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The effectiveness of Jiawei Huan Shao Dan in treating senile frailty syndrome: study protocol for a randomized controlled trial

[La efectividad de Jiawei Huan Shao Dan en el tratamiento del síndrome de fragilidad senil: Protocolo de estudio para un ensayo controlado aleatorio]

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Abstract: The pathogenesis of senile frailty syndrome is not yet clear, and there is no recommended drug treatment. Therefore, finding effective medications and improving clinical efficacy are the issues causing main delays and difficulties in furthering our understanding and treatment of this condition. A randomized double-blind placebo-controlled study will be conducted. A total of 60 eligible patients with senile frailty syndrome will be enrolled and randomly assigned to one of two groups: a control group and an experimental group. After 12 weeks of intervention and a 1-month follow-up period, the efficacy and safety of Jiawei Huan Shao Dan (JWHSD) in the patients will be observed and their degrees of weakness and cognitive function evaluated. If the present trial is successful, it will provide patients and doctors with a new, more effective method of alleviating senile frailty syndrome.

Keywords: Senile frailty syndrome; Jiawei Huan Shao Dan; Traditional Chinese Medicine; Randomized controlled clinical trial; Aged

Resumen: La patogenia del síndrome de fragilidad senil aún no está clara, y no existe un tratamiento farmacológico recomendado. Por lo tanto, encontrar medicamentos efectivos y mejorar la eficacia clínica son los problemas que causan principales retrasos y dificultades en la comprensión y tratamiento de esta condición. Se llevará a cabo un estudio aleatorio doble ciego controlado con placebo. Un total de 60 pacientes elegibles con síndrome de fragilidad senil serán reclutados y asignados aleatoriamente a uno de dos grupos: un grupo de control y un grupo experimental. Después de 12 semanas de intervención y un período de seguimiento de 1 mes, se observarán la eficacia y seguridad de Jiawei Huan Shao Dan (JWHSD) en los pacientes, así como sus grados de debilidad y función cognitiva. Si el presente ensayo tiene éxito, proporcionará a pacientes y médicos un nuevo método más efectivo para aliviar el síndrome de fragilidad senil.

Palabras clave: Síndrome de fragilidad senil; Jiawei Huan Shao Dan; Medicina tradicional china; Ensayo clínico controlado aleatorio; Ancianos

INTRODUCTION

Senile frailty syndrome is a group of complex syndromes related to aging. It most commonly manifests as physical weakness, weight loss, and cognitive impairment, leading to sickness and death. The incidence of senile frailty syndrome has increased significantly in recent years, seriously affecting the life expectancy and quality of life of the elderly and increasing their economic burden on society (Kane *et al*., 2017). Therefore, studying the pathogenesis of senile frailty syndrome and formulating effective prevention and treatment measures to reduce the morbidity, disability, and mortality of the elderly, improve their quality of life and life expectancy, and reduce social and economic burdens are of great importance.

According to Fried *et al*. (2001), frailty involves multiple pathogeneses and risk factors, and three or more of the following criteria should be met for its diagnosis: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. This is the oldest and most widely used method of frailty assessment.

An epidemiological investigation and evaluation of senile frailty syndrome revealed that the prevalence rate of the condition in less developed areas of China is higher than in developed areas (Tian *et al*., 2019), and several studies have been conducted to assess the incidence of frailty in various populations. Ren *et al*. (2019), assessed asthenia in 1,217 elderly people in communities and pension institutions in Guangzhou and identified an asthenia rate of 10.3%. Zhao *et al*. (2018), conducted frailty assessments of 479 elderly people in community and pension institutions in Nanjing and found that the incidence of frailty was 30.7%. Hou *et al*. (2018), evaluated asthenia in 237 elderly people in nursing institutions in Chengdu and reported that the incidence of asthenia was 55.69%. The same study also found that the prevalence of frailty in the hospital population was higher than in the community population. Wu *et al*. (2021), evaluated frailty in 314 elderly patients and found that the incidence was 34.4%, while the incidence of pre-frailty was 41.2%. Finally, Qin *et al*. (2020), conducted an assessment of asthenia among 408 elderly people in a community in Shanghai and found that the incidence of asthenia was 5.6%.

Although the pathogenesis of senile frailty syndrome is not yet clear, it has been suggested that it is related to the inflammatory mechanism, immune mechanism, and metabolic abnormalities associated with aging (Walston *et al*., 2006). Inflammatory factors (such as C-reactive protein, interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and white blood cells) have been linked to age-related frailty and may act on the musculoskeletal, immune, and cardiovascular systems to cause frailty (Fulop *et al*., 2010). Low levels of insulin-like growth factor 1, high levels of serum fibroblast growth factor 23, and increased levels of testosterone and neopterin may also be associated with senile frailty syndrome (Mohr *et al*., 2007; Ramanathan *et al*., 2013; Beben *et al*., 2016), but the specific mechanisms need to be investigated further.

Senile frailty syndrome is often accompanied by multiple diseases. For instance, Crow *et al*. (2018), found that patients with senile frailty syndrome are often complicated with cardiovascular disease, diabetes, and other basic diseases as well as sarcopenia, arthritis, stroke, chronic obstructive pulmonary disease, and cognitive impairment. At present, it is agreed that a variety of interventions should include recommendations for physical activity and reasonable exercise, nutritional assessment and adequate nutritional supplements (especially protein, vitamin D, and antioxidant nutrients), cognitive training, comprehensive assessment of the elderly, the management of multiple chronic diseases and comorbidities, the management of rational drug use, and comprehensive care. Comprehensive intervention is vital to improving the debilitating state of frailty, postponing functional decline, and reducing the occurrence of adverse health outcomes (Fiatarone *et al*., 1994; Morley, 2011; Lin *et al*., 2015). However, there is currently no recommended drug treatment for senile frailty syndrome. Therefore, finding effective medications and improving clinical efficacy are the main issues causing delays and difficulties in furthering our understanding and treatment of this condition. Furthermore, it is difficult to achieve a comprehensive therapeutic effect for this group of complex syndromes by intervening with a single approach.

In Traditional Chinese Medicine (TCM), it is believed that senile frailty syndrome is caused by deficiency and is characterized by the decline of the zang-fu organs and a deficiency of qi, blood, Yin, and Yang (Meng *et al*., 2020). Therefore, TCM may have unique advantages in the treatment of senile frailty syndrome by following the principles of strengthening and replenishing the deficiency, discharging the reality, and taking a holistic approach

to treatment. Thus, TCM can be expected to reduce the symptoms of the disease through multiple approaches and provide an effective method of preventing and treating senile frailty syndrome.

Huan Shao Dan, a medicine administered in TCM, treats the heart, spleen, and kidneys simultaneously while nourishing the essence, qi, and spirit. It is clinically applied to a variety of cardiovascular and cerebrovascular diseases, cognitive disorders, osteoporosis, and other diseases. At present, it is often combined with donepezil to increase the activity of glutathione peroxidase, reduce malondialdehyde content, and inhibit neuronal apoptosis in the treatment of mild to moderate vascular dementia (Xu *et al*., 2020). In recent years, studies have shown that the medicine has effects on dementia relief (Kelaiditi *et al*., 2014; Qiao *et al*., 2019), anti-aging (Wu, 2016) and anti-depression (Liu *et al*., 2019), showing a good curative effect trend. However, the systematic review of its clinical curative effect and the interpretation of its mechanism are key scientific problems that need to be solved.

The present study used Jiawei Huan Shao Dan (JWHSD), which has evolved from TCM's Huan Shao Dan, as a therapeutic intervention in patients with senile frailty syndrome to observe the effects of the medicine on frailty and cognitive impairment. The study also conducted a preliminary exploration of the medicine's curative mechanism to provide safe and effective methods to prevent and treat the disease.

JWHSD is an enhancement of the classical formula "Huan Shao Dan," originally documented in "Yang's Family Collection of Prescriptions." This adaptation excludes Fennel Fruit (*Foeniculum vulgare*) and Paper Mulberry Fruit (*Broussonetia papyrifera*), and incorporates White Atractylodes (*Atractylodes macrocephala*), Chinese Astragalus (*Codonopsis pilosula*), Oriental Arborvitae Seed (*Platycladus orientalis*), and Fermented Aspergillus (*Aspergillus oryzae*).

The Monarch drugs of this formula include Desert Cistanche (*Cistanche deserticola*), Ba Ji Tian or Morinda Root (*Morinda officinalis*), Prepared Rehmannia (*Rehmannia glutinosa*), and Goji Berry (*Lycium barbarum*). These four herbs are synergistically combined to enrich the essence and benefit the marrow.The Ministerial drugs consist of White Atractylodes (*Atractylodes macrocephala*) and Chinese Astragalus (*Codonopsis pilosula*), which strengthen the spleen and augment qi, thus reinforcing the postnatal foundation. The Adjuvant drugs include Polygala (*Polygala tenuifolia*), Chinese Yam (*Dioscorea opposita*), Dogwood Fruit (*Cornus officinalis*), Tatarinow's Sweet Flag (*Acorus tatarinowii*), Water Plantain (*Alisma plantago-aquatica*), White Poria (*Poria cocos*), Schisandra Berry (*Schisandra chinensis*), and Oriental Arborvitae Seed (*Platycladus orientalis*), which work together to calm the mind and facilitate the interaction between the heart and kidney, as well as to aid digestion and regulate the middle burner, preventing potential stagnation and over-supplementation that could impact the spleen and stomach negatively.The Envoy drugs are Ox Knee (*Achyranthes bidentata*) and Eucommia Bark (*Eucommia ulmoides*), known for their nourishing effects on the liver and kidneys, and for strengthening the sinews and bones.

The harmonious integration of these herbs in the JWHSD formula aims to nourish and support both the congenital and acquired aspects of one's constitution, promoting brain health and the generation of marrow. This comprehensive approach addresses the heart, spleen, and kidneys concurrently, and replenishes the body's essence, qi, and spirit. It is tailored to the specific physiological and pathological mechanisms associated with the decline in health commonly observed in middle age and old age. Recent clinical research has indicated that Huan Shao Dan has the potential to enhance cognitive functions in patients (Qiao *et al*., 2019; Xu *et al*., 2020).

In JWHSD, *Foeniculi fructus* and *Broussonetiae fructus* are removed to avoid drying and hotting discomfort caused by drugs, while *Atractylodes macrocephala* Koidz and *Codonopsis radix* are added to invigorate the spleen and qi and strengthen the physical quality. Semen Platycladi is added to nourish the heart and soothe the nerves, and medicated Divine Comedy is added to help with digestion and avoid excessive nutrition, which can cause the stagnation of the spleen and stomach. At present, there is not enough clinical data to prove that JWHSD has a significant effect on senile frailty, so more data from clinical experimentation needs to be collected to evaluate its efficacy and explain its mechanism of action.

The main purpose of this study is to evaluate the degree of weakness and cognitive function in patients with senile asthenia who received treatment with JWHSD. The secondary purpose is to assess the daily living ability, nutritional status, psychological status, and safety of these patients. Previous studies have identified a relationship between inflammation and cognitive function, e.g., pro-inflammatory factors

in aged mice increased after surgery, high levels of TNF-α and IL-6 may be related to the decline of postoperative cognitive ability (Gong *et al*., 2020) and lymphocyte levels may be related to cognitive ability (Fung *et al*., 2020). Therefore, the present study will also evaluate serum IL-6, TNF-α, and lymphocyte subsets to explore the pathogenesis of senile frailty syndrome. It is hoped that this study will provide a basis for future large-sample multi-center clinical research and lay the foundation for the formation of a comprehensive

TCM treatment plan that can effectively prevent and treat senile frailty syndrome.

METHODS

Study design

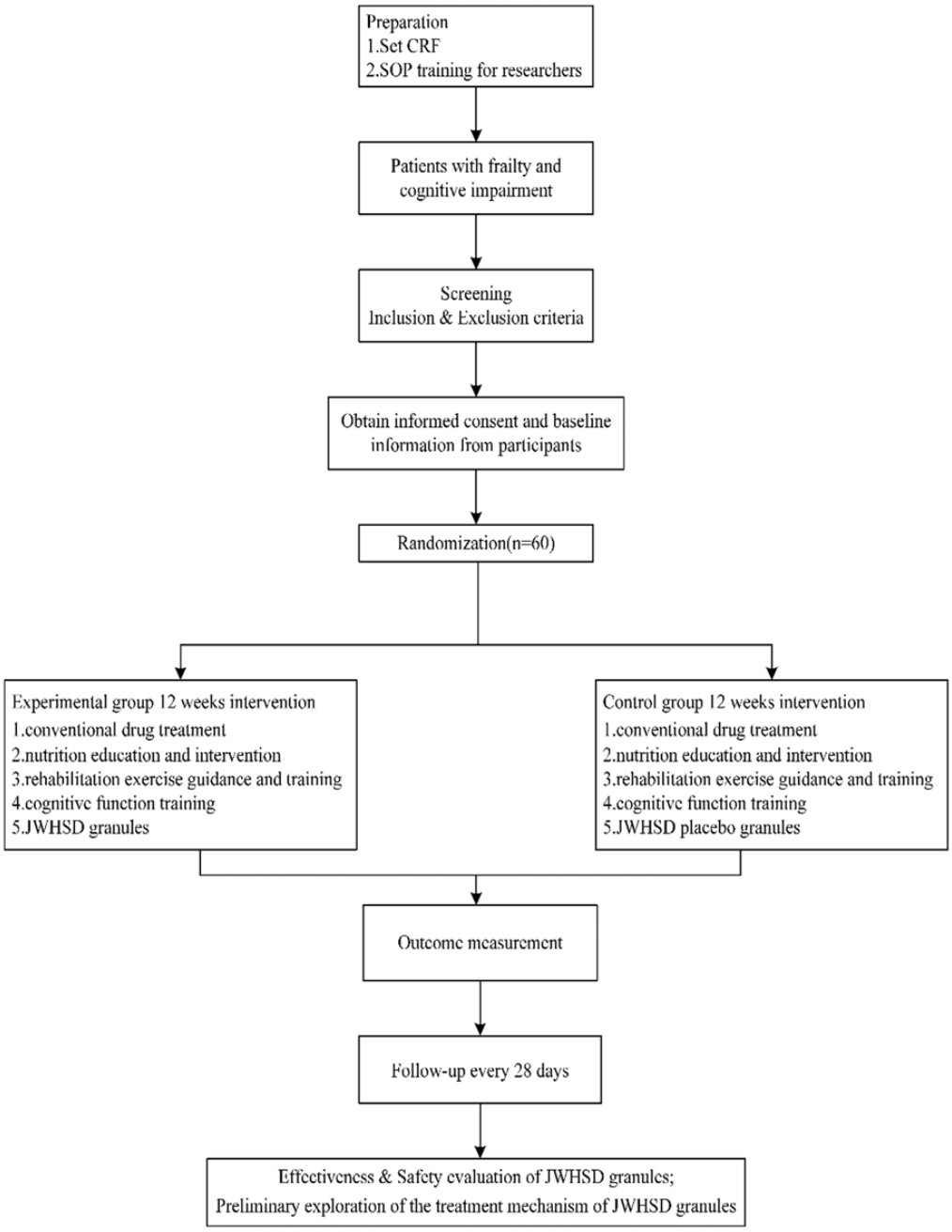

Figure No. 1
The flow chart of a randomized controlled trial of using Jiawei Huan Shao Dan (JWHSD) for assessing the effectiveness on senile frailty syndrome. CRF: case report form; SOP: standard operating procedure

This will be a double-blind randomized, placebo-controlled study. A total of 60 patients who meet the inclusion and exclusion criteria will be enrolled and randomly assigned to one of two groups: a control group and an experimental group. After 12 weeks of intervention and a 1-month follow-up period, the effectiveness and safety of JWHSD will be evaluated by comparing the various indicators of the two groups, including several scales assessing mental state, daily living ability, nutritional status, biochemical indicators, and biological indicators.

As a research institution, the China–Japan Friendship Hospital will conduct standard operational procedural training and supervise the entire research process. All the patients will be enrolled from the China–Japan Friendship Hospital. The flow chart of this study trial is shown in Figure No. 1.

Participant requirements

Patients with a diagnosis of senile frailty syndrome and cognitive impairment will be included in the study. The criteria for the diagnosis of senile frailty syndrome and cognitive impairment are detailed in the inclusion criteria below.

Table No. 1
Fried frailty criteria

The FRAIL Scale			
Number	**Criterion**	**Male**	**Female**
1	Shrinking: Unintentional weight loss	⩾ 4.5kg in previous year; or weight loss	⩾5% of previous year's body weight
2	Walking time(4.57m)	Height ⩽ 173cm : ⩾ 7 s Height > 173cm : ⩾ 6 s	Height ⩽ 159 cm: ⩾ 7 s Height > 159cm : 6 s
3	Hand grip strength(kg)	BMI ⩽ 24Kg/m^2 : ⩽ 29 BMI24.1 ~ 28 Kg/m^2 : ⩽ 30 BMI > 28Kg/m^2 : ⩽ 32	BMI ⩽ 23 Kg/m^2 : ⩽ 17 BMI23.1~26 Kg/m^2 : ⩽ 17.3 BMI26.1~29 Kg/m^2 : ⩽ 18 BM I> 29 Kg/m^2 : ⩽ 21
4	Physical activity*(MLTA)	< 383 kcal/week (About 2.5 h walk)	< 270 kcal/week (About 2 h walk)
5	Fatigue	Score 2-3 points for any question of CES-D In the past week, how many days did the following phenomena occur? (1) I feel that everything I do requires effort. (2) I cannot walk forward. Score: 0 point: < 1 d; 1 point: 1-2 d; 2 points: 3-4 d; 3 points: > 4 d	

Note: (1) BMI: Body Mass Index; **MLTA**: Minnesota Leisure Time Physical Activity Questionnaire; **CES-D**: Center for Epidemiological Studies-Depression; (2) *It consumes about 150 kcal of energy for 60 minutes of walking. **(3) Frail**: ≥ 3 criteria present; **Intermediate or Pre-Frail**: 1 or 2 criteria present; **Robust**: 0 criteria present

①The inclusion criteria will comprise the following: (1) The patient's diagnosis of senile frailty syndrome is undertaken according to fried frailty criteria (see Table No. 1), (2) the patient meets the diagnostic criteria for cognitive impairment according to the 2018 Chinese Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Impairment, and their cognitive dysfunction score on the Mini-Mental State Examination (MMSE) scale is lower than 27 (see Table No. 2), (3) the patient is ≥65 years of age, and (4) the patient provides signed informed consent. Patients of any gender can be included.

②The exclusion criteria will comprise the following: (1) patients with severe cognitive dysfunction, limited voluntary activities, or who are unable to complete the evaluation, (2) patients in the acute or terminal stage of the disease, (3) patients with severe cardiovascular disease, cerebrovascular disease, digestive disease, respiratory disease, hematological disease, or malignant tumors, (4) patients taking other medications that might affect

this study, e.g., hormones or immunosuppressants, (5) patients known to be allergic to the basic therapeutic drugs, or patients with sensitive skin, (6) patients who are participating in other clinical trials or who have done so in the last three months, and (7) patients whom the investigator considers unsuitable for participation in the clinical trial.

Table No. 2
Mini-mental State Examination

Maximum Score	Patient's score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials : _____
5		"1 would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65...) Stop after five answers.
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		Repeat the Chinese phrase : "Forty-four stone lions."
3		"Take the paper in your right hand, fold it in half, and put it on your left leg" (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Sample size

This will be an exploratory study. As there are no relevant data to support the calculation of the sample size, it has been selected based on the objective conditions of the research period and study budget. It is planned to initially enroll 60 patients diagnosed with senile frailty syndrome.

Randomization

A block randomization method will be used to enroll the patients into each group. An appropriate segment length will be selected, and SAS v.9.4 statistical software will be used to generate a random sequence of 60 subjects; the participants will be organized into a control group and experimental group at a ratio of 1:1, listing the serial number as 01–60. The treatment allocation will be assigned a consecutively numbered medication based on a random sequence. An independent clinical statistician will record the method, process, and results and will keep the random sequence for each patient, which will be saved as a file in a sealed envelope to be checked if

necessary. In the case of an emergency clinical event, an individual's randomized code and group assignment can be identified quickly using their sealed file. Once an envelope has been opened, whether intentionally or not, it will be recorded carefully on the case report form (CRF), and the patient will be withdrawn from the study.

Blinding

The study drugs required by each participant will be packed in a box on which will be printed "For clinical research use only" along with the drug number, quantity, usage, dosage, storage conditions, expiration date, drug supply unit, and other information.

The study drugs will be kept in special containers and sealed, and a dedicated drug administrator will be responsible for their management. A special clinical trial drug-use record form will be created to record the date of release of the trial drug, drug number, participant's name (pinyin abbreviation), number of drugs used, number of drug recalls, and date of recall; this form will be signed by the drug administrator. Detailed records of the number of drugs taken and returned by the participants will be used to assess and record each patient's compliance with the medications.

The number of cases and the method of grouping will be generated using SAS v.9.4 software by personnel who are not associated with the data management and statistical analysis of the study.

Quality control and data management

This study has been registered in the China–Japan Friendship Hospital and approved by its ethics committee. The research process, data collection, sorting, and preservation of the study will be supervised by the Drug Clinical Trial Center of the China–Japan Friendship Hospital.

Statistical analysis

The statistical analysis will be performed using SPSS 20.0 software. Measurement data will be shown as mean ± standard deviation, and a Student's t-test will be used for comparisons between groups. A value of $p<0.05$ will be considered statistically significant.

Patient and public involvement

Neither the patients nor their family members participated in the study design. The results will be widely disseminated in scientific reports and academic conferences to benefit policy makers, clinicians, and patients.

Ethics and dissemination

The study has been registered at the China–Japan Friendship Hospital and approved by the hospital's ethics committee under approval number 2021-87-k52. All volunteers will provide signed informed consent, which is in line with the ethical principles of the Helsinki Declaration. The participants will be reimbursed for treatment during the study period. The use of data will follow the rules of the hospital's data supervision committee. Biological samples will be treated in accordance with the national guidelines for biological waste management and disposal. The results will be published in international peer-reviewed journals and at academic conferences and will also be communicated to the patients by telephone. The patients' post-study health statuses will be monitored during the follow-up period.

Interventions

Treatment program

Patients who meet the inclusion criteria will receive an information form and will be required to provide written consent to participate in the trial. Then, they will participate in the trial, receive trial-specific identification numbers, and be assigned to a group according to a random sequence. A baseline measurement for each participant will be obtained, including age, gender, and body mass index. The research program flow is shown in Appendix No. 1. All outcome measurements will be recorded by medical staff who are familiar with the management of these assessments and will be unaware of the participants' group allocations.

All participants will receive basic treatment, including long-term use of drugs, nutrition education, rehabilitation exercise guidance, and cognitive function training (for patients with routine underlying diseases).

In addition to the basic treatment, patients in the experimental group will be given one bag of JWHSD granules twice a day. The granules will be administered after being dissolved in warm water. Meanwhile, patients in the control group will be given one bag of JWHSD placebo granules twice a day. The granules will be administered after being dissolved in warm water. The therapeutic JWHSD granules and placebo granules will be prepared by Beijing Temages Pharmaceutical Co., Ltd. (China).

Research steps

Screening period

The screening period consists of the following five steps:
(1) All participants will be required to sign informed consent forms.
(2) Demographic data (age, gender, height, weight, etc.) will be recorded.
(3) Comorbidities and treatment conditions, such as cardiovascular diseases, cerebrovascular diseases, and diabetes, will be recorded.
(4) A safety check (including routine blood tests, liver function, kidney function, and an electrocardiogram) will be undertaken.
(5) The inclusion and exclusion criteria will be examined.

Collection of baseline measurements

After the screening period, the enrolled patients will have the following baseline measurements collected:
(6) Physical examination of body temperature, blood pressure, respiratory rate, pulse, etc.
(7) MMSE score
(8) Tilburg Frailty Indicator (TFI) score
(9) Montreal Cognitive Assessment (MoCA) score
(10) Activities of Daily Living (ADL) score
(11) Nutritional Risk Screening (NRS 2002) score
(12) Mental state assessment: Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) scores
(13) Detection of serum IL-6, TNF-α, and serum lymphocyte subsets
(14) Randomization

Intervention period

The intervention period will take place over the course of four visits, as follows:
Visit 1 (day 1 of enrollment):
(1) Drug distribution
(2) Adverse event record
(3) Combined medication record
Visit 2 (day 29 of enrollment):
(4) Drug distribution
(5) Adverse event record
(6) Combined medication record
Visit 3 (day 57 of enrollment):
(7) Drug distribution
(8) Adverse event record
(9) Combined medication record
Visit 4 (day 84 of enrollment):
(10) Assessment of MMSE score
(11) Assessment of TFI score
(12) Assessment of MoCA score
(13) Assessment of ADL score
(14) Assessment of NRS 2002 score
(15) Mental state assessment (HAM-D and HAM-A scores)
(16) Detection of serum IL-6, TNF-α, and serum lymphocyte subsets
(17) Physical examination
(18) Adverse event record
(19) Combined medication record
(20) Safety check

Follow-up consultation

The follow-up consultation will take place 30 days after discharge and will be conducted as a telephone interview to obtain the following:
(21) Adverse event record
(22) Combined medication record

Jiawei Hua Shao Dan granules

JWHSD granules are a Chinese herbal medicine compound preparation. The main components are shown in Table No. 3. This medicine is produced and packaged by Beijing Temages Pharmaceutical Co., Ltd. under China Pharmaceutical Production license no. 20180032. The results of drug quality testing will be consistent with the quality standards specified in the Pharmacopoeia of the People's Republic of China, 2015.

Table No. 3
Main components of Jiawei Huashao Dan (JWHSD)

CHINESE NAME	LATIN NAME	AMOUNT(G)
SHU DI HUANG	*Cooked radix rehmannia*	15
SHAN YAO	*Rhizoma Dioscoreae*	15
CHUAN NIU XI	*Radix Cyathulae*	10
GOU QI ZI	*Fructus Lycii*	15
SHAN ZHU YU	*Fructus Corni*	15
FU LING	*Poria*	15
DU ZHONG	*Cortex Eucommiae*	12

WU WEI ZI	*Fructus Schisandrae Chinensis*	10
ROU CONG RONG	*Herba Cistanches*	15
SHI CHANG PU	*Rhizoma Acori Tatarinowii*	10
BA JI TIAN	*Radix Morindae Officinalis*	10
YUAN ZHI	*Radix Polygalae*	10
SHENG BAI ZHU	*Rhizoma Atractylodis Macrocephalae*	15
DANG SHEN	*Radix Codonopsis*	15
CHAO SHEN QU	Medicated Leaven	10
BAI ZI REN	*Seman Platycladi*	15

Placebo

The placebo will be prepared in accordance with the requirements of the General Guidelines for Clinical Research of New Chinese Medicines. It will be produced and packaged by Beijing Temages Pharmaceutical Co., Ltd under China Pharmaceutical Production license No. Jing 20180032. The placebo will be made from granules with dextrin as the main ingredient. Dextrin is an intermediate product of starch decomposition and has no pharmacological activity. The placebo's dosage, color, and usage will be the same as those of the JWHSD granules. The drug instructions for the JWHSD granules and the placebo granules are completely consistent.

Combined medication and treatment

During the trial, participants will maintain any medications used for the treatment of concomitant diseases before enrollment, and any dosage adjustment will be recorded. During the trial, no other" TCMs for frailty or cognitive impairment will be permitted. Any drugs used during the trial will be recorded and explained in detail in the study cases, including the name of the drug, the method of use, the dosage, and the reason for use, so that it can be analyzed and reported in the summary.

Adverse reactions and risk prevention

Definition of adverse events

An adverse medical event is an event that occurs after a patient or clinical trial participant takes a drug but does not necessarily have a causal relationship with that drug. A serious adverse event is defined as a medical event that requires hospitalization or the prolonging of hospitalization, causes disability, affects work ability, threatens life, causes death, or causes congenital malformations during the clinical trial. Serious adverse events are categorized according to severity as mild, moderate, or severe. A mild adverse event is an event that can be tolerated, does not affect the treatment, does not require special treatment, and does not affect the participant's recovery. A moderate adverse event is unbearable, requires special treatment, and has a direct impact on the participant's recovery. A severe adverse event endangers the life of the participant, causes death or disability, and requires immediate emergency treatment.

Observation of adverse events

Any adverse events, such as a patient's subjective discomfort or laboratory test abnormalities, will be treated seriously and analyzed carefully, and immediate measures will be taken to protect the patient's safety.

Observation: The occurrence of adverse events in patients during the study will be closely observed, with particular attention given to the occurrence and severity of, for example, abnormal liver and kidney function indexes and dizziness. Patients will be required to truthfully report any changes in their condition after medication, and leading questions will be avoided. While observing the curative effects, investigators will also pay attention to any adverse reactions, including symptoms, signs, and laboratory tests.

Medical support for participants: When an adverse event is discovered, investigators will implement the necessary treatment measures according to the condition and decide whether to terminate the study. The measures taken during the trial will include unchanged dosage, reduced dosage, suspension of medication, discontinuation of medication, and termination of the study. Investigators will follow up an adverse event until the symptoms disappear or stabilize. More serious adverse events will be followed up for a longer period. Follow-up methods include hospitalization, outpatient clinics, and telephone interviews. Adverse events occurring at the end of the study will be followed up within one month. Follow-up investigations will be conducted in cases of drug

withdrawal due to adverse events and adverse reactions, and detailed records of their continuity, outcome, disappearance, etc., will be made.

Outcome measurements

Curative effect observation indicators

Tilburg Frailty Indicator

The TFI scale covers three aspects of frailty, i.e., physical, psychological, and social, using a two-category scoring method. The scoring range is from 0 to 15, with a score of 5 and above indicating frailty. The higher the score, the more severe the level of frailty.

Mini-Mental State Examination

The MMSE scale is simple, easy to use, and is widely applied both in China and abroad. It is the preferred scale for cognitive function assessment. It covers seven aspects: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language, and visual space. A score of 27–30 is considered normal, <27 indicates cognitive dysfunction, 21–26 indicates mild dementia, 10–20 indicates moderate dementia, and 0–9 indicates severe dementia.

Montreal Cognitive Assessment

The MoCA scale assesses many different cognitive domains and takes into account differences in education level. It covers the following aspects: attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation, and orientation force. If the number of years of education ≤ 12, 1 point is added, and the maximum score is 30. A score ≥ 26 is considered normal.

Secondary outcome indicators

Assessment of Daily Living score

The ADL scale will be used to assess daily living. The lowest total ADL score is 14 points, which is considered normal; scores > 14 indicate different degrees of dysfunction.

Assessment of nutritional status

The NRS 2002 scale will be used for the assessment of nutritional status. It is the first tool to use evidence-based medicine to develop nutritional risk screening for patients. A total score ≥ 3.0 indicates that a patient is at risk of malnutrition.

Assessment of mental state

Patients' mental states will be assessed using the HAM-D and HAM-A scales. On the HAM-D scale, a score < 9 points is considered normal, 9–19 points indicate suspected depression, 20–34 points confirm depression, and a score ≥ 35 points indicates severe depression. On the HAM-A scale, a score < 7 points is considered normal, 7–13 points indicate suspected anxiety, 14–20 points confirm anxiety, 21–28 points indicate obvious anxiety, and a score ≥ 29 points indicates severe anxiety.

Detection of serum IL-6 and TNF-α

An enzyme-linked immunosorbent assay will be used to detect the levels of IL-6 and TNF-α in the peripheral blood of the patients.

Detection of serum lymphocyte subsets

Serum lymphocyte subsets will be detected and analyzed by the Laboratory Department of the China–Japan Friendship Hospital.

Safety test indicators

Safety test indicators will include routine blood and urine tests, electrocardiograms, liver function tests, and renal function tests. If an abnormality occurs after treatment, it will be reviewed at an appropriate time, recorded, and comprehensively analyzed to identify whether it is related to the study drug.

Regardless of whether or not an adverse event is related to the study drug, it will be recorded in detail in the CRF, including the time of occurrence, symptoms, signs, severity, duration, laboratory test indicators, treatment methods, progress, results (cure/improvement/sequelae/death/unclear), and follow-up time. Any combined medication will also be recorded in detail to analyze the correlation between the adverse event and the study drug. The record will be signed and dated.

Adverse events will be followed up and observed until they return to normal or baseline levels or until the investigator can reasonably explain the abnormality and considers that a follow-up consultation is unnecessary to ensure the safety of the participant.

DISCUSSION

Frailty refers to a syndrome affecting elderly people, who have increased vulnerability caused by degenerative changes and a variety of chronic diseases. With the development of an aging

population, age-related diseases have become a significant problem, but they are not impossible to prevent or control (Mohr *et al*., 2007). Prior to the present study, careful searches of PubMed, ScienceNet, EMBASE, CNKI (including the China doctoral/master's thesis database and the China conference full-text database), Wanfang Data, the VIP journal integration platform, and the Chinese biomedical database (SinoMed) were performed. Little clear evidence for the treatment of senile frailty syndrome was uncovered, and no relevant trials on the use of TCM as a treatment for the condition were collected. Therefore, it was decided to conduct a multi-center randomized double-blind controlled clinical trial to closely study the efficacy and safety of TCM in the treatment of senile frailty syndrome. Due to the lack of effective evidence and drug treatments, an integrated TCM and Western medicine approach was chosen to ensure patient compliance and meet ethical considerations (nutrition education and intervention, rehabilitation exercise guidance and training, and cognitive function training are the most common clinical treatment methods for senile frailty syndrome).

This key clinical trial has the following advantages: (1) The study was designed as a randomized double-blind placebo-controlled clinical trial founded on evidence-based medicine, which is considered the most authoritative research method for treatment evaluation. (2) The clinical trial will be carried out in a class III hospital. To ensure the quality of the study, all staff involved must complete the standard operating procedural training for the study protocol prior to recruitment. However, the design of the study also has some potential limitations since the small sample size could affect the reliability of the final results.

CONCLUSION

Currently, there is no published study protocol for randomized controlled trial evaluating the effectiveness of TCM interventions in patients with senile frailty syndrome. This paper showed a more adequate study protocol of a randomized controlled trial for assessing the effectiveness of JWHSD in treating senile frailty syndrome, and will provide evidence-based evidence for using TCM for treating of senile frailty syndrome and slow the process of the disease in further clinical trial. Meanwhile, this study protocol will provide patients and doctors with a new, more effective method of alleviating senile frailty syndrome. In the context of an aging global population, the results of this study could be used to provide information for future international guidelines.

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REFERENCES

Beben T, Ix JH, Shlipak MG, Sarnak MJ, Fried LF, Hoofnagle AN, Chonchol M, Kestenbaum BR, de Boer IH, Rifkin DE. 2016. Fibroblast growth factor-23 and frailty in elderly community-dwelling individuals: The cardiovascular health study. **J Am Geriatr Soc** 64: 270 - 276. **https://doi.org/10.1111/jgs.13951**

Crow RS, Lohman MC, Titus AJ, Bruce ML, Mackenzie TA, Bartels SJ, Batsis JA. 2018. Mortality risk along the frailty spectrum: Data from the National Health and Nutrition Examination Survey 1999 to 2004. **J Am Geriatr Soc** 66: 496 - 502. **https://doi.org/10.1111/jgs.15220**

Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ. 1994. Exercise training and nutritional supplementation for physical frailty in very elderly people. **N Engl J Med** 330: 1769 - 1775. **https://doi.org/10.1056/NEJM199406233302501**

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular health study collaborative research group. 2001. Frailty in older adults: evidence for a phenotype. **J Gerontol A Biol Sci Med Sci** 56: M146 – M156. **https://doi.org/10.1093/gerona/56.3.m146**

Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, Pawelec G. 2010. Aging frailty and age-related diseases. **Biogerontology** 11: 547 - 563. **https://doi.org/10.1007/s10522-010-9287-2**

Fung ITH, Sankar P, Zhang Y, Robison LS, Zhao X, D'Souza SS, Salinero AE, Wang Y, Qian J, Kuentzel ML, Chittur SV, Temple S, Zuloaga KL, Yang Q. 2020. Activation of group 2 innate lymphoid cells alleviates aging-associated cognitive decline. **J Exp Med** 217: e20190915. **https://doi.org/10.1084/jem.20190915**

Gong M, Wang G, Li G, Liu J, Sun P, Xu L, Li J, Guo Y, Zhang M. 2020. Dysfunction of inflammation-resolving pathways is associated with postoperative cognitive decline in elderly mice. **Behav Brain Res** 27: 386.

https://doi.org/10.1016/j.bbr.2020.112538

Hou XL, Gao J, Wu CX, Bai DZ, Xiang YP, Li X, Guo XX, Yu JY. 2018. Frailty status and analysis of elderly in nursing institutions. **Chin J Nursing** 53: 88 - 93.

Kane AE, Gregson E, Theou O, Rockwood K, Howlett SE. 2017. The association between frailty, the metabolic syndrome, and mortality over the lifespan. **Geroscience** 39: 221 - 229. **https://doi.org/10.1007/s11357-017-9967-9**

Kelaiditi E, van Kan GA, Cesari M. 2014. Frailty: role of nutrition and exercise. **Curr Opin Clin Nutr Metab Care** 17: 32 - 39. **https://doi.org/10.1097/MCO.0000000000000008**

Lin HC, Wang CH, Tsai FJ, Hwang KP, Chen W, Lin CC, Li TC. 2015. Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: a nationwide population-based cohort study. **Diabetologia** 58: 79 - 86. **https://doi.org/10.1007/s00125-014-3400-z**

Liu L, Zhou YL, Gao LJ, Li LL, Zhou YN, Lu RL, Liu TT, Zhu XL. 2019. **Effects of Huanshaodan on HPGA axis function in chronic unpredictable mild stress depression rats**; Proceedings of the 2nd National Anxiety Forum of Integrated Chinese and Western Medicine, the 18th National Annual Meeting of Psychiatric Professional Committee of Chinese Association of Integrated Chinese and Western Medicine and the 3rd Beijing-Tianjin-Hebei Annual Meeting of Integrated Chinese and Western Medicine psychiatry, Beijing, China.

Meng KH, Qi H, Chen M. 2020. Discussion on TCM pathogenesis and treatment of senile frailty syndrome. **Yunnan J Tradit Chin Med Chin Materia Med** 41: 16 - 19.

Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. 2007. Testosterone, sex hormone-binding globulin, and frailty in older men. **J Am Geriatr Soc** 55: 548 - 555. **https://doi.org/10.1111/j.1532-5415.2007.01121.x**

Morley JE. 2011. Frailty: diagnosis and management. **J Nutr Health Aging** 15: 667 - 670. **https://doi.org/10.1007/s12603-011-0338-4**

Qiao LJ, Li WH, Chen WY, Zhang W, Hu HM. 2019. Theoretical exploration and case analysis of the correspondence between Huan Shao Dan treatment and syndrome differentiation in Alzheimer's disease. **Chin J Modern Distance Educ Chin Tradit Med** 17: 92 - 94.

Qin L, Liang ZZ, Ge LB, Chen L, Huo Y, Li Q. 2020. Influencing factors of frailty syndrome in elderly people in the Community. **China General Practice** 23: 598 - 603.

Ramanathan R, Kohli A, Ingaramo MC, Jain A, Leng SX, Punjabi NM, Walston JD, Fedarko NS. 2013. Serum chitotriosidase, a putative marker of chronically activated macrophages, increases with normal aging. **J Gerontol A Biol Sci Med Sci** 68: 1303 -1309.

Ren QZ, Zhou JJ, Zheng YJ. 2019. Prevalence and influencing factors of frailty among elderly people in Guangzhou city. **China Public Health** 35: 413 - 417. **https://doi.org/10.11847/zgggws1120522**

Tian P, Yang N, Hao QK, Peng C. 2019. Prevalence of senility in China: a systematic evaluation. **Chin J Evid-Based Med** 19: 656 - 664.

Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP. 2006. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. **J Am Geriatr Soc** 54: 991 - 1001. **https://doi.org/10.1111/j.1532-5415.2006.00745.x**

Wu CF. 2016. **Huan Shaodan study on anti-aging effect of male and female aged rats**. Chongqing University.

Wu F, Wang XY, Li Z, Wan JJ, Tao XB. 2021. Frailty status and influencing factors in elderly hospitalized patients. **J Changzhi Med Coll** 35: 95 - 99.

Xu X, Zhang ZP, Jiang TY, Ren LM, Zhang SH, Tan JF. 2020. Effects of Huan Shao Dan combined with Donepezil on serum GSH-Px and MDA levels in patients with vascular dementia. **Chin J Mod Drug Appl** 14: 182 - 184.

Zhao YY, Ding YP, Li XW. 2018. Frailty among institutionalized elderly people in Nanjing city: prevalence and risk factors. **China Public Health** 34: 550 - 553. **https://doi.org/10.11847/zgggws1112389**

Appendix No. 1
Research flow chart

Time / Task	Screening	V1	V2	V3	V4	V5
	Before enrollment	Intervention	Intervention	Intervention	Intervention	Follow-up
	D -1-0	D1	D29	D57	D84 (End of treatment)	30 days after treatment
Sign informed consent	√					
Fill in general information	√					
Medical history and treatment history	√					
Review inclusion and exclusion criteria	√					
Combined medication		√	√	√	√	√
Effectiveness observation						
Tilburg Frailty Indicator	√				√	
Mini Mental State E xamination	√				√	
Montreal Cognitive Assessment	√				√	
Activity of Daily Living	√				√	
Nutritional Risk Screening	√				√	
Mental state assessment includes Hamilton Depression Scale	√				√	
Hamilton Anxiety Scale	√				√	
Serum IL-6, TNF-α and serum lymphocyte subset detection.	√				√	
Safety index						

Adverse events	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√
Blood routine	√				√	
Liver function (ALT, AST, GGT, Tbil)	√				√	
Renal function (Cr, BUN)	√				√	
Electrocardiogram	√				√	
Other						
Randomization		√				
Drug distribution		√	√	√		