A randomized, double-blind, placebo-controlled exploratory study on compound Ciwujia granules in the treatment of depression (heart and spleen deficiency syndrome)

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Researcher Information Form

1.Principal Investigator

Name	Degree	Title	Medical Qualification	GCP Training (Yes/No)	Project Role
Liu Lanying	Master	Chief Physician	Licensed Clinician	Yes	Study Design

2. Study Team Members

Name	Institution	Title	Medical Qualification	GCP Training (Yes/No)	Project Role
Li Wei	Shanghai Mental Health Center	Attending Physician	Licensed Clinician	Yes	Quality Control
Li Wangtao	Shanghai Mental Health Center	Resident Physician	TCM Practitioner	Yes	Study Coordination
Tian Fei	Shanghai University of Traditional Chinese Medicine	Resident Physician	TCM Practitioner	No	Data Processing
Guo Yihan	Shanghai University of Traditional Chinese Medicine	Resident Physician	TCM Practitioner	Yes	Sample Collection
Wu Jingjing	Shanghai Mental Health Center	Attending Physician	TCM Practitioner	Yes	Intervention Implementation
Xing Mengjuan	Shanghai Mental Health Center	Attending Physician	Licensed Clinician	Yes	Intervention Implementation

3. Sponsor

Sponsor Name	Address
Shanghai Mental Health Center	No. 600 Wanping South Road, Xuhui District, Shanghai

4. Study Site

Shanghai Mental Health Center

Address: No. 600 Wanping South Road, Xuhui District, Shanghai

Research topic

A randomized, double-blind, placebo-controlled exploratory study on compound Ciwujia granules in the treatment of depression (heart and spleen deficiency syndrome)

1 Introduction

1.1 Background

Major depression disorder (MDD) refers to a type of mood disorder caused by a variety of reasons with significant and persistent depressive symptoms as the main clinical feature. Its core symptoms are low mood and loss of interest that are out of proportion to the situation. It can cause patients to lose their social functions and reduce their quality of life, and increase the risk of suicide. It is one of the main factors in the global burden of disease [1]. The World Health Organization predicts that by 2030, it will rank first in the total global burden of human disease. Since 2010, depressive disorder has become the second leading cause of years of healthy life lost (YLD) in China [2]. The lifetime prevalence of depression in my country is 6.8% [3]. It has a serious impact on public health and has brought huge burdens to individuals, families and society.

Whether during the acute phase, continuation phase, or maintenance phase of MDD, clinical guidelines recommend first-line antidepressant medications for adult patients. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, and citalopram, are the most commonly used first-line antidepressants in clinical practice. SSRIs exhibit high selectivity for serotonin (5-HT) reuptake inhibition, with minimal effects on norepinephrine, dopamine, histamine, and cholinergic neurotransmission. They are well absorbed orally, have relatively high bioavailability, good tolerability, and favorable adherence, making them suitable for various types of depression. A large number of randomized controlled trials (RCTs) have demonstrated that SSRIs are significantly more effective than placebo in treating depression, and there is no significant difference in overall efficacy among different SSRIs. However, approximately 30%–40% of patients are classified as treatment-resistant due to poor response or insensitivity to SSRIs [4]. Moreover, SSRIs are associated with several limitations, including delayed onset of action, residual symptoms, and the need for long-term medication. Therefore, there is an urgent need to explore alternative treatment strategies that offer a faster onset of effect, better tolerability, improved efficacy, and fewer side effects.

In China, many patients with depression either refuse treatment with Western medications or are unable to tolerate them. This presents an opportunity for exploring Traditional Chinese Medicine (TCM) as an alternative approach to treating depression. In TCM, depression falls under the category of "Yu syndrome", which is considered a type of emotional disorder. According to TCM theory, Yu syndrome arises from dysfunction of the internal organs and imbalance of Qi, blood, Yin, and Yang. The most commonly observed TCM patterns include liver Qi stagnation with spleen deficiency, dual deficiency of the heart and spleen, liver Qi stagnation, and kidney deficiency with liver constraint.

Compound Ciwujia Granules is a proprietary Chinese medicine developed and marketed by Heilongjiang Quanle Pharmaceutical Co., Ltd. It is currently approved for the treatment of insomnia and other neurological and psychiatric disorders. This formulation consists of two traditional Chinese medicinal herbs: *Eleutherococcus senticosus* and *Schisandra chinensis*. *Eleutherococcus senticosus* contains a variety of active chemical constituents, including eleutherosides, polysaccharides, carotenoids, syringin, isofraxidin glycosides, ethyl galactoside, and lignan diglucosides. These compounds have demonstrated pharmacological effects such as anti-fatigue, anti-inflammatory, neurotransmitter regulation, and anti-apoptotic activities. Due to these properties, it is widely used in the treatment of neurological disorders [5]. Modern studies have shown that polysaccharides extracted from *Eleutherococcus senticosus* exert antidepressant effects by modulating neuroinflammation [6]. *Schisandra chinensis* contains a variety of bioactive compounds, including lignans, triterpenoids, sesquiterpenes, essential oils, polysaccharides, flavonoids, and organic acids. Among these, lignans are considered the primary active constituents. Representative lignan compounds include schisandrol A, schisandrin A, and schisandrin B [7]. Modern pharmacological studies have demonstrated that *Schisandra chinensis* possesses multiple therapeutic effects, including modulation of the central nervous system, cardiovascular protection, immune enhancement, as well as antibacterial and antimicrobial activities[8]. In TCM, *Eleutherococcus senticosus* is used to tonify Qi and strengthen the spleen, nourish the kidney, and calm the spirit. *Schisandra chinensis* replenishes Qi, generates body fluids, nourishes the kidney, and calms the mind. When used in combination, these two herbs work synergistically to tonify both the spleen and kidney, soothe the spirit, and calm the mind. This pairing

is especially beneficial in alleviating symptoms associated with the heart-spleen deficiency pattern, such as lack of interest or motivation, general fatigue, poor appetite, insomnia, and excessive dreaming.

To further investigate the clinical efficacy and safety of Compound Ciwujia Granules in patients with MDD, we have designed a randomized, placebo-controlled clinical trial. This study aims to systematically evaluate the therapeutic effects and underlying mechanisms of Compound Ciwujia Granules in the onset and progression of MDD, in order to provide clinical evidence to support its application in the treatment of depression.

2 Research Purpose

2.1 Main Purpose

The primary objective of this study is to evaluate the therapeutic efficacy of Compound Ciwujia Granules in the treatment of depression.

2.2 Secondary Purpose

1. To evaluate the safety and tolerability of Compound Ciwujia Granules in participants with depression, as compared to placebo.
2. To assess the overall clinical efficacy of Compound Ciwujia Granules, as compared to placebo, using a Traditional Chinese Medicine (TCM) symptom score scale.

2.3 Exploratory purpose

1. To evaluate the efficacy of Compound Ciwujia Granules in improving insomnia symptoms associated with depression, as compared to placebo, using the Pittsburgh Sleep Quality Index (PSQI).
2. To assess the effect of Compound Ciwujia Granules on anxiety symptoms comorbid with depression, as compared to placebo, using the Hamilton Anxiety Rating Scale (HAMA).
3. To evaluate the impact of Compound Ciwujia Granules on inflammatory levels in patients with depression by measuring serum inflammatory cytokines.

3 Research Design

3.1 Types of Experimental Designs

This study is a single-center, randomized, double-blind, placebo-controlled trial

designed to evaluate the safety and efficacy of Compound Ciwujia Granules in participants with MDD.

3.2 Randomization method

Heilongjiang Quanle Pharmaceutical Co., Ltd. will provide the study medication during the trial. The medication boxes contain all drugs required for the treatment period, and each box is labeled with a unique identification number. Both the active drug and placebo are packaged identically in the study to ensure blinding.The assignment of medication numbers to the study drugs is based on a randomized sequence. Eligible participants will be randomly assigned in a 1:1 ratio to receive either Compound Ciwujia Granules or placebo.A random number generator in a computerized system will be used to create the allocation sequence. These random numbers will be sealed in sequentially numbered, opaque envelopes. When a participant is enrolled, the corresponding envelope will be opened to reveal the randomization code. This process will be conducted by personnel independent of the clinical trial.Investigators will register enrolled patients and dispense medication according to the randomization schedule. All patients, attending physicians, scale evaluators, prescribing psychiatrists, and statisticians will remain blinded to treatment allocation throughout the study.

3.3 Intervention Protocol

Experimental Group:

Participants will receive Compound Ciwujia Granules, administered twice daily, one sachet (8g) each time. The dosing schedule should be relatively fixed, taken half an hour after breakfast and dinner, continuously for 56 days.

Participants who are already taking SSRIs will continue their original dosage and frequency as previously prescribed.

Control Group:

Participants will receive placebo granules matching Compound Ciwujia Granules in appearance and dosage, administered twice daily, one sachet (8g) each time. The dosing schedule should be relatively fixed, taken half an hour after breakfast and dinner, continuously for 56 days.

Participants who are already taking SSRIs will continue their original dosage and frequency as previously prescribed.

The treatment duration for both groups is 56 days. Efficacy and safety evaluations will be conducted at the end of the treatment course. Throughout the treatment period,

patients will be monitored and any side effects or adverse reactions will be documented. Participants are required to promptly report any adverse events occurring during or after the treatment.

4 Study Subjects

The study subjects are patients diagnosed with depressive disorders attending the outpatient clinic of Shanghai Mental Health Center. All participants will provide written informed consent prior to enrollment.

4.1 Sample Size

Based on the guidelines in *Determining Sample Size for Pilot Studies in Traditional Chinese Medicine Clinical Research* [9], this study is designed as an exploratory pilot trial to test the scientific validity and feasibility of the study design. A total of 60 participants will be enrolled, with 30 subjects per group.

4.2 Inclusion Criteria

1. Meet the diagnostic criteria for Major Depressive Disorder according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) and the criteria for a depressive episode based on the Mini-International Neuropsychiatric Interview (M.I.N.I.).
2. Meet the diagnostic criteria for heart-spleen deficiency syndrome in Traditional Chinese Medicine [10], characterized by:
   - Primary symptoms: excessive worrying, palpitations, shortness of breath, and a sallow complexion;
   - Secondary symptoms: dizziness, fatigue, spontaneous sweating, poor appetite, loose stools;
   - Tongue and pulse: pale and tender tongue with teeth marks on the edges, white tongue coating, and a thin weak pulse.
3. Total score on the 17-item Chinese version of the Hamilton Depression Rating Scale (HAMD-17) between 8 and 24.
4. Score ≤21 on the Hamilton Anxiety Rating Scale (HAMA).
5. Outpatient men and women aged 18 to 65 years (inclusive).
6. Education level of junior high school or above, capable of completing self-assessment scales.
7. Currently taking a stable dose of a single SSRI medication for at least 6 weeks,

with a Clinical Global Impression – Severity of Illness scale (CGI-SI) score ≥4 at screening and baseline.

8. Willing to participate voluntarily and provide written informed consent.

4.3 Exclusion Criteria

1. History or diagnosis of any of the following conditions: depressive disorder related to organic mental disorders; clinically significant neurological diseases (including epilepsy, encephalopathy); any neurodegenerative diseases; moderate to severe head trauma or other neurological conditions potentially affecting central nervous system function.
2. Current diagnosis of any DSM-5 mental disorder other than depression, including schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, anxiety disorders, obsessive-compulsive and related disorders, somatic symptom and related disorders, substance-related and addictive disorders (except caffeine and nicotine), or a positive urine drug screen at screening.
3. History of suicide attempts or, in the investigator's judgment, current significant suicide risk, or any affirmative ("yes") response to questions 1-5 of the Columbia-Suicide Severity Rating Scale (C-SSRS).
4. Presence of other serious systemic diseases, or severe cardiac, hepatic, or renal insufficiency (including alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels greater than 1.5 times the upper limit of normal).
5. Pregnant or breastfeeding women, or women who may become pregnant during the study and cannot use effective contraception.
6. Acute or chronic infectious diseases, autoimmune diseases, allergies, cancer, or stroke within the past month.
7. Participation in other clinical drug trials within the past month.
8. History of psychosurgery, deep brain stimulation (DBS), or electroconvulsive therapy (ECT).

4.4 Withdrawal Criteria

1. Participants who experience allergic reactions, severe adverse events, other complications, or special physiological changes, for which the investigator determines that study treatment should be discontinued.
2. Participants who, for any reason, are unwilling or unable to continue the clinical trial and request withdrawal from the study.

3. Participants who do not explicitly request withdrawal but discontinue medication and assessments, resulting in loss to follow-up.
4. Participants who become unblinded during the study.
5. Participants who become pregnant.

The investigator should also consider withdrawal based on the participant's specific condition in the following situations:

- Participants who develop serious drug-related hepatic or renal toxicity as judged by the investigator.
- Participants who experience other serious adverse events that require hospitalization or prolonged hospitalization. If these events do not impact safety and efficacy evaluations, withdrawal may not be necessary.
- Participants who develop comorbidities, complications, or special physiological changes that may render continued participation inappropriate.
- Participants who use prohibited medications or treatments as specified in the study protocol.

For participants who withdraw or drop out, investigators should attempt to maintain contact by home visits, scheduled follow-ups, telephone calls, or letters. The last date of medication use should be recorded, and as many assessment items as possible should be completed. For those withdrawing due to allergic reactions, adverse events, or treatment failure, investigators should provide appropriate medical care based on the participant's condition.

The reasons for withdrawal must be documented in the participant's medical records, case report forms (CRF), and electronic case report forms (eCRF).

4.5 Criteria for Study Termination

1. Study termination refers to the premature cessation of the entire clinical trial before its planned completion. The primary purpose of terminating a study is to protect participant rights, ensure research quality, and avoid unnecessary economic losses. The criteria for study termination include:
2. Serious safety issues arise during the study, requiring immediate termination of the trial.
3. It becomes evident during the study that the investigational product lacks practical value, warranting termination to avoid delaying effective treatment for participants and to prevent unnecessary economic loss.

4. Significant flaws are identified in the clinical trial protocol that impede the assessment of the drug's efficacy, or major deviations occur during implementation that make continued evaluation of the product's effects unfeasible.
5. The sponsor requests termination due to financial, administrative, or other reasons.
6. The National Medical Products Administration (NMPA) mandates the termination of the study for any reason.

4.6 Concomitant Medications

All concomitant medications or treatments used by participants from the time of signing the informed consent until the end of the follow-up period must be recorded, except for the investigational product. Common intravenous solvents such as sodium chloride injection or glucose injection do not need to be documented. Medications used solely for examinations, skin tests, or wound dressings are also exempt from recording. Investigators should request participants to bring all medications and medication containers they are currently using to each follow-up visit. Concomitant medications will be reviewed and documented in detail in the original medical records, including the generic name (or name of other therapies), dosage and administration, start date, and indication (or reason for use).

4.6.1 Permitted Concomitant Medications or Treatments

During the treatment period, aside from the originally prescribed SSRI medication and the investigational drug, the use of other medications should be minimized whenever possible. If the investigator determines that additional treatment is necessary for the participant's condition and does not interfere with the study medication, appropriate therapies or treatments may be administered based on clinical judgment (excluding medications or treatments prohibited by the study protocol).

New-generation non-benzodiazepine hypnotics (including zolpidem, zopiclone, eszopiclone, and zaleplon) may be taken before bedtime, with a cumulative duration not exceeding two weeks.

For participants receiving long-term treatment for chronic somatic diseases, the type and dosage of medications should be kept as stable as possible throughout the trial.

4.6.2 Prohibited Concomitant Medications or Treatments

During the entire study period, the use of any medications or treatments that may affect the efficacy and safety evaluation of the investigational product is strictly prohibited. Specifically:

- The use of any antidepressant medications other than the investigational drug is

prohibited, including but not limited to monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and any traditional Chinese medicine or proprietary Chinese medicine with antidepressant effects.

- The use of benzodiazepine-class sedative-hypnotics, all anxiolytics, all antipsychotics, mood stabilizers, and similar central nervous system drugs is prohibited during the study.

5 Study Procedures and Workflow

5.1 Study Steps and Methods

5.1.1 Screening/Baseline Phase

During this visit, the following activities will be completed:

1. The investigator explains the study details, and the participant signs the informed consent form.
2. The investigator confirms the participant's eligibility according to inclusion and exclusion criteria.
3. Collection of basic participant information, physical measurements, and vital signs assessment.
4. Demographic information: name, sex, phone number, ethnicity, age, occupation, etc.
5. Physical measurements: height, weight.
6. Vital signs: temperature (T), heart rate (HR), respiration rate (R), blood pressure (BP), etc.
7. Medical history, including past illnesses, medication history, personal history, and current illness.
8. Administration of questionnaires/scales to the participant:
   1) 17-item Hamilton Depression Rating Scale (HAMD-17);
   2) Traditional Chinese Medicine symptom score scale;
   3) Hamilton Anxiety Rating Scale (HAMA);
   4) Pittsburgh Sleep Quality Index (PSQI);
   5) Clinical Global Impression – Improvement scale (CGI-I);
   6) Columbia-Suicide Severity Rating Scale (C-SSRS).
9. Serum inflammatory marker testing: collection of 5 ml fasting venous blood to measure serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) using enzyme-linked immunosorbent assay (ELISA).

10. Safety assessments including:
    1) Electrocardiogram (ECG);
    2) Complete blood count (CBC): red blood cells (RBC), white blood cells (WBC), hemoglobin (Hb), platelets (PLT);
    3) Urinalysis: white blood cells (WBC), protein (PRO);
    4) Liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL);
    5) Renal function tests: blood urea nitrogen (BUN), serum creatinine (Scr);
    6) Pregnancy test.
11. Dispensing of the investigational medication.
12. Scheduling of the next visit.

5.1.2 Intervention Phase

The intervention phase lasts 8 weeks, with visits every 4 weeks, totaling 2 visits. At each visit, the following procedures will be completed:

1. Vital signs assessment: temperature (T), heart rate (HR), respiration rate (R), blood pressure (BP), etc.
2. Administration of questionnaires/scales:
    1) 17-item Hamilton Depression Rating Scale (HAMD-17);
    2) Traditional Chinese Medicine symptom score scale;
    3) Hamilton Anxiety Rating Scale (HAMA);
    4) Pittsburgh Sleep Quality Index (PSQI);
    5) Columbia-Suicide Severity Rating Scale (C-SSRS);
    6) Treatment Emergent Symptom Scale (TESS).
3. Dispensing of investigational medication.
4. Collection of used investigational medication and packaging.
5. Recording of adverse events.
6. Scheduling the next visit.
7. At the week 8 visit, participants will undergo serum inflammatory marker testing and safety assessments, identical to those conducted at baseline.

5.1.3 Follow-up Phase

During the follow-up visit, the following assessments will be conducted:

1. Administration of questionnaires/scales:
    1) 17-item Hamilton Depression Rating Scale (HAMD-17);
    2) Traditional Chinese Medicine symptom score scale;

3) Hamilton Anxiety Rating Scale (HAMA);
4) Pittsburgh Sleep Quality Index (PSQI);
5) Columbia-Suicide Severity Rating Scale (C-SSRS);
6) Treatment Emergent Symptom Scale (TESS).

5.2 Study Flowchart

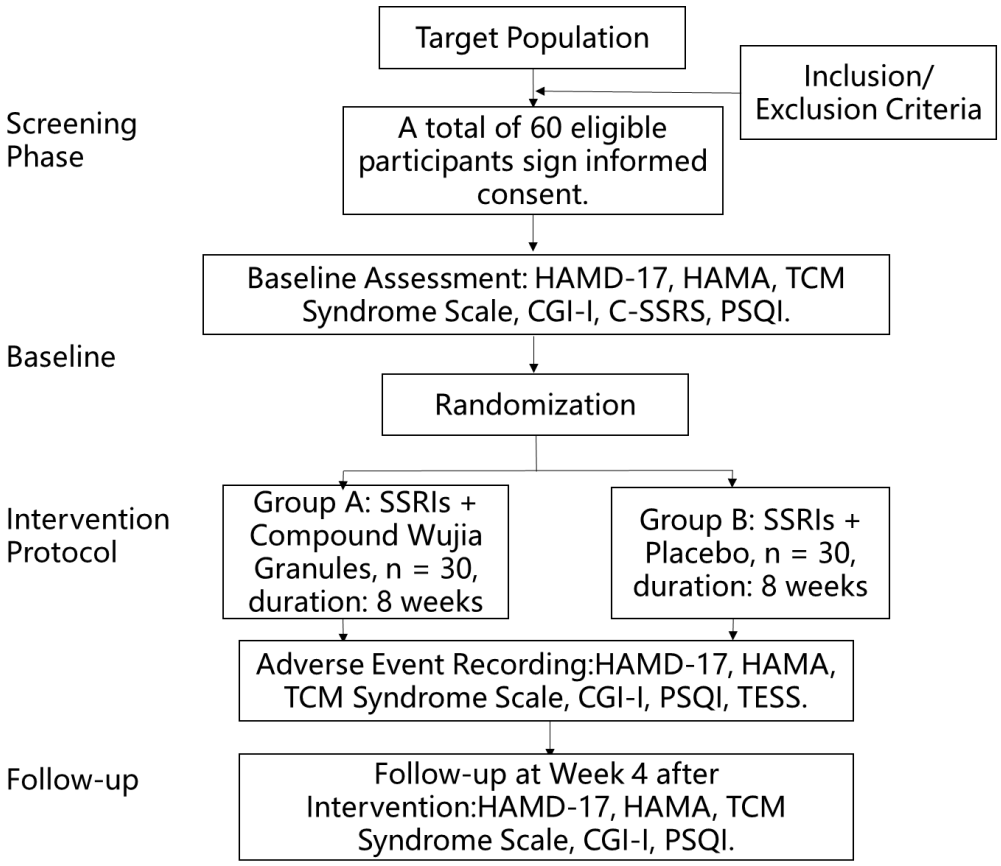

Figure 1. Study Flowchart

5.3 Research Schedule

Table1 Research Schedule

Stages	Screening period	Baseline	Treatment period		4 weeks after treatment
Visits	V1	V2	V3	V4	V5
Visits time	W1	W1	W4	W8	W12
Sign informed consent form	X				
Inclusion and exclusion criteria	X				
Medical history collection	X				
Randomization		X			

Demographic data	X				
Laboratory testing	X			X	
Scale testing		X	X	X	X

6 Clinical Assessments and Measures to Ensure Participant Compliance

6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in HAMD-17 score from baseline to the end of treatment at Day 56 (Week 8). The percentage reduction in HAMD-17 score after treatment is calculated as follows: Reduction rate = (Baseline HAMD-17 score – Week 8 HAMD-17 score) / Baseline HAMD-17 score. A reduction rate of ≥50% is considered clinically effective.

6.2 Secondary Efficacy Endpoints

Secondary efficacy will be assessed by: Improvement of TCM syndrome scores using the TCM symptom scale; Improvement of anxiety symptoms assessed by the Hamilton Anxiety Rating Scale (HAMA); Improvement of insomnia measured by the Pittsburgh Sleep Quality Index (PSQI); Improvement in overall function evaluated by the Clinical Global Impression (CGI) scale. Additionally, changes in serum inflammatory markers will be observed to evaluate the anti-inflammatory effects of Compound Ciwujia Granules.

6.3 Study Scales

6.3.1 Hamilton Depression Scale-17，HAMD-17

The Hamilton Depression Rating Scale-17 (HAMD-17) is one of the most commonly used clinician-administered scales for assessing depressive states in psychiatric practice. Previous studies have demonstrated that the scale has good reliability and validity. The scale uses a 5-point scoring system to evaluate the severity of depressive symptoms, with higher total scores indicating more severe depression. A total score above 24 indicates severe depression; a score above 17 indicates mild to moderate depression; and a score below 7 indicates absence of depressive symptoms.

6.3.2 TCM Symptom Scale

In clinical trials, this scale is used to dynamically monitor changes in patients'

TCM syndromes before and after treatment (e.g., changes in total scores), providing scientific evidence for the efficacy of traditional Chinese medicine. The scale is developed based on the efficacy evaluation criteria outlined in the *Guiding Principles for Clinical Research on New Traditional Chinese Medicines* issued by the National Health Commission and the *Guidelines for Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Depression* published by the Chinese Medical Association.

6.3.3 Hamilton Anxiety Scale，HAMA

The Hamilton Anxiety Rating Scale (HAMA) is a clinician-administered scale used to assess the severity of anxiety symptoms in patients with neurosis and other disorders. Previous studies have demonstrated good reliability and validity of this scale. According to the assessment criteria provided by the Chinese Psychiatric Scale Cooperative Group, a total score above 29 indicates severe anxiety; above 21 indicates definite significant anxiety; above 14 indicates definite anxiety; above 7 suggests possible anxiety; and below 7 indicates no anxiety symptoms. In previous research, a cutoff score of 14 is often used. Higher total scores represent more severe anxiety symptoms.

6.3.4 Clinical Global Impression–Improvement scale (CGI-I)

The Clinical Global Impression–Improvement scale (CGI-I) is a patient self-rated scale using an 8-point scoring system ranging from 0 to 7. The participant evaluates their current condition compared to the baseline at enrollment. The score interpretation is as follows:

0 – Not assessed;

1 – Very much improved;

2 – Much improved;

3 – Minimally improved;

4 – No change;

5 – Minimally worse;

6 – Moderately worse;

7 – Very much worse.

6.3.5 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a patient self-rated questionnaire assessing sleep quality. It is simple to administer and demonstrates good reliability and validity. The scale uses a 0 to 3 scoring system, with a total score range from 0 to 21.

Higher scores indicate poorer sleep quality.

6.4 Safety Indicators

Safety assessments will be conducted at Weeks 4 and 8.

Safety and tolerability will be evaluated through adverse event (AE) reports, physical examinations, electrocardiograms (ECG), vital signs, and clinically significant changes in laboratory test results.

1) **Vital Signs and Physical Measurements (Height and Weight)**

According to the study assessment schedule and medical necessity, seated vital signs (temperature, blood pressure, and pulse rate) as well as height and weight will be recorded during scheduled visits.

2) **Electrocardiogram (ECG)**

A 12-lead ECG will be recorded at scheduled visits per the study assessment plan or as medically indicated.

3) Physical Examination

Participants will undergo a comprehensive physical examination as specified in the study assessment schedule. The examination should include at least the following areas: HEENT (head, eyes, ears, nose, and throat), neck, lymph nodes, lungs, cardiovascular system, abdomen, skin, and musculoskeletal system. The assessment will be conducted by the principal investigator or a medically qualified designee. If a participant discontinues the study for any reason, an attempt should be made to perform a final physical examination. Physical examinations may also be performed at any time based on the investigator's judgment.

4) Laboratory Assessments

On Day 1 (baseline) and at Week 8 of treatment, 5 ml of venous blood and 10 ml of urine will be collected from participants for laboratory tests. The laboratory assessments will include the following:

1) Hematology: Hemoglobin, hematocrit, platelets, complete blood count (CBC) with differential, and absolute neutrophil count;
2) Blood Biochemistry: Sodium, potassium, chloride, calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), phosphorus, bicarbonate, total protein, albumin, total bilirubin, glucose, creatinine, blood urea nitrogen (BUN), and uric acid;
3) Urinalysis: At scheduled visits according to the study assessment schedule

and medical necessity, tests will include pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and occult blood. If blood, protein, or leukocytes are positive, microscopic examination will be performed to further evaluate abnormal results;

4) Pregnancy Testing: Serum pregnancy tests will be conducted at baseline and scheduled follow-ups in the central laboratory as per the study assessment schedule. Urine pregnancy tests will be performed at the study center prior to dosing, at baseline, and at subsequent scheduled visits according to the assessment plan or at the investigator's discretion.

Any laboratory test results outside the normal reference ranges must be brought to the attention of the study physician (investigator or sub-investigator). The investigator will determine the clinical significance of abnormal values. If necessary, repeat laboratory testing may be conducted.

5) Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool used to evaluate suicidal ideation and behavior [11]. This tool uses a series of simple, easy-to-understand questions that anyone can answer to assess an individual's risk of suicide. The responses help the user determine whether a person is at risk for suicide, evaluate the severity and immediacy of that risk, and measure the level of support the person requires.

If the investigator determines that a participant is at risk of suicide or self-harm, appropriate measures must be taken to ensure the participant's safety and obtain a mental health evaluation. The participant must be immediately withdrawn from the study.

6) **Treatment Emergent Symptom Scale (TESS)**

The Treatment Emergent Symptom Scale (TESS) was developed by the U.S. National Institute of Mental Health in 1973 to assess adverse reactions experienced by patients during treatment. Each adverse symptom is evaluated based on severity, its relationship to the medication, and any measures taken. The scale includes an overall severity rating (TESS-A) and an individual distress rating (TESS-B), with lower scores indicating better tolerance [12].

6.5 Measures to Ensure Participant Compliance

Regular contact and communication with participants will be maintained. Physical examinations and scale assessments will be conducted periodically. Additionally, health consultations, health education sessions, group fitness, or wellness activities will be

organized to ensure timely feedback of relevant information during the trial period.

7 Adverse Events

7.1 Adverse Events

7.1.1 Definition of Adverse Events

An adverse event (AE) refers to any unfavorable medical occurrence in a patient or clinical trial participant who has received a pharmaceutical product or treatment, which does not necessarily have a causal relationship with the treatment.

A serious adverse event (SAE) refers to any adverse event occurring during a clinical trial that results in hospitalization or prolongation of existing hospitalization, disability, impairment of work capacity, life-threatening conditions, death, or congenital abnormalities.

7.1.2 Classification of Adverse Events

Mild: The participant can tolerate the event; it does not affect treatment and requires no special intervention. It has no impact on the participant's recovery.

Moderate: The event is difficult for the participant to tolerate and requires special intervention. It has a direct impact on the participant's recovery.

Severe: The event is life-threatening, causes death or disability, and requires immediate emergency treatment.

7.1.3 Recording, Reporting, and Management of Adverse Events

Recording of Adverse Events: During the trial, adverse events (AEs) must be accurately recorded on the adverse event case report forms, including the time of onset, severity, duration, interventions taken, and outcomes. Any clinically significant abnormal laboratory results, vital signs, electrocardiograms (ECGs), or other examination findings should be documented by the investigator or sub-investigator in the "Pre-existing Conditions and Study Adverse Events" section of the case report form (CRF). If a clinically significant diagnosis can be made, it should be recorded as an adverse event. For findings without a clear diagnosis, the clinical significance will be determined by the investigator, and findings deemed clinically significant will be recorded as adverse events.

Reporting of Adverse Events: Upon discovery of a serious adverse event (SAE), the investigator must report it to the designated personnel approved by the principal

investigator (PI) within 24 hours. Initial reporting is by telephone, followed immediately by submission of a completed SAE report form specific to this study. SAEs include but are not limited to: death; hospitalization or prolonged hospitalization; life-threatening conditions (imminent risk of death); persistent or significant disability or incapacity; congenital anomalies or birth defects; or any event the investigator deems significant for any reason.

Management of Adverse Events: Any serious adverse reaction occurring during the trial must be promptly managed to ensure participant safety and immediately reported to the institutional ethics committee. The investigator should complete the "Serious Adverse Event Report Form" and notify the contact persons listed in the informed consent form (ICF) with phone numbers. All adverse events must be followed up with detailed documentation of management and outcomes until resolved or the condition is stabilized. For abnormal laboratory results, follow-up should continue until values return to normal. Follow-up methods may include hospitalization, outpatient visits, home visits, phone calls, or correspondence, depending on the severity of the adverse reaction. If participants sustain injury related to the study, appropriate compensation should be provided.

8 Drug Management

8.1 Investigational Drug

The investigational drug and placebo are provided by Heilongjiang Quanle Pharmaceutical Co., Ltd. and meet quality standards. Storage conditions: Store in a cool, dry, and dark place, out of reach of children.

8.2 Dosage and Administration

Compound Eleutherococcus Senticosus Granules (Marketing Authorization Holder: Heilongjiang Quanle Pharmaceutical Co., Ltd., Drug Approval Number: Z20025148, Batch Number: 20220301): Main components are Eleutherococcus senticosus extract and Schisandra chinensis extract. Oral administration, one sachet (8g) per dose, twice daily. Treatment duration is 8 weeks.

Placebo for Compound Eleutherococcus Senticosus Granules: same as above (details omitted).

8.3 Drug Packaging

The investigational drugs are packaged in boxes. The labels on the boxes include

information such as drug number, quantity, specifications, dosage instructions, storage conditions, and precautions.

8.4 Drug distribution

The investigational drugs are centrally stored by the clinical department and managed by a drug administrator who is not directly involved in the clinical trial. The administrator is responsible for the storage, dispensing, collection, record-keeping, and return or retrieval of the investigational drugs. After a participant is enrolled, the drug administrator dispenses the medication according to the drug number assigned by the participant's randomization code. The investigational drug is dispensed at the start of medication and any remaining drugs, empty boxes, and empty sachets are collected at each visit or the final visit.

Storage of Investigational Drugs: A management system for investigational drugs during the trial period is established. The drugs are stored in a dedicated cabinet in a well-ventilated, dry, and temperature-controlled environment, and are managed uniformly by the drug administrator.

9 Quality Control and Assurance of the Clinical Trial

Researchers must fulfill their respective responsibilities and strictly follow the clinical trial protocol, using standard operating procedures (SOPs) to ensure the implementation of quality control (QC) and quality assurance (QA) systems for the clinical trial. All observations and findings during the trial must be verified, and quality control must be conducted at every stage of data processing to ensure data completeness, accuracy, authenticity, and reliability.

Study Monitoring: Project member Li Wei will conduct regular monitoring throughout the research progress. The monitor must ensure that the clinical facilities at the study site meet the requirements, that researchers adhere to the trial protocol and accurately record trial results. During each monitoring visit, the monitor must also review participant documentation and ensure every participant has signed the informed consent form. All study procedures are governed by standardized operating procedures.

Research Staff Qualifications: Researchers must be physicians trained in clinical trials and work under the guidance of senior professionals.

Scale Consistency Testing: Consistency testing will be conducted on the primary cognitive function and symptom evaluation scales.

Symptom Quality Control: This study uses an integrated Traditional Chinese and

Western medicine scale for depressive symptoms syndrome differentiation, which has demonstrated good reliability and validity.

During the entire study, the research team will hold weekly coordination meetings to discuss project progress and plan subsequent steps.

Reducing Placebo Effect Bias: The placebo and investigational drug are identical in appearance (shape, color), smell, taste, and packaging, prepared and coded by Heilongjiang Quanle Pharmaceutical Co., Ltd. Neither researchers nor participants can predict group assignment. At the end of the study, a blinding efficacy assessment will be conducted with participants and researchers. If a significant placebo effect is detected, the possible reasons will be analyzed and discussed, and the effect size difference between placebo and investigational groups will be reported.

10 Data Management and Statistical Analysis Plan

10.1 Data Management

This study uses EpiData 3.1 for data entry, implementing double data entry and verification.

1. EpiData Database Construction: The data manager will construct the database based on the study protocol and case report forms.
2. Data Entry: Clinical researchers or designated data entry personnel (clinical coordinators) will promptly and accurately enter data from the case report forms into EpiData. EpiData is not considered the original record; its content originates from the case report forms and study visit manuals.
3. Data Locking and Export:After each participant completes the trial and the data is verified by the monitor, the data manager will lock the data. During the trial, locked data can be exported in real time for interim analysis as needed. After all participants' trial data are locked, the data manager will export the data to the designated database for final statistical analysis by statisticians.

10.2 Statistical Analysis

The study data will be analyzed using SPSS version 23.0 software. Categorical variables will be presented as counts and percentages [n (%)], and comparisons between groups will be performed using the Chi-square (χ^2) test. Continuous variables that follow a normal distribution will be expressed as mean ± standard deviation (mean ± SD); those that do not follow a normal distribution will be presented as median (minimum,

maximum) [Median (min, max)]. If the data meet the assumptions of normality and homogeneity of variance, one-way analysis of variance (ANOVA) will be used for group comparisons. When statistically significant differences are detected, the Least Significant Difference (LSD) method will be applied for pairwise comparisons between groups. If the data do not meet normality or homogeneity of variance assumptions, the non-parametric Kruskal-Wallis H test will be used for multiple independent samples. If significant differences are found, the Games-Howell test will be used for pairwise comparisons. A p-value less than 0.05 ($P < 0.05$) will be considered statistically significant.

10.3 Data Traceability Requirements

The data collection for this study is managed by the Shanghai Mental Health Center. It is required to ensure the authenticity, completeness, and confidentiality of the clinical trial data. The data management process must comply with relevant regulations to guarantee the traceability of clinical trial data.

Researchers should truthfully, thoroughly, and carefully complete all questionnaire items as per the requirements, ensuring that the content is accurate and reliable. All observations and findings in the study must be verified to ensure that all conclusions are based on original data. After the questionnaires are completed and reviewed by the principal investigator, they will be securely stored by designated personnel in a locked cabinet within the research office. All procedures are documented. The safekeeping of research files, data processing, and related test results are managed by designated staff.

11 Ethics Requirements

11.1 Ethics Committee Review

The study protocol, written informed consent form, and materials directly related to participants must be submitted to the Ethics Committee of Shanghai Mental Health Center. The study may only commence after receiving written approval from this Ethics Committee. Researchers must submit an annual progress report to the Ethics Committee of Shanghai Mental Health Center at least once a year (if applicable). Upon study termination and/or completion, researchers must notify the Ethics Committee of Shanghai Mental Health Center in writing. Researchers must promptly report any changes occurring during the study (such as amendments to the protocol and/or informed consent documents) to the Ethics Committee. Such changes must not be implemented before receiving approval from the Ethics Committee, except when changes are necessary to

eliminate obvious and immediate risks to participants. In such cases, the Ethics Committee of Shanghai Mental Health Center will be informed accordingly.

11.2 Informed Consent

Researchers must provide participants or their legal guardians with an informed consent form that is easy to understand and approved by the Ethics Committee of Shanghai Mental Health Center. Participants or their legal guardians should be given sufficient time to consider participation in the study. Participants must not be enrolled before obtaining their signed written informed consent. During the participant's involvement in the study, all updated versions of the informed consent form and related written information will be provided to the participant. The informed consent form shall be retained as an important document related to human subject research for future reference.

12 Confidentiality Measures

The results of this study may be published in academic journals; however, participant information will be kept confidential in accordance with legal requirements. Except when required by applicable laws, participants' personal information will not be disclosed. When necessary, government regulatory authorities and the Ethics Committee of Shanghai Mental Health Center, as well as relevant personnel, may review participant records as per regulations.

13 Trail expected progress

Annual	Annual Project Plan and Objectives
2025 Annual	**Quarter 2:** Complete literature review and manuscript writing; Obtain ethical approval; Register the clinical trial. **Quarter 3:** Enroll and randomly assign 20 eligible patients; Conduct intervention and follow-up visits. **Quarter 4:** Enroll and randomly assign another 20 eligible patients; Conduct intervention and follow-up visits. **Node goals:** Complete enrollment, intervention, and evaluation of 40 study participants

2026 Annual	**Quarter 1:** Enroll and randomly assign 20 eligible patients; Conduct intervention and follow-up visits. **Quarter 2:** Summarize and clean data; Perform data analysis; Write and submit manuscript; Prepare research summary report; Complete project defense and closure. **Node goals:** Complete data organization, project defense, and project closure.

References

[1] Liu T, Lu J, Lukasiewicz K, et al. Stress induces microglia-associated synaptic circuit alterations in the dorsomedial prefrontal cortex[J]. Neurobiology of Stress, 2021, 15: 100342.

[2] Simon G E, Moise N, Mohr D C. Management of Depression in Adults: A Review[J]. JAMA, 2024, 332(2): 141-152.

[3] 过伟峰, 曹晓岚, 盛蕾, 等. 抑郁症中西医结合诊疗专家共识[J]. 中国中西医结合杂志, 2020, 40(2): 141-148.

[4] Thase M E. New medications for treatment-resistant depression: a brief review of recent developments[J]. CNS spectrums, 2017, 22(S1): 39-48.

[5] Li X T, Zhou J C, Zhou Y, et al. Pharmacological effects of Eleutherococcus senticosus on the neurological disorders[J]. Phytotherapy Research, 2022, 36(9): 3490-3504.

[6] 丁继红, 姜春玉, 杨乐, 等. 刺五加多糖调控 PI3K/Akt/mTOR 通路改善大鼠抑郁行为的作用[J]. 食品工业科技, 2022, 43(11): 369-375.

[7] 王佳伟, 吴垚, 马叶子, 等. 北五味子化学成分、药理作用及临床应用研究进展[J]. 陕西中医药大学学报, 2025: 1-10.

[8] A multidimensional strategy for uncovering comprehensive quality markers of Schisandra chinensis (Turcz.) Baill based on pharmacodynamics and chemical properties[J]. Phytomedicine, 2022, 106: 154273.

[9] 张颖, 王俊慧, 胡烨胤, 等. 中医药临床研究中预试验样本量的确定[J]. 中医杂志, 2021, 62(4): 307-311.

[10] Guidelines for the diagnosis and treatment of depressive disorders by integrating Chinese and Western medicine (English edition) - PubMed[EB/OL]. [2025-04-08].

[11] Posner K, Brown G K, Stanley B, 等. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults[J]. The American Journal of Psychiatry, 2011, 168(12): 1266-1277.

[12] 张明园. 副反应量表(TESS)[J]. 上海精神医学, 1984(2): 77-80.