, aspartate aminotransferase, and total bilirubin), and kidney function (including serum creatinine, urea nitrogen, and uric acid) and electrocardiogram examinations. Among these examinations, if the baseline level is normal and the indicator level at follow-up exceeds twice the upper limit of the normal reference value or is reported as qualitatively abnormal, it will be considered an AE. The incidences of symptomatic hypoglycemia and gastrointestinal symptoms will be monitored with emphasis. Symptomatic hypoglycemia is defined as a blood glucose level lower than 3.9 mmol/L accompanied by hypoglycemic symptoms, such as palpitations, sweating, hunger, tremors, and anxiety. We will document the time, location, course of disease, clinical manifestations, management, and outcome of each AE. The correlation between AEs and PLR treatment will be comprehensively

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evaluated by clinicians based on the following factors: 1) whether there is a reasonable temporal relationship between the occurrence of the AE and the administration of PLR; 2) whether the AE can be explained by other factors; 3) whether the AE has been reported in previous literature or has reasonable biological mechanisms; 4) whether the AE disappears or alleviates after the discontinuation or reduction of PLR; and 5) whether the same AE recurs after readministering PLR. A serious AE is defined as an AE that leads to hospitalization or a prolonged hospital stay, affects work ability, endangers life, or causes disability, congenital malformations, or death. Any serious AEs will be immediately reported to the hospital ethics committee.

Schedule of visits

Study visits will be conducted at baseline and at weeks 4, 8, and 12. During the baseline visit, we will collect demographic data, disease history, and medication history; examine baseline vital signs, blood glucose indicators, blood lipid indicators, and safety indicators; and measure baseline scores on the severity of symptom and quality of life scales. At each subsequent follow-up visit, we will perform examinations or measurements of vital signs, blood glucose indicators, and symptom and quality of life scales and record compliance with interventions, newly emerged diseases or disease progression, the dose of hypoglycemic drugs, and AEs. At the last follow-up, we will additionally examine lipid indicators and laboratory indicators related to safety. The time window for each follow-up visit is ±3 days from the scheduled visit date. If a patient fails to complete the follow-up within the scheduled time for any reason, we will consider this visit as lost to follow-up and no longer collect the data from this visit.

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The detailed follow-up arrangement is shown in Figure 2.

Quality control and data management

A steering committee composed of endocrinology experts, herbal medicine experts, statistics experts, ethics experts, and the director of the research hospital will be established. This committee will be responsible for formulating and reviewing the study protocol, establishing standard operating procedures, and organizing and supervising the quality of implementation. This trial has no interim analysis plan, but the steering committee can decide to conduct an interim analysis depending on the progress of the trial and determine whether to prematurely terminate the trial based on the results of the interim analysis, such as when the interventions are unlikely to achieve any significant efficacy or there are major safety issues. Each research hospital will be equipped with two full-time clinical research coordinators, who are responsible for cooperating with clinicians to conduct research visits. All researchers will fully study the study protocol and undergo training on standard operating procedures. Every patient participating in the trial will receive one-on-one reception, including disease consultation, the completion of case report forms, the collection of biological samples, and the distribution of PLR or placebo samples. To increase compliance, we will first obtain thorough informed consent for each participant, including randomization grouping, potential benefits and side effects of each group, and the responsibilities for participating in the study. The trust of patients in clinicians and their interest in the research are the core factors to guarantee compliance. Second, clinical research coordinators will actively remind patients when the planned follow-up date is

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approaching and respond to patients' inquiries regarding health or the study protocol at any time. In addition, we will provide participants with free PLR and placebo samples and free research-related examinations, as well as transportation subsidies for each return visit (100 yuan per person per visit). Patients in the placebo group will be compensated with the same amount of PLR samples as those in the experimental group after the completion of the trial. To verify the compliance of the self-reported dose of the trial samples, patients will be required to return the empty packaging bags of the consumed samples and the packaging bags of the remaining samples for obtaining free samples in the next month and transportation subsidies.

An independent data monitoring committee will be established to manage the research data and regularly inspect the quality of data collection. The original data will be recorded in paper case report forms and stored in locked boxes at each research center. After the completion of the data collection, the data of the paper case report forms will be re-entered into the electronic database constructed by Microsoft Access by two independent staff members, with cross-verification to ensure accuracy. All patient information will be kept strictly confidential.

Sample size calculation

There are no previous clinical studies comparing PLR with a placebo for T2DM. Based on clinical considerations and expert opinions, we anticipate the mean difference (δ) in the reduction of the primary outcome (i.e., the change in HbA1c levels at week 12) between the PLR group and the placebo group to be 0.50% and the common standard deviation (σ) between the groups to be 0.75%. With the assumed type I error

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probability of 0.05 and type II error probability of 0.20, along with a potential 20% loss to follow-up, a sample size calculation formula of the superiority design indicates that at least 47 cases are needed for each group. To increase the credibility of subgroup analyses, we plan to expand the sample size to 100 cases for each group within the limits of funding support, resulting in a total of 200 cases.

Statistical analysis

Descriptive statistics will be conducted for baseline characteristics, where continuous variables will be presented as means and standard deviations, and categorical variables will be presented as frequencies and percentages. The analysis of efficacy outcomes will use the full analysis set based on the modified intention-to-treat principle, encompassing the population that has received at least one dose of the PLR or placebo after randomization and has outcome data of at least one follow-up. The estimation of intergroup differences in continuous outcomes will employ a repeated-measures mixed effects model, in which age (continuous), body mass index (continuous), baseline HbA1c (continuous), and use of insulin (binary) are fixed-effect covariates, and research center, time, and interaction of time and group are random-effect covariates. The effect size on continuous outcomes will be least-square mean differences and 95% confidence intervals (CIs). The estimation of intergroup differences in binary outcomes will employ a repeated-measures generalized linear mixed model with the logit link, with the same covariates. The effect size on binary outcomes will be odds ratios and 95% CIs. Missing values in outcomes will be imputed via the multiple imputation method based on the regression model, where covariates

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include age, body mass index, baseline HbA1c, use of insulin, and the research center. One hundred imputed datasets will be generated and used to fit the statistical models, and the results will be averaged as the final effect estimate. The analysis of safety outcomes will be based on the safety set, defined as the population that has received at least one dose of PLR or placebo.

To verify the robustness of the results of the efficacy analysis, the following sensitivity analyses will be conducted: 1) using the per-protocol set, which is defined as the population that has consumed more than 80% of the PLR or placebo samples, has not violated the intervention and cointervention requirements, has not adjusted the dose of hypoglycemic drugs or added new hypoglycemic drugs compared with the baseline prescription, has no major violations of the dietary control requirements, has not been unblinded, and has completed the week 12 visit; 2) Abstaining from imputing missing values; and 3) Adjusting any additional unbalanced baseline characteristics in the statistical models.

To provide evidence for precise treatment, we will conduct subgroup analyses stratified by the following factors for the primary outcome: 1) Age (< 65 years versus ≥ 65 years); considering the potential impact of age on drug absorption and metabolism ability, it is anticipated that participants aged < 65 years will achieve superior efficacy; 2) baseline body mass index (< 23.0 kg/m^2 versus ≥ 23.0 kg/m^2); considering the potential effects of PLR on inhibiting abnormal leptin receptors, it is anticipated that participants with a body mass index ≥ 23.0 kg/m^2 will achieve superior efficacy; 3) baseline HbA1c level (< 9% versus ≥ 9%); considering the impact of baseline HbA1c

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control on the absolute level of HbA1c reduction, it is anticipated that participants with a baseline HbA1c ≥ 9% will achieve superior efficacy; and 4) the use of insulin (yes versus no); considering the potentially stronger masking effect of insulin on the efficacy of PLR, it is anticipated that participants not receiving insulin will achieve superior efficacy.

All analyses will not adjust the significance boundary; that is, a p value less than 0.05 will be considered statistically significant. All the statistical analyses will be performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

The trial design has not yet involved patients or public.

Ethics approval and consent to participate

The protocol has been approved by the Ethics Committees of the First Affiliated Hospital of Nanchang University (approval number: IIT[2024]LLS No.303) and the Affiliated Hospital of Jiangxi University of Chinese Medicine (approval number: JZFYLL2024006200087). The trial will be conducted in strict accordance with the Declaration of Helsinki and Good Clinical Practice standards. The patient informed consent form contains the process of the trial and the possible benefits and risks. There is no ancillary or posttrial care, and patients will receive free treatment if any intervention-related adverse effects occur. Details of the collection and use of participant data are described in the Informed Consent Form (Additional file 3). The

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investigators will initiate the study with the patient after he or she has signed the informed consent form. Participants can voluntarily withdraw from the trial at any time for any reason without affecting subsequent treatment. If important modifications are made to the study protocol, we will submit it to the Ethics Committee for re-examination.

DISCUSSION

There are more than 20 species of plants belonging to the genus Pueraria worldwide, primarily distributed in subtropical and temperate regions [33]. China constitutes the distribution center of the genus Pueraria, comprising approximately ten species. Among them, *Pueraria lobata* (Wild.) Ohwi and *Pueraria montana* var. thomsonii are the species endowed with the most abundant resources and the widest cultivation scope, and their roots are also the types legally defined as medicinal and edible herbs in China [34,35]. Compared with that in Pueraria thomsonii radix, the total flavonoid content in PLR, particularly puerarin, is significantly greater. Therefore, PLR holds greater medicinal value and is more prevalently employed in herbal prescriptions than Pueraria thomsonii radix [36]. As a result, we chose PLR as the evaluation object in this trial.

This study will be the first RCT to evaluate the efficacy and safety of PLR as an adjunctive treatment for T2DM. Previous clinical trials concerning the hypoglycemic effect of PLR focused on herbal formulas containing PLR (e.g., Gegen Qinlian Decoction) or PLR extracts (e.g., Puerarin injection). The indirectness of these trials in

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reflecting the effect and safety of PLR on T2DM should be negligible. In addition, previous studies also have substantial methodological limitations, such as the absence of blinding, failure to implement allocation concealment, and irrational statistical analysis methods. In contrast, this RCT will adopt double-blinding for both patients and clinicians by establishing a placebo control, standardizing the implementation of randomization and allocation concealment procedures, and undertaking rigorous quality control during the follow-up stage. In the statistical analysis, the main analysis will be based on the full analysis set constructed based on the modified intention-to-treat principle, which will obtain a relatively conservative effect estimate (i.e., unfavorable to PLR). Moreover, we will fit appropriate multivariate models for different types of outcomes to overcome the potential confounding biases related to the center effect and other covariates. These methodological advantages enable our study to yield accurate estimates regarding the effects of PLR.

Although herbal formulas containing PLR or puerarin injection may also have hypoglycemic effects, it is necessary to investigate the individual hypoglycemic effects of PLR. If this RCT ultimately demonstrates that the daily dose of PLR is effective and safe for T2DM patients, it will lead to multiple positive impacts. First, the supplementary hypoglycemic effect of PLR will facilitate the control of blood glucose at an ideal level, delay the progression of T2DM, and ultimately reduce the risk of diabetic complications. If PLR is verified to be safe, it could be used to replace some doses of hypoglycemic drugs to mitigate adverse drug reactions. Owing to its medicinal and edible properties, PLR can be directly consumed as food or added to daily edible

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products such as tea or beverages in numerous countries, which will contribute to improving compliance with long-term use by patients with T2DM. In addition, PLR is an inexpensive herb. Consumed at the daily dose of this trial, the cost per month of PLR is only approximately two dollars. Therefore, the complementary treatment of PLR may also assist in reducing the medical costs of patients with T2DM.

One potential limitation of this study lies in the assessment of certain subjective outcomes, namely, the Diabetic Symptom Severity Grading Scale and the Diabetes-Specific Quality of Life Scale, which might be influenced by disparities in the comprehension of subjective items among participants or clinicians. To minimize deviation from cognitive factors, we will establish evaluation criteria for each scale item in the training of the standard operating procedure and guide the participants to accurately understand their condition. Another potential limitation is that some participants may be difficult to adhere to the 12-week intervention and follow-up plan. To improve participant compliance, we will maintain communication with all participants throughout the follow-up process, answer patients' consultations on the condition at any time, and offer research subsidies for all participants and compensation of PLR samples for the placebo group.

In summary, to date, no rigorous RCTs have assessed the effects of PLR on the clinical outcomes of patients with T2DM. This study will have a sufficient sample size to obtain accurate effect estimates and will conduct a follow-up for up to three months to verify the long-term safety and patient compliance with the daily consumption of PLR. The research findings may provide new options and evidence-based regimens for

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the management of T2DM.

Trial status

The protocol version is 1.1, developed on May 31, 2024. The trial began recruiting on July 25, 2024, and is anticipated to finish in June 2025.

Acknowledgments

Not applicable.

Contributions

JC and JW designed the study, developed the statistical analysis plan and drafted the manuscript. LY, QX, JZ, XY, TF, RF, and CL were involved in the study design, communicated with the community centers, and revised the manuscript; YZ and WZ provided critical methodological advice and revised the manuscript; ZL and XZ conceived and designed the study, reviewed the manuscript, and acts as guarantors. All authors have contributed to writing the manuscript as detailed, and no professional writers have been involved. All authors have read and approved the final version of the manuscript.

Availability of data and material

The datasets collected during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Legends of Figures

Figure 1. Flowchart of the study process.

Figure 2. Schedule of the study visits.

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Figure 1

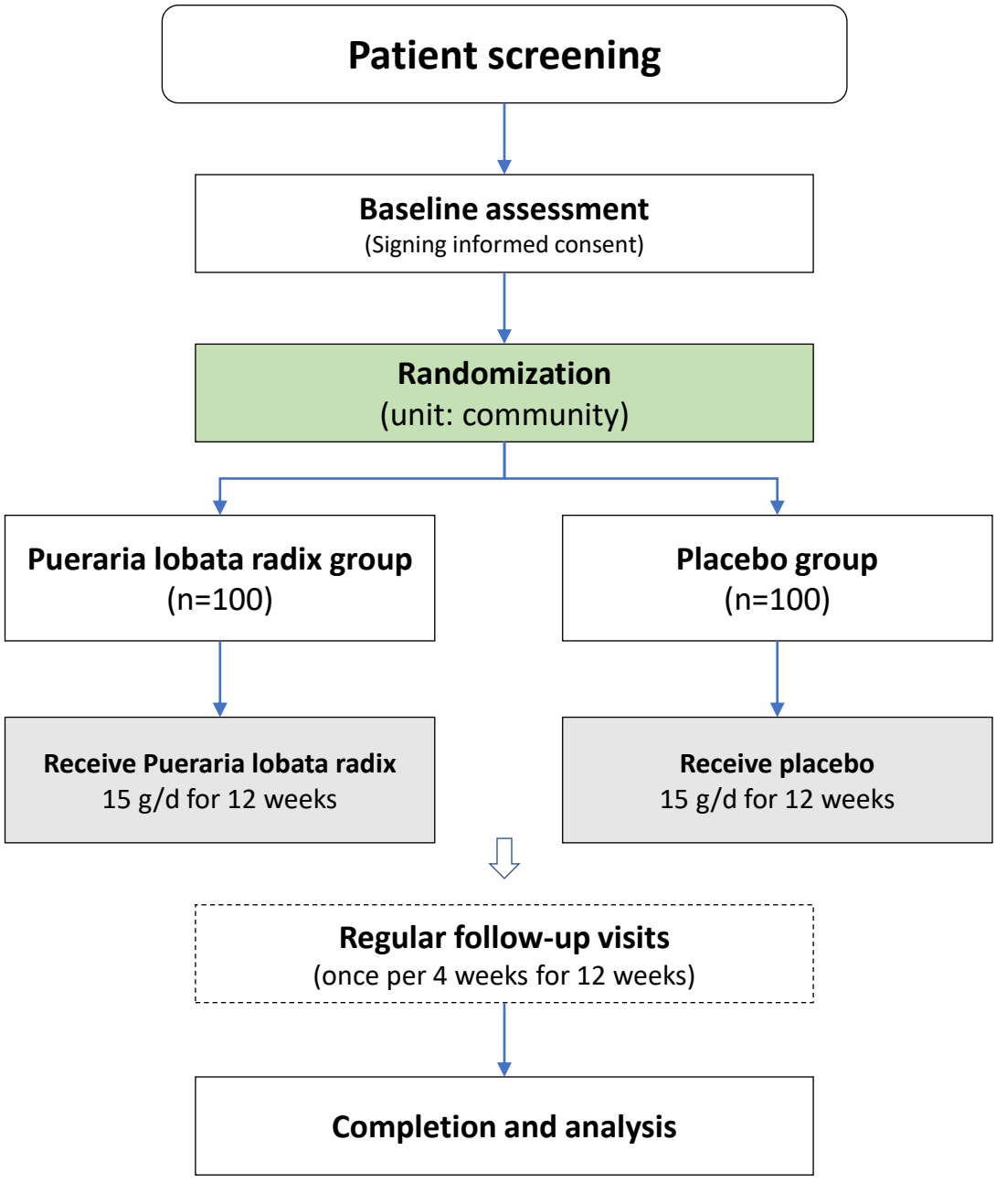

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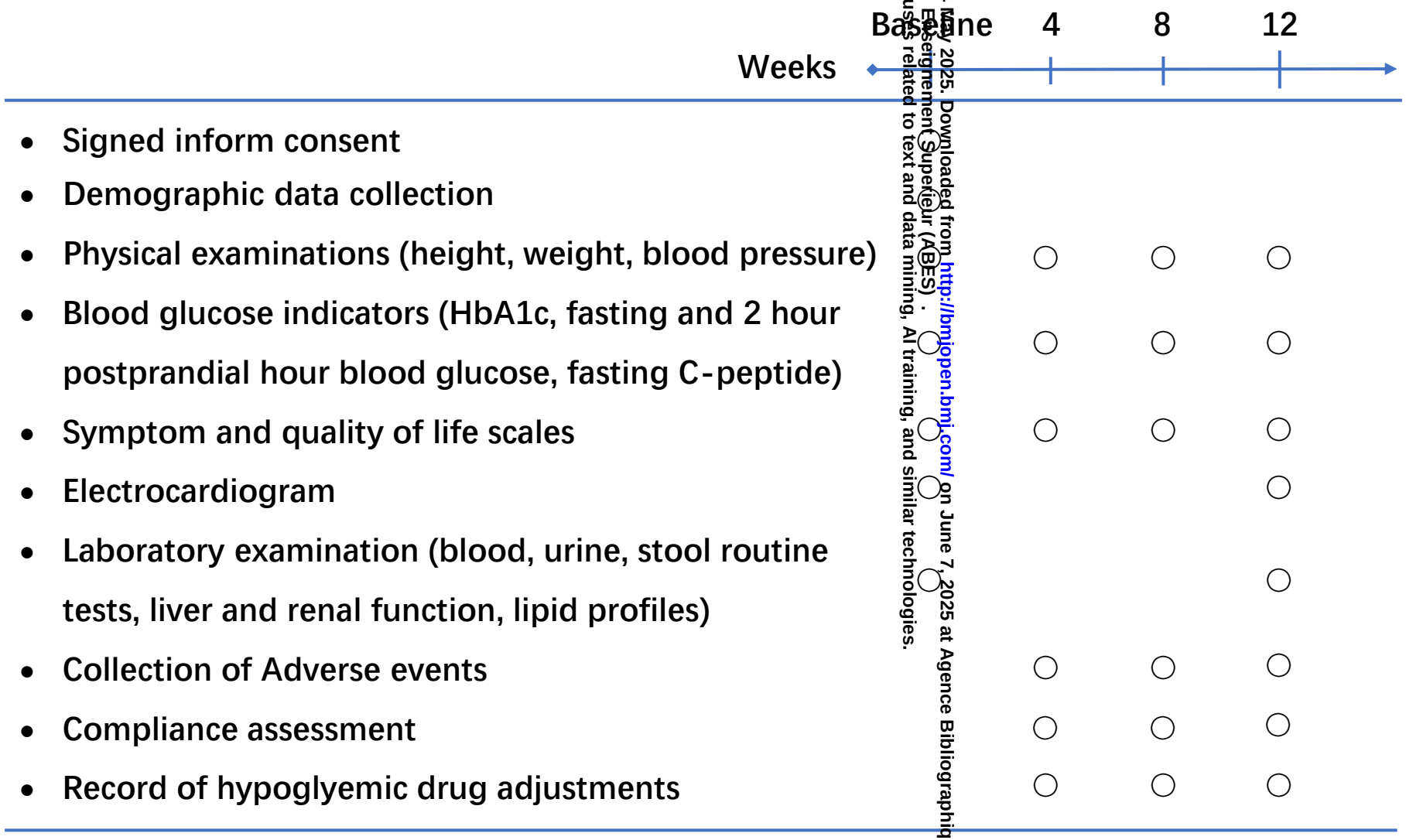
Figure 2



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Contents of Additional Files

Additional file 1: Diabetic Symptom Severity Grading Scale

Additional file 2. Diabetes-Specific Quality of Life Scale (DSQL)

Additional file 3. Informed consent form (translated)

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Additional file 1. Diabetic Symptom Severity Grading Scale

Items	Severity			
Thirst and desire to drink	None ☐	Mild ☐	Moderate ☐	Severe ☐
Frequent hunger and excessive eating	None ☐	Mild ☐	Moderate ☐	Severe ☐
Frequent urination	None ☐	Mild ☐	Moderate ☐	Severe ☐
Frequent nocturia	None ☐	Mild ☐	Moderate ☐	Severe ☐
Unsmooth defecation	None ☐	Mild ☐	Moderate ☐	Severe ☐
Dry stool	None ☐	Mild ☐	Moderate ☐	Severe ☐
Frequent defecation	None ☐	Mild ☐	Moderate ☐	Severe ☐
Upset mood	None ☐	Mild ☐	Moderate ☐	Severe ☐
Hot hands and feet	None ☐	Mild ☐	Moderate ☐	Severe ☐
Abdominal distension	None ☐	Mild ☐	Moderate ☐	Severe ☐
Heaviness of the head and body	None ☐	Mild ☐	Moderate ☐	Severe ☐
Lethargy and fatigue	None ☐	Mild ☐	Moderate ☐	Severe ☐
Shortness of breath and disinclination to speak	None ☐	Mild ☐	Moderate ☐	Severe ☐
Palpitation	None ☐	Mild ☐	Moderate ☐	Severe ☐
Insomnia	None ☐	Mild ☐	Moderate ☐	Severe ☐
Forgetfulness	None ☐	Mild ☐	Moderate ☐	Severe ☐
Low back pain	None ☐	Mild ☐	Moderate ☐	Severe ☐
Weakness of the waist and knees	None ☐	Mild ☐	Moderate ☐	Severe ☐
Cold hands and feet	None ☐	Mild ☐	Moderate ☐	Severe ☐
Excessive sweating	None ☐	Mild ☐	Moderate ☐	Severe ☐
Edema	None ☐	Mild ☐	Moderate ☐	Severe ☐
Chest and hypochondriac pain	None ☐	Mild ☐	Moderate ☐	Severe ☐
Numbness of limbs	None ☐	Mild ☐	Moderate ☐	Severe ☐
Pain in limbs	None ☐	Mild ☐	Moderate ☐	Severe ☐

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Additional file 2. Diabetes-Specific Quality of Life Scale (DSQL)

Question	Option				
1. Generally, how much damage does diabetes cause to your health?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
2. Do you often have uncomfortable physical sensations such as itchy skin, numbness, and pain in limbs?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
3. How much interference does the uncomfortable physical sensation cause to your life?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
4. Do you feel that it is increasingly difficult to see things?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
5. How much impact does the decline in vision have on your daily life?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
6. Do you feel that it is increasingly difficult to hear others clearly?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
7. How much impact does the decline in hearing have on your daily life?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
8. Do you often feel chest pain, chest tightness, and palpitations?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
9. Do you feel that your skin and feet are prone to infection?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
10. How much impact does the infection of skin/feet have on your life?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
11. Do you feel that your response ability to external things has declined?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
12. Do you feel hungry?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
13. Has diabetes brought inconvenience to your daily life?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
14. Do you think about what diabetes means to you?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
15. Are you worried that you will suddenly die?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
16. Does diet control make you feel annoyed?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
17. Does regular self-testing of glucose or going to the hospital for glucose testing make you feel troublesome?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
18. Do you feel nervous or uneasy because of diabetes?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
19. Are you satisfied with your current treatment effect?	☐None	☐A little	☐Satisfied	☐ Very satisfied	☐Extremely
20. Do you believe that you can overcome the troubles of the disease?	☐None	☐A little	☐Believe	☐ Believe very much	☐Extremely
21. Has diabetes damaged your interpersonal relationships?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
22. Do you feel that you are despised because of	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always

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having diabetes?					
23. Has diabetes affected your status and role at home or at work?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe
24. Do you often communicate with the surrounding patients about the experience, problems and knowledge related to diabetes?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
25. Do you have any adverse drug reactions such as allergies and nausea after taking the medicine?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
26. Do you have hypoglycemic reactions such as palpitations, dizziness, and sweating?	☐None	☐Occasionally	☐Sometimes	☐Often	☐Always
27. How much restriction does diet control have on your living habits?	☐None	☐Mild	☐Moderate	☐Severe	☐Extremely severe

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Additional file 3. Informed consent form (translated)

Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomized controlled trial

Patient Informed Consent Form

Dear Patient,

You are invited to participate in a clinical trial, "Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomized controlled trial", sponsored by Jiangxi University of Chinese Medicine in conjunction with the Affiliated Hospital of Jiangxi University of Chinese Medicine and The First Affiliated Hospital of Nanchang University. Here, we provide the details of this trial.

1. Background and Objectives

This trial aims to provide preliminary data on the efficacy and safety of Pueraria lobata radix as an adjuvant treatment for type 2 diabetes mellitus. If the results of future trials confirm that Pueraria lobata radix is effective and safe for treating type 2 diabetes mellitus, it could serve as an effective adjuvant dietotherapy for treating type 2 diabetes mellitus.

2. Introduction to "Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomized controlled trial"

Type 2 diabetes mellitus has become a global epidemic with high comorbidities and high mortality. Active prevention, early diagnosis, and effective treatment have become crucial. Pueraria lobata radix, a medicinal and edible herb in China, has been repeatedly shown to have hypoglycemic effects in animal experiments. However, there are no data from clinical trials on the efficacy and safety of Pueraria lobata radix as an adjuvant treatment for type 2 diabetes mellitus. Therefore, Jiangxi University of Chinese Medicine has led this randomized controlled trial to evaluate the efficacy and safety of Pueraria lobata radix dietotherapy as an adjuvant treatment for type 2 diabetes mellitus.

3. Requirements for Participating in This Study

The clinicians and clinical research coordinators responsible for this study will communicate the requirements for participating in this study with you. You need to

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fully introduce your past medical history to the clinician or clinical research coordinator. If you meet the following criteria judged by the clinician, you can enter the screening process of this trial. Under the condition of meeting all the following conditions, you can participate in this study:

Inclusion Criteria

1) Diagnosed with T2DM according to the criteria of the American Diabetes Association [30], that is, fasting blood glucose (FBG) ≥ 126 mg/dl (7.0 mmol/l) or blood glucose ≥ 200 mg/dl (11.1 mmol/l) 2 hours after oral administration of 75 g glucose or HbA1c ≥ 6.5% (48 mmol/mol).
2) Aged between 18 and 80 years.
3) Treatment-naïve patients or patients who are receiving regular drug hypoglycemic treatment (both oral hypoglycemic drugs and insulin are allowed, regardless of the type and dose).
4) Blood glucose has not been effectively controlled for the past three months, defined as an HbA1c between 6.5% and 10.5%.
5) Agree to the requirements of dietary control during the study period.
6) Voluntarily participate and sign the informed consent form.

Exclusion Criteria

1) Type 1 diabetes mellitus, gestational diabetes mellitus, or other special types of diabetes mellitus.
2) Experienced acute complications of T2DM, such as ketoacidosis, hyperosmolar coma, and lactic acidosis.
3) Pregnant or lactating women, or women planning to become pregnant.
4) A history of allergy to PLR.
5) Complicated with severe dysfunction of important organs, such as the heart, liver, and kidney; malignant tumors; or severe mental disorders.
6) Poor expected compliance.
7) Currently participating in other clinical trials.

4. Research Stages

If you participate in this study, you will be randomly assigned to receive either 15 g of Pueraria lobata radix granule or placebo granule intervention once a day for 12 consecutive weeks.

The entire research cycle will last for 12 weeks, and the Pueraria Lobata granules will be provided by Jiangxi University of Chinese Medicine. You need to try to keep the current dosage and type of hypoglycemic drugs unchanged.

At the baseline visit, we will register your demographic information and measure the baseline indicators. There will subsequently be three follow-up visits, each occurring every four weeks. During the follow-up, indicators related to blood glucose, routine blood tests, routine urine tests, routine stool + occult blood tests,

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electrocardiograms, liver and kidney functions, blood lipids, vital signs, symptoms or quality of life scales, self-reported adverse events, compliance, and combined medication will be examined.

5. Cessation/withdrawal criteria

(1) Voluntarily request withdrawing.

(2) Cannot be contacted during follow-up.

(3) Withdrawal from the trial due to adverse reactions.

6. Possible Benefits of Participating in the Study

Patients participating in this trial will receive free research-related examinations, free Pueraria lobata radix or placebo samples (patients in the placebo group will receive the same amount of Pueraria lobata radix granules as the trial group after completing the study and unblinding), and a transportation subsidy of 100 yuan for each follow-up visit (issued after the last visit).

7. Participating in the Study/Withdrawing from the Study Midway/Terminating the Study

Whether to participate in this study depends entirely on your voluntary choice. You can refuse to participate in this study or withdraw from it at any time during the study process. This will not affect the relationship between you and your doctor, nor will it cause any loss of medical or other benefits.

8. Confidentiality in the Trial

If you agree to participate in this study, your medical records will be reviewed and kept by the executors and supervisors of this study and cannot be taken away or copied. All the information collected about you during the study will be kept strictly confidential, and only your contact information will be listed in the form of identifiable information. We will keep this form in a secure database for future contact with you by phone if necessary. However, during data analysis, all the data will be deidentified, and no personal information will be disclosed in future publications or other published articles.

9. Risks and Discomforts in the Trial

Pueraria lobata radix is a substance recognized by Chinese regulations for both medicinal and food uses; that is, it can be consumed as food, so its overall safety is good. Previous studies have shown that Pueraria lobata radix is cold in nature. Consuming a large amount of Pueraria lobata radix or consuming Pueraria lobata radix on an empty stomach may cause certain discomfort to the gastrointestinal tract, such as occasional bloating and abdominal pain. In addition, hypoglycemic treatment may increase the risk of hypoglycemia. Any scientific research has risks, discomforts, and inconveniences. Therefore, you should carefully consider this before agreeing to participate in any clinical study.

10. Trial Expenses

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During the clinical research period, the sponsor will provide samples for free until the end of the trial and cover the examination expenses stipulated in the protocol during the research period. During this study, if there are serious adverse reactions related to the test samples, the sponsor will reimburse the corresponding treatment expenses and provide corresponding economic compensation for the research-related damage in accordance with the provisions of relevant laws and regulations in China.

The treatment and examinations required for other diseases you have concurrently will not be covered by reimbursement.

11. This consent form is in duplicate, with one copy held by the research unit and one copy held by the subject.

Signature Page

(If you or your family member/guardian agree to participate in this study, please read the relevant statements carefully and sign.)

I have been informed of the purpose, methods, possible risks, discomforts, and related benefits of this trial.

I confirm that I have spent sufficient time reading and understanding the above content. The doctor has explained the medical terms used therein to me, and the researchers have given satisfactory answers to all my questions about the study.

I understand that I can voluntarily withdraw from this study at any time without affecting the doctor–patient relationship and treatment in the future. I know that if I have any questions during the trial, I should contact the attending doctor in time.

I voluntarily participate in this trial and serve as a subject of this trial.

Signature of subject or designated agent: _____
Date: _____ Year _____ Month _____Day

I have truthfully informed the research object (or designated agent) of the purpose, content, benefits, and possible adverse reactions of this study. I have asked the party concerned if they have any questions about this study and have explained as much as I can.

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Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: rationale, design, and protocol for a randomised controlled trial

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Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: rationale, design, and protocol for a randomised controlled trial

Author

Jianrong Chen,[1] Jiancheng Wang,[1] Lixia Yuan,[2] Qiuyun Xue,[2] Jieyi Zhou,[2] Xiang Ye,[3] Qihui Fan,[3] Ruting Feng,[3] Chenxi Li,[3] Yan Zhang,[1] Weifeng Zhu[2], Zhengfeng Li,[3*] Xu Zhou[2*]

Affiliation

[1] Department of Endocrinology and Metabolism, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi, China

[2] Evidence-based Medicine Research Centre, Jiangxi University of Chinese Medicine, Nanchang 330006, Jiangxi, China

[3] Department of Diabetes and Endocrinology, The Affiliated Hospital of Jiangxi University of Chinese Medicine, Nanchang 330006, Jiangxi, China

[*] Corresponding authors:

Xu Zhou (Email: zhouxu_ebm@hotmail.com), Evidence-based Medicine Research Centre, Jiangxi University of Chinese Medicine, Mei Ling Avenue No. 1688, Nanchang 330004, Jiangxi, China. Phone: +8618870050733, Fax: +86079187118012

Zhengfeng Li (Email: lzfjxutcm2025@163.com), Department of Diabetes and

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Endocrinology, The Affiliated Hospital of Jiangxi University of Chinese Medicine,

Bayi Avenue No.445, Nanchang 330006, Jiangxi, China

Word count: 4700

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Abstract

Introduction The current pharmacological management of type 2 diabetes mellitus (T2DM) faces challenges such as low rates of optimal glycaemic control, high incidences of adverse drug reactions, and suboptimal treatment compliance. Pueraria lobata radix (PLR), a medicinal and edible herb, has shown hypoglycaemic effects in animal models. However, existing clinical studies have only assessed the hypoglycaemic effect of PLR-containing herb formulas or PLR extract preparations. The aim of this study is to investigate the efficacy and safety of using PLR solely as an adjuvant therapy for T2DM.

Methods and analysis This study is a multicentre, randomised, double-blind, placebo-controlled trial. Two hundred patients with T2DM will be randomly allocated to either the PLR group or the placebo group for a consecutive 12-week intervention. Regular visits will be conducted at weeks 4, 8, and 12 following the initiation of the study to evaluate the efficacy and safety of PLR. The primary outcome is the change in haemoglobin A1c (HbA1c) from baseline at week 12. Secondary outcomes include changes in HbA1c from baseline at weeks 4 and 8; the HbA1c response rate (< 7%), changes in fasting blood glucose, two-hour blood glucose, fasting C-peptide, body mass index, severity of diabetes symptoms, quality of life from baseline at weeks 4, 8, and 12; and changes in blood lipid indicators at week 12. Safety outcomes include the incidences of total adverse events (AEs), serious AEs, and PLR-related AEs.

Ethics and dissemination The protocol has been approved by the Ethics Committees of the First Affiliated Hospital of Nanchang University (approval number:

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IIT[2024]LLS No.303) and the Affiliated Hospital of Jiangxi University of Chinese Medicine (approval number: JZFYLL2024006200087). We will disseminate the study findings through publications in peer-reviewed journals and conference presentations.

Trial registration number: ClinicalTrials.gov NCT06494683.

Keywords: Pueraria lobata radix; Type 2 diabetes mellitus; Efficacy; Safety; Randomised controlled trial

Strengths and limitations of this study

- This trial will employ rigorous methodological safeguards, including multicentre recruitment, block randomization, allocation concealment, double blinding, and placebo control, to balance both known and unknown confounders and minimise the placebo effect.
- Multiple compliance-guarantee measures, blinded outcome assessments, and reasonable statistical analysis plans will improve trial quality and yield accurate evaluation results.
- A sample size of 200 participants will be sufficient to ensure the statistical power and the credibility of the pre-specified primary and subgroup analyses.
- A potential limitation of the study is that patients may not fully adhere to the 12-week *Pueraria lobata* radix or placebo regimen.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with the highest prevalence.[1] Data released by the International Diabetes Federation in 2021 indicated that the number of patients with T2DM among the population aged 20--79 has soared to 537 million, accounting for 10.5% of the total global population, and it is predicted that the number will escalate to 783 million by 2045.[2] The chronic hyperglycaemic state leads to multiple complications, such as cardiovascular diseases, strokes, blindness, renal failure, and foot ulcers.[3,4] These serious consequences are among the chief causes of premature mortality and reduced life expectancy in humans.[5,6] Furthermore, the medical expenditures associated with T2DM impose an immense socioeconomic burden—the total global medical expenses for T2DM in 2021 amount to $966 billion, representing a 27.1% increase from 2019.[7] This figure, if considered a country's GDP, could secure 18th rank globally.[8]

T2DM is conventionally managed through oral hypoglycaemic drugs and insulin.[9] These drugs can increase insulin levels, alleviate insulin resistance, and achieve the goal of lowering blood glucose. However, a significant proportion of patients still fail to attain optimal blood glucose control.[10,11] The principal cause of this problem is the limited hypoglycaemic ability of existing oral hypoglycaemic drugs.[12,13] For example, a network meta-analysis of multiple hypoglycaemic drugs revealed that, compared with that of placebo, the reduction in haemoglobin A1c (HbA1c) ranged from -1.48% for the highest semaglutide to only -0.50% for the lowest dipeptidyl peptidase-4 inhibitors.[14] Secondary failure is also a challenging issue. For example, 42% of T2DM

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patients who received metformin, a first-line monotherapy drug, experienced secondary failure during the average follow-up period of 27.6 months, corresponding to a failure rate of 17% per year.[15] The combination of multiple hypoglycaemic drugs is a way to solve these issues; however, it considerably increases adverse drug reactions, such as hypoglycaemia[16] and gastrointestinal symptoms[17]. Moreover, compliance is a crucial factor affecting the effectiveness of hypoglycaemic drugs. A survey has revealed that the proportion of patients with good compliance with hypoglycaemic drugs is less than 40%.[18] Adverse drug reactions and complex treatment regimens (combination therapy or the requirement for injection) are the primary reasons for poor patient compliance.[19-21] Therefore, it is imperative to explore complementary therapies that can enhance efficacy, safety, and long-term compliance for the management of T2DM.

Pueraria lobata radix (PLR; Chinese name: Gegen) is the dry root of the leguminous plant *Pueraria lobata* (Willd.) Ohwi. In East Asian countries, particularly in China, PLR has been used as an ingredient in traditional herbal prescriptions for T2DM. For example, Gegen Qinlian Decoction, composed of PLR, Scutellaria baicalensis, Coptis chinensis, and Glycyrrhiza uralensis, has been found to significantly reduce the level of blood glucose and increase the level of serum insulin.[22,23] Isoflavones in PLR, such as daidzein, genistein, and puerarin, have been shown to have hypoglycaemic activity. The mechanism of hypoglycaemic action may involve multiple signalling pathways, such as the PI3K-Akt, PPAR, and HIF-1 pathways.[24-26] Recent studies have also found that the polysaccharides contained in PLR also have hypoglycaemic effects, which improve insulin resistance in mice by regulating the

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PPAR signalling pathway.[27]

In China, PLR is a medicinal and edible herb, as stipulated by regulations; that is, based on traditional consumption experience, it is considered to have food-level safety and can be made directly into foods or serve as a food ingredient. The safety evaluation of standardised PLR extracts also reached a conclusion of being favourable safety.[28] These facts provide a prerequisite for its application in the dietotherapy of T2DM. However, to date, all clinical studies regarding the hypoglycaemic effect of PLR have focused on PLR-containing herbal formulas or preparations of PLR extracts, and there is no evidence from randomised controlled trials (RCTs) for assessing PLR alone for adjunctive hypoglycaemic management. Therefore, we plan to conduct an RCT to assess the efficacy and safety of PLR as an adjuvant therapy in the management of T2DM.

METHODS AND ANALYSIS

Study design

This study will be a multicentre, randomised, parallel-group, double-blind, placebo-controlled trial. This protocol has been registered at clinicaltrials.gov (identifier: NCT06494683). Participants will be recruited at the First Affiliated Hospital of Nanchang University and the Affiliated Hospital of Jiangxi University of Chinese Medicine. Eligible patients with T2DM will be randomly assigned to either the PLR group or the placebo group. The reporting of this trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials Standard Protocol Items:

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Recommendations for Interventional Trials (SPIRIT) statement.[29] The study process is shown in Figure 1.

Eligibility criteria

Participants will be recruited during physicians' regularly scheduled outpatient clinics, with advertisements by online and offline posters. Potential candidates will be evaluated by clinicians with professional qualifications in endocrinology to determine whether they meet the following inclusion criteria to participate in this trial:

1) Diagnosed with T2DM according to the criteria of the American Diabetes Association, that is, fasting blood glucose (FBG) ≥ 126 mg/dl (7.0 mmol/l) or blood glucose ≥ 200 mg/dl (11.1 mmol/l) 2 hours after oral administration of 75 g glucose or HbA1c ≥ 6.5% (48 mmol/mol).[30]
2) Treatment-naïve patients (including newly diagnosed or previously diagnosed but untreated) or those who have been receiving regular hypoglycaemic drugs for at least three months (both oral hypoglycaemic drugs and insulin are allowed, regardless of the type and dose).
3) Blood glucose has not been effectively controlled for the past three months, defined as an HbA1c between 6.5% and 10.5%.
4) Aged between 18 and 80 years.
5) Agree to the requirements of dietary control during the study period (see paragraph 3 of the "Interventions and cointerventions" section).
6) Voluntarily participate and sign the informed consent form.

Patients with the following conditions will not be eligible to participate:

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1) Type 1 diabetes mellitus, gestational diabetes mellitus, or other special types of diabetes mellitus.
2) Experienced acute complications of T2DM, such as ketoacidosis, hyperosmolar coma, lactic acidosis, and acute hypoglycaemia.
3) Irregular hypoglycaemic treatment patterns, such as intensive therapy phases or inconsistent daily medication types/dosages.
4) Pregnant or lactating women or women planning to become pregnant.
5) A history of allergy to PLR.
6) Complicated with severe dysfunction of important organs, such as the heart, liver, and kidney; malignant tumours; or severe mental disorders.
7) Anticipated poor compliance, such as remote residence from the study site, frequent work-related travel, and a clinician-determined history of medication nonadherence.
8) Currently participating in other clinical trials.

Interventions and cointerventions

Participants in the PLR group and the placebo group will receive PLR and placebo treatment, respectively, once daily for 12 weeks, with a dosage of 15 g per dose. This dosage adopts the upper limit of the Chinese Pharmacopoeia-recommended daily range (10–15 g/d, established by the Chinese National Pharmacopoeia Committee based on traditional clinical experience) to prioritise safety while maximizing therapeutic efficacy.[31] The 12-week intervention period is determined by referencing previous RCTs of herbal formulas containing PLR to align with the anticipated efficacy onset

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period of PLR,[23] while also ensuring sufficient time for HbA1c to accurately reflect glycaemic changes.[32] PLR and placebo will be made into granules that can be dissolved in warm water for convenient administration. To produce granules, PLR decoction pieces will be fully soaked and then decocted with water three times, and all the decocted liquids will be combined, concentrated, and dried to form granules. The placebo granules will be made by blending lactose, caramel colour, sunset yellow, and PLR essence. There will be no or almost no difference in colour, smell, taste, appearance, or packaging between the PLR and placebo preparations.

During the study period, untreated participants will receive hypoglycaemic drugs following standard treatment protocols, with the initial type and dosage of hypoglycaemic drugs maintained. For participants already on regular hypoglycaemic drug regimens, the drug type and dosage will be sustained throughout the study period. When clinicians determine that a participant's blood glucose levels become uncontrolled (either too high or too low), rescue treatment will be implemented. A high blood glucose level is defined as an FBG level exceeding 270 mg/dl (15.0 mmol/l) during weeks 1-6 or exceeding 239 mg/dl (13.3 mmol/l) during weeks 7-12, according to the FDA's recommendations.[33] Rescue treatment for high blood glucose levels includes upward titration of current antidiabetic medications to their maximum as per prescribing information. If blood glucose levels remain unacceptably high, additional hypoglycaemic drugs will be introduced, prioritizing metformin (to be gradually titrated to a maximum dose of 2 g/d) followed by glimepiride (to be gradually titrated to a maximum dose of 6 mg/d). A low blood glucose level is defined as an FBG level

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less than 70 mg/dl (3.9 mmol/l). In such cases, the original hypoglycaemic drug dosage will be reduced to maintain the FBG level above 70 mg/dl, with complete discontinuation if necessary. For acute hypoglycaemic episodes, rescue treatment will involve the administration of 15–20 g of rapid-acting carbohydrates (e.g., sugary beverages, candy, or honey) to resolve symptoms. All rescue treatments will be documented and considered in per-protocol population analysis.

All participants will be required to regulate their diet, including restricting the intake of monosaccharides, daily fat intake, and total calories based on body weight, and to adhere to a diet pattern of small and frequent meals, a light diet, and punctual eating. Other herbal remedies will be prohibited. Treatment of comorbidities, such as hypertension and dyslipidaemia, as well as adverse reactions during the study period, is permitted. In the event of a violation of the intervention or cointervention protocol, participants should truthfully report the type and dosage of the violation and make detailed records, while subsequent interventions and visits will proceed.

Randomization and Blinding

An independent randomization centre will be established to generate and manage random sequences. The "blockrand" function in R 4.1.0 (Ross Ihaka, Robert Gentlemen, New Zealand) will be used to generate random sequences with mixed block lengths of 4, 6, or 8, featuring a 1:1 allocation ratio between the PLR group and the placebo group. One random sequence with a fixed seed will be generated for each research centre. Sealed packaging will be adopted to conceal random sequences. First, the central pharmacy will arrange the PLR and placebo samples according to the random

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sequences and then affixes sequential numbers on the packaging. When patients participate in the trial, the samples will be distributed according to the enrolment sequence. Therefore, neither the clinicians nor the participants can be aware of the grouping results. Before the completion of data analysis, all participants, clinicians, outcome evaluators, and data analysts will be blinded to the randomised grouping. In the case of serious adverse events (AEs) during the study, emergency unblinding is allowed to provide necessary information for treatment.

Outcomes

Efficacy outcomes

The primary outcome for efficacy assessment is the change in HbA1c at week 12 from baseline. Secondary efficacy outcomes include 1) changes in HbA1c at weeks 4 and 8 from the baseline; 2) the HbA1c response rate at weeks 4, 8, and 12, defined as HbA1c < 7.0%; 3) changes in other blood glucose indicators at weeks 4, 8, and 12, including FBG, 2-hour postprandial blood glucose, and fasting C-peptide; 4) changes in body mass index, systolic blood pressure, and diastolic blood pressure at weeks 4, 8, and 12; 5) changes in levels of blood lipid indicators at week 12, including total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol; 6) changes in the severity of diabetic symptoms at weeks 4, 8, and 12 evaluated by the score of the Diabetic Symptom Severity Grading Scale in the *Clinical Research Guiding Principles for New Drugs of Chinese Medicine*;[34] the scale contains 24 items and assesses the main symptoms of diabetes, such as excessive thirst and desire to drink, excessive eating and

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easy to be hungry, frequent urination, and frequent nocturia, with each item scoring 0 to 3 (total 0 to 72) and a higher score indicating more severe symptoms; 7) changes in the quality of life of patients at weeks 4, 8, and 12 evaluated by the score of the Diabetes-Specific Quality of Life Scale;[35] the scale contains 27 items and assesses the impact of diabetes on the quality of life of patients in four dimensions of physiology, psychology, society, and treatment, with each item scoring 0 to 4 (total 0 to 108) and a higher score indicating a poorer quality of life; and 8) changes in the dose of hypoglycaemic drugs at weeks 4, 8, and 12 from the baseline.

Safety outcomes

Safety outcomes include the incidences of any AEs, serious AEs, and PLR-related AEs within 12 weeks. An AE is defined as any adverse symptom or event that is not related to the natural progression of the patient's original disease. The data sources for safety evaluation include tests of blood, urine, and stool routine; stool occult blood; FBG; liver function (including alanine aminotransferase, aspartate aminotransferase, and total bilirubin); and kidney function (including serum creatinine, urea nitrogen, and uric acid) and electrocardiogram examinations. Among these examinations, if the baseline level is normal and the indicator level at follow-up exceeds twice the upper limit of the normal reference value or is reported as qualitatively abnormal, it will be considered an AE. The incidences of symptomatic hypoglycaemia and gastrointestinal symptoms will be monitored with emphasis. Symptomatic hypoglycaemia is defined as a blood glucose level lower than 3.9 mmol/L accompanied by hypoglycaemic symptoms, such as palpitations, sweating, hunger, tremors, and anxiety. We will

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document the time, location, course of disease, clinical manifestations, management, and outcome of each AE. The correlation between AEs and PLR treatment will be comprehensively evaluated by clinicians based on the following factors: 1) whether there is a reasonable temporal relationship between the occurrence of the AE and the administration of PLR; 2) whether the AE can be explained by other factors; 3) whether the AE has been reported in previous literature or has reasonable biological mechanisms; 4) whether the AE disappears or alleviates after the discontinuation or reduction of PLR; and 5) whether the same AE recurs after readministering PLR. A serious AE is defined as an AE that leads to hospitalization or a prolonged hospital stay, affects work ability, endangers life, or causes disability, congenital malformations, or death. Any serious AEs will be immediately reported to the hospital ethics committee.

Schedule of visits

Study visits will be conducted at baseline and at weeks 4, 8, and 12. During the baseline visit, we will collect demographic data, disease history, and medication history; examine baseline vital signs, blood glucose indicators, blood lipid indicators, and safety indicators; and measure baseline scores on the severity of symptoms and quality of life scales. At each subsequent follow-up visit, we will perform examinations or measurements of vital signs, blood glucose indicators, and symptom and quality of life scales and record compliance with interventions, newly emerged diseases or disease progression, the dose of hypoglycaemic drugs, and AEs. At the last follow-up, we will additionally examine lipid indicators and laboratory indicators related to safety. The time window for each follow-up visit is ±3 days from the scheduled visit date. If a

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patient fails to complete the follow-up within the scheduled time for any reason, we will consider this visit as lost to follow-up and no longer collect the data from this visit. The detailed follow-up arrangement is shown in Figure 2.

Quality control and data management

A steering committee composed of endocrinology experts, herbal medicine experts, statistics experts, ethics experts, and the director of the research hospital will be established. This committee will be responsible for formulating and reviewing the study protocol, establishing standard operating procedures, and organizing and supervising the quality of implementation. This trial has no interim analysis plan, but the steering committee can decide to conduct an interim analysis depending on the progress of the trial and determine whether to prematurely terminate the trial based on the results of the interim analysis, such as when the interventions are unlikely to achieve any significant efficacy or when there are major safety issues. Each research hospital will be equipped with two full-time clinical research coordinators, who are responsible for cooperating with clinicians to conduct research visits. All researchers will fully study the study protocol and undergo training on standard operating procedures. Every patient participating in the trial will receive one-on-one reception, including disease consultation, the completion of case report forms, the collection of biological samples, and the distribution of PLR or placebo samples. To increase compliance, we will first obtain thorough informed consent for each participant, including randomization grouping, the potential benefits and side effects of each group, and the responsibilities for participating in the study. The trust of patients in clinicians and their interest in the

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research are the core factors to guarantee compliance. Second, clinical research coordinators will actively remind patients when the planned follow-up date is approaching and respond to patients' inquiries regarding health or the study protocol at any time. In addition, we will provide participants with free PLR and placebo samples and free research-related examinations, as well as transportation subsidies for each return visit (100 yuan per person per visit). Patients in the placebo group will be compensated with the same amount of PLR samples as those in the experimental group after the completion of the trial. To verify the compliance of the self-reported dose of the trial samples, patients will be required to return the empty packaging bags of the consumed samples and the packaging bags of the remaining samples for obtaining free samples in the next month and transportation subsidies.

An independent data monitoring committee will be established to manage the research data and regularly inspect the quality of data collection. The original data will be recorded in paper case report forms and stored in locked boxes at each research centre. After the completion of the data collection, the data of the paper case report forms will be re-entered into the electronic database constructed by Microsoft Access by two independent staff members, with cross-verification to ensure accuracy. All patient information will be kept strictly confidential.

Sample size calculation

No prior clinical studies have directly compared PLR with a placebo in the treatment of T2DM. However, a meta-analysis of 17 RCTs investigating Gegen Qinlian decoction (an herbal formulation primarily containing PLR) demonstrated a −0.65%

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greater reduction in HbA1c compared to control groups (exercise and diet control) after 8–12 months of intervention.[23] Drawing from these findings, combined with our empirical clinical observations of PLR therapeutic effects and expert consensus, we anticipate the mean difference (δ) in the reduction of the primary outcome (i.e., the change in HbA1c levels at week 12) between the PLR group and the placebo group to be 0.50% and the common standard deviation (σ) between the groups to be 0.75%. With the assumed type I error probability of 0.05 and type II error probability of 0.20, along with a potential 20% loss to follow-up, a sample size calculation formula of the superiority design indicates that at least 47 cases are needed for each group. To increase the credibility of subgroup analyses, we plan to expand the sample size to 100 cases for each group within the limits of funding support, resulting in a total of 200 cases.

Statistical analysis

Descriptive statistics will be conducted for baseline characteristics, where continuous variables will be presented as means and standard deviations, and categorical variables will be presented as frequencies and percentages. The analysis of efficacy outcomes will use the full analysis set based on the modified intention-to-treat principle, encompassing the population that has received at least one dose of the PLR or placebo after randomization and has outcome data of at least one follow-up. The estimation of intergroup differences in continuous outcomes will employ a repeated-measures mixed effects model, in which age (continuous), body mass index (continuous), baseline HbA1c (continuous), and use of insulin (binary) are fixed-effect covariates, and research centre, time, and interaction of time and group are random-

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effect covariates. The effect size on continuous outcomes will be least-square mean differences and 95% confidence intervals (CIs). The estimation of intergroup differences in binary outcomes will employ a repeated-measures generalised linear mixed model with the logit link, with the same covariates. The effect size on binary outcomes will be odds ratios and 95% CIs. Missing values in outcomes will be imputed via the multiple imputation method based on the regression model, where covariates include age, body mass index, baseline HbA1c, use of insulin, and the research centre. One hundred imputed datasets will be generated and used to fit the statistical models, and the results will be averaged as the final effect estimate. The analysis of safety outcomes will be based on the safety set, defined as the population that has received at least one dose of PLR or placebo.

To verify the robustness of the results of the efficacy analysis, the following sensitivity analyses will be conducted: 1) using the per-protocol set, which is defined as the population that has consumed more than 80% of the PLR or placebo samples, has not violated the intervention and cointervention requirements, has not adjusted the dose of hypoglycaemic drugs or added new hypoglycaemic drugs compared with the baseline prescription, has no major violations of the dietary control requirements, has not been unblinded, and has completed the week 12 visit; 2) abstaining from imputing missing values; and 3) adjusting any additional unbalanced baseline characteristics in the statistical models.

To provide evidence for precise treatment, we will conduct subgroup analyses stratified by the following factors for the primary outcome: 1) Age (< 65 years versus

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≥ 65 years); considering the potential impact of age on drug absorption and metabolism ability, it is anticipated that participants aged < 65 years will achieve superior efficacy; 2) baseline body mass index (< 23.0 kg/m^2 versus ≥ 23.0 kg/m^2); considering the potential effects of PLR on inhibiting abnormal leptin receptors, it is anticipated that participants with a body mass index ≥ 23.0 kg/m^2 will achieve superior efficacy; 3) baseline HbA1c level (< 9% versus ≥ 9%); considering the impact of baseline HbA1c control on the absolute level of HbA1c reduction, it is anticipated that participants with a baseline HbA1c ≥ 9% will achieve superior efficacy; and 4) the use of insulin (yes versus no); considering the potentially stronger masking effect of insulin on the efficacy of PLR, it is anticipated that participants not receiving insulin will achieve superior efficacy.

All analyses will not adjust the significance boundary; that is, a p value less than 0.05 will be considered statistically significant. All the statistical analyses will be performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

The trial design has not yet involved patients or the public.

DISCUSSION

There are more than 20 species of plants belonging to the genus Pueraria worldwide, primarily distributed in subtropical and temperate regions.[36] China constitutes the distribution centre of the genus Pueraria, comprising approximately ten

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species. Among them, *Pueraria lobata* (Wild.) Ohwi and *Pueraria montana* var. thomsonii are the species endowed with the most abundant resources and the widest cultivation scope, and their roots are also the types legally defined as medicinal and edible herbs in China.[37,38] Compared with that in Pueraria thomsonii radix, the total flavonoid content in PLR, particularly puerarin, is significantly greater. Therefore, PLR holds greater medicinal value and is more prevalently employed in herbal prescriptions than Pueraria thomsonii radix.[39] As a result, we chose PLR as the evaluation object in this trial.

This study will be the first RCT to evaluate the efficacy and safety of PLR as an adjunctive treatment for T2DM. Previous clinical trials concerning the hypoglycaemic effect of PLR focused on herbal formulas containing PLR (e.g., Gegen Qinlian decoction) or PLR extracts (e.g., Puerarin injection). The indirectness of these trials in reflecting the effect and safety of PLR on T2DM should be negligible. In addition, previous studies also have substantial methodological limitations, such as the absence of blinding, failure to implement allocation concealment, and irrational statistical analysis methods. In contrast, this RCT will adopt double-blinding for both patients and clinicians by establishing a placebo control, standardizing the implementation of randomization and allocation concealment procedures, and undertaking rigorous quality control during the follow-up stage. In the statistical analysis, the main analysis will be based on the full analysis set constructed based on the modified intention-to-treat principle, which will obtain a relatively conservative effect estimate (i.e., unfavourable to PLR). Moreover, we will fit appropriate multivariate models for

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different types of outcomes to overcome the potential confounding biases related to the centre effect and other covariates. These methodological advantages enable our study to yield accurate estimates regarding the effects of PLR.

Although herbal formulas containing PLR or puerarin injection may also have hypoglycaemic effects, it is necessary to investigate the individual hypoglycaemic effects of PLR. If this RCT ultimately demonstrates that the daily dose of PLR is effective and safe for T2DM patients, it will lead to multiple positive impacts. First, the supplementary hypoglycaemic effect of PLR will facilitate the control of blood glucose at an ideal level, delay the progression of T2DM, and ultimately reduce the risk of diabetic complications. If PLR is verified to be safe, it could be used to replace some doses of hypoglycaemic drugs to mitigate adverse drug reactions. Owing to its medicinal and edible properties, PLR can be directly consumed as food or added to daily edible products such as tea or beverages in numerous countries, which will contribute to improving compliance with long-term use by patients with T2DM. In addition, PLR is an inexpensive herb. Consumed at the daily dose of this trial, the cost per month of PLR is only approximately two dollars. Therefore, the complementary treatment of PLR may also assist in reducing the medical costs of patients with T2DM.

Although RCTs balance both known and unknown confounders across groups through randomization, absolute residual imbalances may still compromise the accuracy of effect estimates. Therefore, adjusting for confounders remains necessary in RCTs, with their selection guided by clinical relevance rather than statistical criteria.[40,41] Based on this principle, we pre-specified age, body mass index, baseline

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HbA1c, use of insulin, research centre, time, and time-by-group interaction as fixed- or random-effect covariates for adjustment. Given the substantial diversity of hypoglycaemic drugs and their potential combinations—which could generate dozens of categories—adjusting for all drug types as confounders would introduce the curse of dimensionality, data sparsity, and overfitting, thereby undermining the reliability of effect estimation.[42-44] To mitigate this, we dichotomised the hypoglycaemic drug factor into "insulin use vs non-use", selecting this classification to maximise clinical heterogeneity. Should any specific hypoglycaemic drug categories demonstrate significant between-group differences in proportions, additional adjustments will be incorporated into sensitivity analyses.

One potential limitation of this study lies in the assessment of certain subjective outcomes, namely, the Diabetic Symptom Severity Grading Scale and the Diabetes-Specific Quality of Life Scale, which might be influenced by disparities in the comprehension of subjective items among participants or clinicians. To minimise deviation from cognitive factors, we will establish evaluation criteria for each scale item in the training of the standard operating procedure and guide the participants to accurately understand their condition. Another potential limitation is that some participants may be difficult to adhere to the 12-week intervention and follow-up plan. To improve participant compliance, we will maintain communication with all participants throughout the follow-up process, answer patients' consultations on the condition at any time, and offer research subsidies for all participants and compensation of PLR samples for the placebo group. A third limitation pertains to the 12-week

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duration, which is insufficient to evaluate the long-term effects of PLR on T2DM outcomes; furthermore, HbA1c measurements at weeks 4 and 8 could be confounded by pre-trial medication use. Should this trial demonstrate statistically significant efficacy in the primary outcome, we will conduct further real-world studies to assess the long-term efficacy and safety profile of PLR in T2DM management.

In summary, to date, no rigorous RCTs have assessed the effects of PLR on the clinical outcomes of patients with T2DM. This study will have a sufficient sample size to obtain accurate effect estimates and will conduct a follow-up for up to three months to verify the long-term safety and patient compliance with the daily consumption of PLR. The research findings may provide new options and evidence-based regimens for the management of T2DM.

Ethics and dissemination

The protocol has been approved by the Ethics Committees of the First Affiliated Hospital of Nanchang University (approval number: IIT[2024]LLS No.303) and the Affiliated Hospital of Jiangxi University of Chinese Medicine (approval number: JZFYLL2024006200087). The trial will be conducted in strict accordance with the Declaration of Helsinki and Good Clinical Practice standards. The patient informed consent form contains the process of the trial and the possible benefits and risks. Patients will receive free treatment if any intervention-related adverse effects occur. Details of the collection and use of participant data are described in the informed consent form (Supplementary file 1). The investigators will initiate the study with the

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patient after he or she has signed the informed consent form. Participants can voluntarily withdraw from the trial at any time for any reason without affecting subsequent treatment.

We will disseminate the study findings through publications in peer-reviewed journals and conference presentations.

Trial status

The protocol version is 1.1, developed on May 31, 2024. The trial began recruiting on July 25, 2024, and is anticipated to finish in October 2025.

Acknowledgements

Not applicable.

Contributions

JC and JW designed the study, developed the statistical analysis plan and drafted the manuscript. LY, QX, JZ, XY, QF, RF, and CL were involved in the study design, communicated with the community centres, and revised the manuscript; YZ and WZ provided critical methodological advice and revised the manuscript; ZL and XZ conceived and designed the study, reviewed the manuscript. XZ acts as the guarantor. All the authors contributed to the writing of the manuscript in detail, and no professional writers were involved. All the authors have read and approved the final version of the manuscript.

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Availability of data and material

The datasets collected during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Figure Legends

Figure 1. Flowchart of the study process.

Figure 2. Schedule of the study visits.

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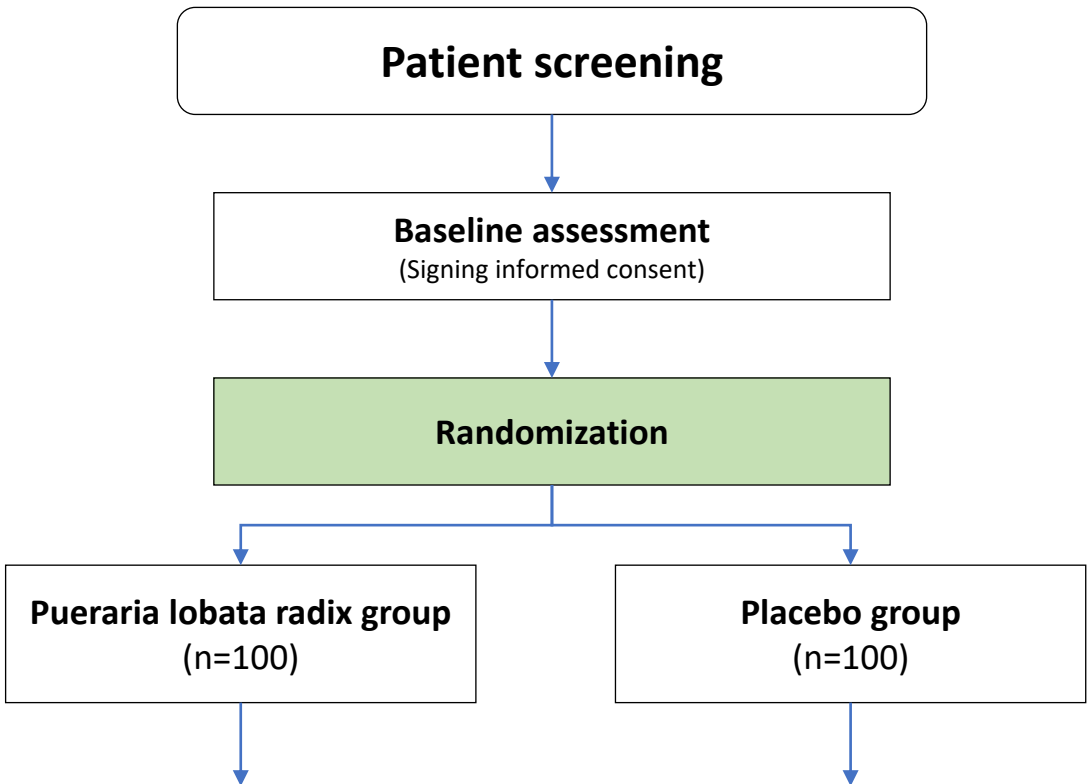

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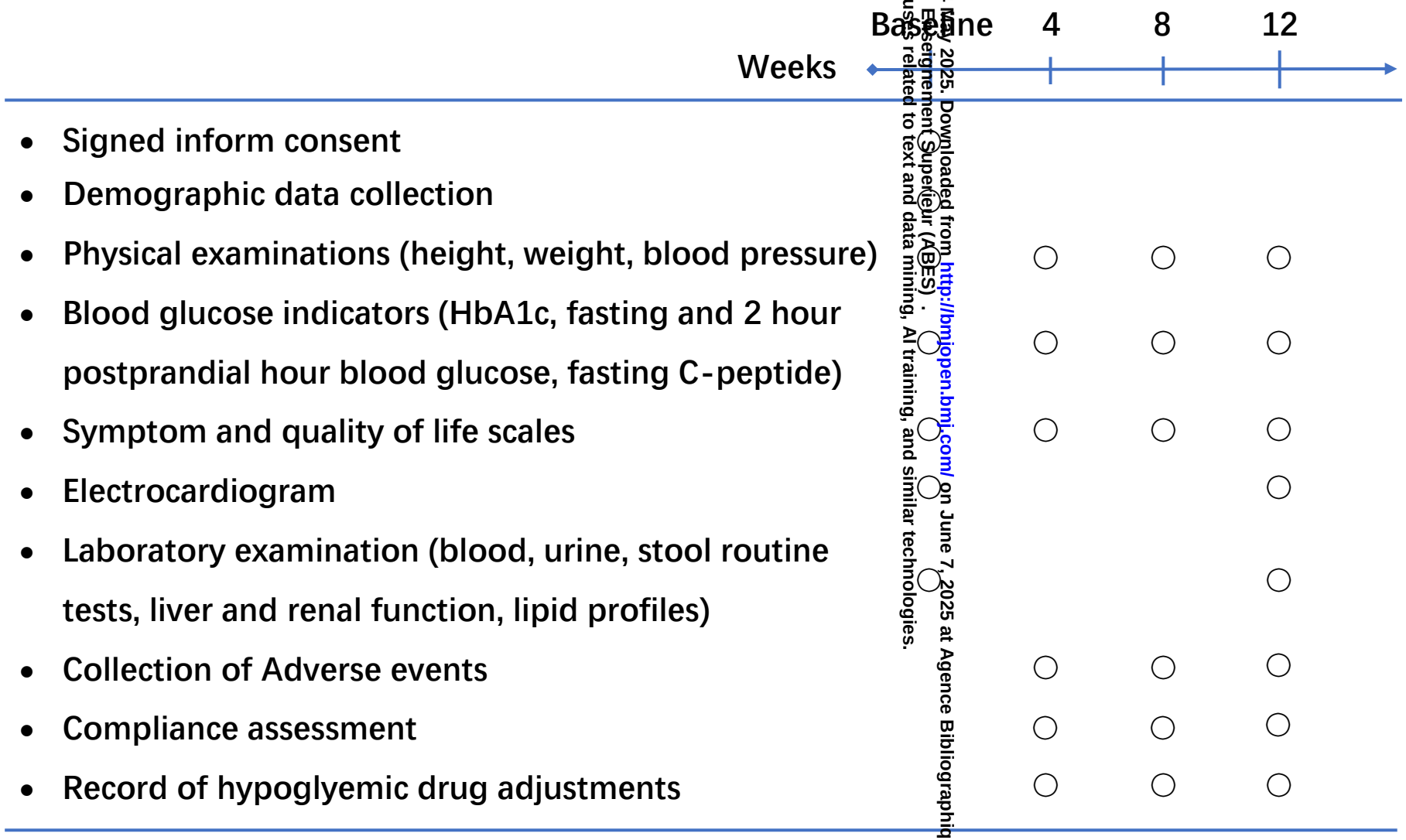

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Supplementary file 1. Informed consent form (translated)

Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomised controlled trial

Patient Informed Consent Form

Dear Patient,

You are invited to participate in a clinical trial, "Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomised controlled trial", sponsored by Jiangxi University of Chinese Medicine in conjunction with the Affiliated Hospital of Jiangxi University of Chinese Medicine and The First Affiliated Hospital of Nanchang University. Here, we provide the details of this trial.

1. Background and Objectives

This trial aims to provide preliminary data on the efficacy and safety of Pueraria lobata radix as an adjuvant treatment for type 2 diabetes mellitus. If the results of future trials confirm that Pueraria lobata radix is effective and safe for treating type 2 diabetes mellitus, it could serve as an effective adjuvant dietotherapy for treating type 2 diabetes mellitus.

2. Introduction to "Efficacy and safety of Pueraria lobata radix as an adjuvant therapy for type 2 diabetes mellitus: a randomized controlled trial"

Type 2 diabetes mellitus has become a global epidemic with high comorbidities and high mortality. Active prevention, early diagnosis, and effective treatment have become crucial. Pueraria lobata radix, a medicinal and edible herb in China, has been repeatedly shown to have hypoglycemic effects in animal experiments. However, there are no data from clinical trials on the efficacy and safety of Pueraria lobata radix as an adjuvant treatment for type 2 diabetes mellitus. Therefore, Jiangxi University of Chinese Medicine has led this randomised controlled trial to evaluate the efficacy and safety of Pueraria lobata radix dietotherapy as an adjuvant treatment for type 2 diabetes mellitus.

3. Requirements for Participating in This Study

The clinicians and clinical research coordinators responsible for this study will communicate the requirements for participating in this study with you. You need to fully introduce your past medical history to the clinician or clinical research coordinator. If you meet the following criteria judged by the clinician, you can enter the screening

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process of this trial. Under the condition of meeting all the following conditions, you can participate in this study:

Inclusion Criteria

1) Diagnosed with type 2 diabetes mellitus according to the criteria of the American Diabetes Association, that is, fasting blood glucose ≥ 126 mg/dl (7.0 mmol/l) or blood glucose ≥ 200 mg/dl (11.1 mmol/l) 2 hours after oral administration of 75 g glucose or HbA1c ≥ 6.5% (48 mmol/mol).
2) Treatment-naïve patients (including newly diagnosed or previously diagnosed but untreated) or those who have been receiving regular hypoglycaemic drugs for at least three months (both oral hypoglycaemic drugs and insulin are allowed, regardless of the type and dose).
3) Blood glucose has not been effectively controlled for the past three months, defined as an HbA1c between 6.5% and 10.5%.
4) Aged between 18 and 80 years.
5) Agree to the requirements of dietary control during the study period (see paragraph 3 of the "Interventions and cointerventions" section).
6) Voluntarily participate and sign the informed consent form.

Exclusion Criteria

1) Type 1 diabetes mellitus, gestational diabetes mellitus, or other special types of diabetes mellitus.
2) Experienced acute complications of type 2 diabetes mellitus, such as ketoacidosis, hyperosmolar coma, lactic acidosis, and acute hypoglycaemia.
3) Irregular hypoglycaemic treatment patterns, such as intensive therapy phases or inconsistent daily medication types/dosages.
4) Pregnant or lactating women or women planning to become pregnant.
5) A history of allergy to Pueraria lobata radix.
6) Complicated with severe dysfunction of important organs, such as the heart, liver, and kidney; malignant tumours; or severe mental disorders.
7) Anticipated poor compliance, such as remote residence from the study site, frequent work-related travel, and a clinician-determined history of medication nonadherence.
8) Currently participating in other clinical trials.

4. Research Stages

If you participate in this study, you will be randomly assigned to receive either 15 g of Pueraria lobata radix granule or placebo granule intervention once a day for 12 consecutive weeks.

The entire research cycle will last for 12 weeks, and the Pueraria Lobata radix granules will be provided by Jiangxi University of Chinese Medicine. You need to try to keep the current dosage and type of hypoglycemic drugs unchanged.

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At the baseline visit, we will register your demographic information and measure the baseline indicators. There will subsequently be three follow-up visits, each occurring every four weeks. During the follow-up, indicators related to blood glucose, routine blood tests, routine urine tests, routine stool + occult blood tests, electrocardiograms, liver and kidney functions, blood lipids, vital signs, symptoms or quality of life scales, self-reported adverse events, compliance, and combined medication will be examined.

5. Cessation/withdrawal criteria

(1) Voluntarily request withdrawing.

(2) Cannot be contacted during follow-up.

(3) Withdrawal from the trial due to adverse reactions.

6. Possible Benefits of Participating in the Study

Patients participating in this trial will receive free research-related examinations, free Pueraria lobata radix or placebo samples (patients in the placebo group will receive the same amount of Pueraria lobata radix granules as the trial group after completing the study and unblinding), and a transportation subsidy of 100 yuan for each follow-up visit (issued after the last visit).

7. Participating in the Study/Withdrawing from the Study Midway/Terminating the Study

Whether to participate in this study depends entirely on your voluntary choice. You can refuse to participate in this study or withdraw from it at any time during the study process. This will not affect the relationship between you and your doctor, nor will it cause any loss of medical or other benefits.

8. Confidentiality in the Trial

If you agree to participate in this study, your medical records will be reviewed and kept by the executors and supervisors of this study and cannot be taken away or copied. All the information collected about you during the study will be kept strictly confidential, and only your contact information will be listed in the form of identifiable information. We will keep this form in a secure database for future contact with you by phone if necessary. However, during data analysis, all the data will be deidentified, and no personal information will be disclosed in future publications or other published articles.

9. Risks and Discomforts in the Trial

Pueraria lobata radix is a substance recognized by Chinese regulations for both medicinal and food uses; that is, it can be consumed as food, so its overall safety is good. Previous studies have shown that Pueraria lobata radix is cold in nature. Consuming a large amount of Pueraria lobata radix or consuming Pueraria lobata radix on an empty stomach may cause certain discomfort to the gastrointestinal tract, such as occasional bloating and abdominal pain. In addition, hypoglycemic treatment may

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increase the risk of hypoglycemia. Any scientific research has risks, discomforts, and inconveniences. Therefore, you should carefully consider this before agreeing to participate in any clinical study.

10. Trial Expenses

During the clinical research period, the sponsor will provide samples for free until the end of the trial and cover the examination expenses stipulated in the protocol during the research period. During this study, if there are serious adverse reactions related to the test samples, the sponsor will reimburse the corresponding treatment expenses and provide corresponding economic compensation for the research-related damage in accordance with the provisions of relevant laws and regulations in China.

The treatment and examinations required for other diseases you have concurrently will not be covered by reimbursement.

11. This consent form is in duplicate, with one copy held by the research unit and one copy held by the subject.

Signature Page

(If you or your family member/guardian agree to participate in this study, please read the relevant statements carefully and sign.)

I have been informed of the purpose, methods, possible risks, discomforts, and related benefits of this trial.

I confirm that I have spent sufficient time reading and understanding the above content. The doctor has explained the medical terms used therein to me, and the researchers have given satisfactory answers to all my questions about the study.

I understand that I can voluntarily withdraw from this study at any time without affecting the doctor–patient relationship and treatment in the future. I know that if I have any questions during the trial, I should contact the attending doctor in time.

I voluntarily participate in this trial and serve as a subject of this trial.

Signature of subject or designated agent: _____

Date: _____ Year _____ Month _____Day

I have truthfully informed the research object (or designated agent) of the purpose, content, benefits, and possible adverse reactions of this study. I have asked the party

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concerned if they have any questions about this study and have explained as much as I can.

Signature of the study investigator：_____
Date: _____ Year _____ Month _____Day

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