Clinical Trial Protocol

Polygonatum Sibiricum for Visceral Obesity and Related Metabolic Abnormalities: A Randomized Controlled Trial and Mechanistic Exploration

Clinical Trial Institution: Zhejiang Provincial Tongde Hospital, Zhejiang Academy of Traditional Chinese Medicine

Registration number: NCT

Protocol Version and Date: V3.0, 2026.07.07

Study Design Category: Intrventionale study (with intervention),Randomized controlled trial (RCT)

I. Basic Study Information

1.Title: A Randomized Controlled Study of Polygonatum sibiricum (Huangjing) for Visceral Obesity and Associated Metabolic Abnormalities, with Mechanistic Exploration

2.Study Period (Start and End): August 2026 – December 2027

3.Funding Source (if self-funded, indicate "self-funded"): Integrated Traditional Chinese and Western Medicine Cross-disciplinary Cultivation Project

4.Study Sites (for multi-center studies, provide center names and principal investigators with titles):

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II. Study Protocol Summary

1.Rationale (Significance, current status, and developmental trends domestically and internationally, with key references)

Obesity, especially visceral obesity characterized by abnormal accumulation of visceral fat, is a major risk factor for type 2 diabetes, metabolic-associated fatty liver disease, and cardiovascular disease

[1]. Compared with body weight or BMI alone, visceral fat better reflects adipose tissue dysfunction and cardiometabolic risk. Visceral adipose tissue has higher lipolytic activity and inflammatory / endocrine effects, promoting ectopic fat deposition, insulin resistance, and chronic low-grade inflammation, thereby driving glucolipid metabolic disorders and multi-organ damage [2,3]. Therefore, strategies targeting "reduction of visceral fat accumulation and improvement of metabolic abnormalities" are more clinically relevant and scientifically meaningful than merely pursuing weight loss.

Current obesity management remains based on lifestyle interventions. Drugs such as GLP-1 receptor agonists and metabolic surgery can achieve significant weight loss, but long-term management still faces challenges including gastrointestinal adverse effects, real-world persistence and adherence issues, high costs, and limited eligibility [4-6]. This highlights the urgent need for safer, long-term applicable interventions that can synergize with lifestyle management, particularly natural products or nutritional strategies that act on visceral fat and metabolic phenotypes.

At the mechanistic level, leptin resistance is a key pathological feature of obesity. Obese individuals often present with hyperleptinemia and blunted leptin signaling, leading to

dysregulation of appetite control, energy metabolism, and adipose endocrine functions, closely linked to insulin resistance, fatty liver, and increased cardiovascular risk [7]. Meanwhile, gut microbiota and their metabolites—short-chain fatty acids (SCFAs)—regulate host energy homeostasis, inflammation, and insulin sensitivity, and can influence lipid oxidation and fat deposition through gut-derived hormone secretion and AMPK-related pathways [8,9]. Thus, constructing a mechanistic chain centered on "gut microbiota – SCFAs – leptin resistance/AMPK" aligns with the current trend in obesity research, moving from phenotype to mechanism and precision intervention.

Polygonatum sibiricum (Huangjing) was first recorded in Shennong's Classic of Materia Medica for its effects of nourishing qi and yin, strengthening the spleen, moistening the lung, and benefiting the kidney. Recent studies have shown that Polygonatum polysaccharides and related extracts can regulate glucose and lipid metabolism, improve intestinal barrier function, remodel gut microbiota, and alleviate metabolic injury [10,11]. However, current evidence remains predominantly preclinical. Although Polygonatum has been used as a component of compound formulas in clinical studies for glucolipid disorders, randomized controlled trials directly targeting obesity—especially with visceral fat accumulation as the

primary outcome—are still scarce [10].

Our team has systematically studied Polygonatum polysaccharides and their active fractions, isolating PCPI, PCPII, and PCPIII, and demonstrating that PCPIII exhibits superior metabolic benefits in vitro and in vivo. Our findings suggest that it regulates candidate genera such as Turicibacter, increases SCFA production, ameliorates leptin resistance, and influences AMPK-related signaling, thereby promoting lipid oxidation and inhibiting abnormal lipid deposition to improve glucose and lipid metabolism [12,13]. Based on this, we propose a randomized controlled clinical trial to evaluate the added benefits of Polygonatum on visceral fat area and associated metabolic abnormalities in adults with visceral obesity, on top of lifestyle intervention, and to explore mechanisms involving gut microbiota, SCFAs, and adipokines. The results are expected to provide preliminary human evidence for translating Polygonatum from basic research to clinical application, and to support the development of safe, long-term applicable food-drug homology TCM nutritional interventions.

Key References:

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obesity to adverse health outcomes. Diabetes Obes Metab. 2025;27(Suppl 2):3-19.

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2.Research Content, Objectives, and Key Scientific Questions

2.1 Research Content

(1) Clinical study: This is a prospective, randomized, open-label, parallel-controlled trial. We will enroll 66 adults with visceral obesity and randomly assign them in a 1:1 ratio to either the Polygonatum intervention group or the control group for 12 weeks. Both groups receive standardized diet, exercise, and behavioral interventions; the intervention group additionally receives oral Polygonatum water decoction. The primary outcome is the change in visceral fat area from baseline to 12 weeks. Secondary outcomes include anthropometric measures (weight, waist circumference, body fat percentage), glucolipid metabolic parameters (lipids, fasting glucose, fasting insulin, HOMA-IR), and hepatic steatosis (UGAP value). Adverse events and adherence will be recorded to comprehensively evaluate efficacy and safety.

(2) Mechanistic exploration: Fecal and fasting blood samples will be collected at baseline and end-of-intervention for 16S rDNA sequencing, targeted SCFA profiling, adipokine (leptin and its receptor) measurement, and expression analysis of relevant molecules in peripheral blood mononuclear cells (PBMCs). Multi-dimensional association analyses integrating clinical phenotypes will be performed to explore mechanisms along the "gut

microbiota – SCFAs – adipokines – AMPK pathway" axis, providing human evidence for Polygonatum's effects on obesity and visceral fat.

2.2 Research Objectives

(1) To evaluate the effects of Polygonatum on visceral fat accumulation and associated glucolipid abnormalities in adults with visceral obesity, and to preliminarily assess its safety.

(2) To explore Polygonatum's modulation of gut microbiota, SCFAs, and leptin resistance, providing preliminary human evidence for its gut-liver axis mechanism.

2.3 Key Scientific Questions

(1) Can standardized Polygonatum decoction, on top of lifestyle intervention, further reduce visceral fat accumulation and improve glucolipid metabolism in adults with visceral obesity, thereby demonstrating clinical value targeting key pathological phenotypes?

(2) Are the clinical benefits of Polygonatum associated with gut microbiota remodeling, alterations in SCFA metabolism, improvement in leptin resistance, and changes in AMPK-related energy signaling, thus providing preliminary human mechanistic evidence?

III. Proposed Research Plan and Feasibility Analysis (including

methods, experimental approaches, key technologies)

1.Research Methods

1.1 Study Design

Single-center, randomized, open-label, parallel-controlled trial. Ethical approval and trial registration (Chinese Clinical Trial Registry) will be obtained before enrollment. An independent statistician will generate a randomization sequence using stratified block randomization, with stratification by sex and baseline visceral fat level.

1.2 Investigational Product and Intervention Protocol

Polygonatum herbal material will be purchased by the Pharmacy Department of Zhejiang Provincial Tongde Hospital, with species authentication. A water decoction will be prepared by the hospital's preparation room. The recommended dose is 15 g/day, taken orally in 1-2 divided doses after meals, for 12 consecutive weeks. The dose is based on human equivalent dose conversion from effective animal doses. Batch number management, dispensing logs, and return of unused medication will be implemented to ensure traceability and compliance.

Both groups receive uniform lifestyle intervention:

(i) Individualized calorie-restricted diets formulated by a dietitian based on basal metabolic rate and activity level, following the

principles of "total calorie control, reduced sugar and fat, regular meals."

(ii) Exercise prescription: moderate-intensity aerobic exercise combined with resistance training, at least 150 minutes per week.

(iii) TCM "preventive treatment" behavioral guidance, including sleep, stress management, and lifestyle education.

1.3 Study Participants

Inclusion Criteria:

(1) Age 18-65 years, both sexes.

(2) BMI >= 24 kg/m2 or body fat percentage >=25% (male) / >=30% (female), and visceral fat area >=100 cm2.

(3) Stable weight in the last 3 months (fluctuation <=5%).

(4) Ability to understand the study, provide written informed consent, and comply with follow-up and assessments.

Exclusion Criteria:

(1) Secondary obesity (e.g., hypothyroidism, Cushing's syndrome, polycystic ovary syndrome).

(2) Prior metabolic surgery or current use of weight-loss medications.

(3) Severe hyperglycemia or dyslipidemia requiring immediate intensive therapy.

(4) Severe cardiovascular/cerebrovascular disease or unstable conditions.

(5) Significant liver or kidney dysfunction (e.g., ALT or AST >2-3x upper normal limit, or eGFR <60 mL/min/1.73m2).

(6) Malignancy, active infection, or autoimmune disease.

(7) Use of antibiotics, probiotics, or other agents affecting gut microbiota within 1 month.

(8) Pregnancy, lactation, or planned pregnancy.

(9) Allergy or intolerance to the investigational product.

(10) Any other condition deemed unsuitable by the investigator.

Discontinuation/Withdrawal Criteria: Participants will be withdrawn if they experience serious adverse events, have poor adherence (medication or follow-up completion <80%), or voluntarily withdraw; reasons will be documented.

1.4 Sample Size Estimation

For a two-arm parallel design, two-sided alpha=0.05, power=80%, and assuming a between-group difference of 10 cm2 and standard deviation of 13 cm2 (based on literature), we calculated 27 participants per group. With a 20% dropout rate, we require 33 per group, totaling 66 participants.

1.5 Statistical Analysis

Analysis sets: Full Analysis Set (FAS), Per-Protocol Set (PPS), and Safety Set (SS). Primary outcome will be compared using analysis of covariance (ANCOVA), adjusting for baseline visceral fat area,

sex, age, and other prespecified covariates. Repeated measures will be analyzed using mixed-effects models. Missing data will be handled primarily via mixed models under missing-at-random assumptions, with multiple imputation for sensitivity analyses. Categorical variables will be analyzed using chi-square test or Fisher's exact test; non-normally distributed continuous variables will use rank-sum tests. Multiple comparisons will be adjusted using FDR. Exploratory subgroup analyses include sex, baseline insulin resistance, and presence of fatty liver.

2.Outcome Measures

2.1 Primary Outcome

Change in visceral fat area from baseline to 12 weeks (within-group difference, between-group difference, and percentage change).

2.2 Secondary Outcomes

(1) Changes in body weight, waist circumference, and body fat percentage at 12 weeks.

(2) Changes in blood lipids, fasting glucose, fasting insulin, and hepatic steatosis (UGAP value) at 12 weeks.

2.3 Safety Outcomes

Adverse events and serious adverse events, adherence, and withdrawal rates.

2.4 Exploratory Outcomes

(1) Gut microbiota: 16S rDNA sequencing to analyze microbial structure, diversity, and differential genera, with focus on Turicibacter and other candidate genera.

(2) Short-chain fatty acids: Targeted GC-MS/MS quantification of SCFAs in feces and serum, focusing on acetate and other metabolites.

(3) Adipokines: ELISA measurement of serum leptin, leptin receptor, adiponectin, etc.

(4) Energy metabolism pathways: PBMC isolation and RT-qPCR for LEPR, AMPK, PGC-1alpha, and related molecular expression.

3.Key Technologies

(1) Standardized RCT and quality control: Randomized, parallel, controlled design with unified eligibility criteria, lifestyle interventions, follow-up schedule, and adherence management to ensure standardized implementation, comparability, and reliable results.

(2) Precise assessment of visceral fat and metabolic phenotype: Bioelectrical impedance analysis for visceral fat area, combined with weight, body fat percentage, waist circumference, and glucolipid parameters, to systematically evaluate Polygonatum's effects on obesity and related metabolic abnormalities.

(3) Multi-dimensional biomarker integration: Combined application

of 16S rDNA sequencing, GC-MS/MS, ELISA, and other techniques to assess gut microbiota, SCFAs, and adipokines, with integrative association analyses linking clinical phenotypes to provide preliminary human evidence for gut-liver axis mechanisms.

4. **Feasibility Analysis**

(1) Solid preclinical foundation: Our team has systematically studied Polygonatum polysaccharides and active fractions, demonstrating significant reductions in visceral fat and improvements in glucolipid metabolism in obese mice, with mechanistic data on gut microbiota remodeling, SCFA metabolism, and AMPK signaling. The active fraction PCPIII has shown promising pharmacodynamic effects, providing a clear material basis and scientific rationale for clinical translation.

(2) Experienced team and mature platform: Our collaborative team includes basic research, endocrinology, and pharmaceutical preparation units, forming an integrated "basic-clinical-translational" system. The Endocrinology Department operates a specialized obesity clinic with ample patient flow. The research institute is equipped with advanced platforms for metabolomics and molecular biology (e.g., Wes automated protein analysis system, mass spectrometers). The preparation center can independently produce

the investigational product, ensuring smooth project execution.

(3) Well-designed and feasible protocol: The prospective, randomized, parallel, controlled exploratory design targets adults with visceral obesity, with visceral fat area as the primary outcome, offering clear objectives and well-defined endpoints. The 12-week intervention period is sufficient to observe changes in visceral fat and metabolic parameters while enhancing participant adherence and completion rates. The overall study structure is hierarchical, with clear priorities, ensuring high practical feasibility.

IV. Participant Recruitment

Recruitment Method: Public advertisement

Start Date: August 2026

Recruitment Materials: Recruitment advertisement

Expected Enrollment: Total 66 (33 intervention, 33 control)

V. Risk/Benefit Assessment

1.Benefits (Individual + Societal)

Individual benefits: Participants may experience reductions in visceral fat area and improvements in glucolipid parameters after 12 weeks of Polygonatum plus standardized lifestyle management. They will also receive free professional dietary guidance, systematic

body composition assessments, and a metabolic health profile, providing evidence-based support for long-term weight management.

Societal benefits: This project will provide the first randomized controlled human evidence for the translation of Polygonatum active fraction PCPIII from basic research to clinical application, elucidate the "gut microbiota – SCFAs – AMPK" mechanistic chain in a human population, enrich the evidence-based medicine framework for food-drug homology TCM interventions in metabolic diseases, and offer a new option for patients who cannot tolerate GLP-1 receptor agonists or seek safe, long-term alternatives.

2.Risks and Mitigation Measures

Main risks: Potential gastrointestinal discomfort or allergic reactions to Polygonatum; assessment bias due to open-label design; and the 20% dropout rate affecting statistical power.

Mitigation measures: Standardized production and batch traceability of the decoction; independent statistician for randomization and blinding of outcome assessors where feasible; establishment of FAS, PPS, and SS analysis sets with sensitivity analyses to verify robustness; discontinuation if adherence <80%; mixed-effects models for missing data handling; and strict privacy protection via coded data and access control.

3.Protection of Vulnerable Populations

We have established clear exclusion criteria to protect vulnerable groups: pregnant, lactating, or planning-to-become-pregnant women are excluded due to insufficient safety data; age lower limit of 18 years to avoid minors; exclusion of severe hepatic/renal dysfunction (ALT/AST >2-3x ULN or eGFR<60), malignancy, active infection, or autoimmune diseases to prevent confounding or added metabolic burden; secondary obesity (e.g., hypothyroidism, Cushing's, PCOS) and recent antibiotic/probiotic use are also excluded to ensure population homogeneity and stable gut microbiota baseline.

VI. Other Issues

Participants will be immediately withdrawn and reasons documented if they experience serious adverse events, voluntarily withdraw, show poor adherence, become pregnant, or develop new major diseases during the study. All biospecimens and study data will be archived according to regulations.

VII. Investigator Information

Principal Investigators

1.Name: Wang Xiaoli

Institution/Department: Zhejiang Provincial Tongde Hospital

Degree/Title: Ph.D. / Chief Physician

Ethics Training: Yes

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2.Name: Dai Guanhai

Institution/Department: Institute of Basic Experimental Research / Institute of Natural Medicines, Zhejiang Academy of TCM

Degree/Title: Senior Professional / Deputy Director

Ethics Training: Yes

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Study Team Members

1.Name: Mao Shengcheng

Institution/Department: Zhejiang Provincial Tongde Hospital

Degree/Title: Attending Physician

Task Assignment: Protocol development, recruitment, follow-up, liaison

Ethics Training: Yes

2.Name: Yu Zhongming

Institution/Department: Zhejiang Provincial Tongde Hospital

Degree/Title: Associate Chief Pharmacist

Task Assignment: Drug preparation

Ethics Training: Yes

3.Name: Ren Zeming

Institution/Department: Institute of Basic Experimental Research / Institute of Natural Medicines, Zhejiang Academy of TCM

Degree/Title: Associate Researcher

Task Assignment: Drug preparation and biochemical assays

Ethics Training: Yes

4.Name: Luo Xi

Institution/Department: Zhejiang Provincial Tongde Hospital

Degree/Title: Associate Chief Technician

Task Assignment: Diet planning (energy calculation)

Ethics Training: Yes

5.Name: Chen Sisi

Institution/Department: Institute of Basic Experimental Research / Institute of Natural Medicines, Zhejiang Academy of TCM

Degree/Title: Assistant Researcher

Task Assignment: Gut microbiota analysis and molecular biology assays

Ethics Training: Yes

6.Name: Dong Yue

Institution/Department: Zhejiang Provincial Tongde Hospital

Degree/Title: Attending TCM Physician

Task Assignment: Follow-up, adverse event recording, biosample

collection and processing

Ethics Training: Yes