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STUDY PROTOCOL

Efficacy and Safety of Bushen Jiedu Tongluo Decoction in Active Rheumatoid Arthritis: Study Protocol for a Multi-Center, Randomized, Double-Blind, Controlled Trial

Yikun He[1,*], Jiaying Shen[1,*], Huihui Wu[1,*], Lan Chen[2], Qian Zhou[3], Qi Wang[4], Yafang Guo[5], Fan Wu[6], Xin Pan[1]

[1]Department of Rheumatology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [2]Department of Traditional Chinese Medicine, Shanghai Sanlin Kangde Community Health Service Center, Shanghai, 200124, People's Republic of China; [3]Department of Traditional Chinese Medicine, Shanghai Nanmatou Community Health Service Center, Shanghai, 200127, People's Republic of China; [4]Department of Traditional Chinese Medicine, Shanghai Punan Hospital of Pudong New District, Shanghai, 200125, People's Republic of China; [5]Department of Traditional Chinese Medicine, Shanghai Pudong Hospital Affiliated to Fudan University, Shanghai, 201399, People's Republic of China; [6]Ultrasound Department, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China

*These authors contributed equally to this work

Correspondence: Fan Wu; Xin Pan, Email wufan12cn@qq.com; panxin66@163.com

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with the primary clinical symptoms of joint swelling and pain. Among the currently available therapeutic agents, methotrexate (MTX) is an internationally recognized first-line disease-modifying antirheumatic drug (DMARD) for RA and is widely used as a basic drug in combination therapies. The Bushen Jiedu Tongluo Decoction (BSJDTL), an herbal formula, has been used for the treatment of RA for more than ten years with a better curative effect. Therefore, we designed a multi-center, randomized, double-blind, placebo-controlled study, to scientifically evaluate the clinical efficacy and safety of BSJDTL for active RA.

Methods: This was a multi-center, randomized, double-blind placebo-controlled trial. A total of 120 adult participants with active RA will be enrolled, with a balanced treatment allocation (1:1). The treatment intervention will be BSJDTL plus the conventional medicine methotrexate, and the control intervention will be placebo plus the conventional drug methotrexate for 24 weeks. In addition, both groups received folic acid during treatment to prevent side effects of methotrexate. The primary outcome was DAS28-ESR. Secondary outcomes included changes in joint symptoms and signs, ESR, CRP, MIF, MMP2, CD147, ICAM-1, VCAM-1, and HIF-1α levels, and joint evaluation via musculoskeletal ultrasound and X-ray.

Discussion: We designed this multi-center, randomized, double-blind, placebo-controlled clinical trial, utilizing assessment of RA activity and imaging techniques (musculoskeletal ultrasound and X-ray) to scientifically evaluate the clinical efficacy and safety of BSJDTL for active RA. The results of this trial may provide insights into improving the clinical symptoms of patients with RA. We hope that this trial will provide preliminary evidence of the efficacy of BSJDTL in treating RA patients and that these results will aid researchers, practitioners, and patients alike.

Aim: This study aimed to clarify the efficacy and safety of BSJDTL in patients with active RA.

Trial Registration: International Traditional Medicine Clinical Trial Registry, ITMCTR2025000194.

Keywords: Bushen Jiedu Tongluo Decoction, efficacy, rheumatoid arthritis, randomized double-blind controlled clinical trial

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical polyarthritis that primarily manifests as synovial joint inflammation and destruction of the bone and cartilage. Its pathogenesis is complex, involves

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multiple cell types, and has a strong tendency for relapse with a high disability rate. Among the currently available therapeutic agents, methotrexate (MTX) is the internationally recognized first-line disease-modifying antirheumatic drug (DMARD) for RA. It is widely used in the early treatment of RA and as a basic drug in combination therapies.[1]

Through long-term clinical practice, the research team has proposed a holistic view of the "deficiency, stasis, and toxicity" mechanism in RA based on Traditional Chinese Medicine (TCM), establishing the "Kidney-Tonifying, Detoxifying, and Meridian-Passing Method" for the treatment of RA, leading to the creation of the Bushen Jiedu Tongluo Decoction (BSJDTL) which has been patented (ZL201610125582.5). This formula has been clinically employed for 15 years in the treatment of RA and has shown remarkable efficacy.[2–6] The formula includes ingredients such as Xianmao, Yinyanghuo, and Xuduan to tonify the kidneys and strengthen bones, relying on the foundation of the Two Immortals Decoction to enhance the kidneys without causing dryness, thus benefiting the essence without stagnation, including Qingfengteng, Rendongteng, and Zhongjiefeng to detoxify, reduce swelling, and promote meridian circulation; Danpi, Chishao, Ezhu, Pianjianghuang, Quanxie, and Wushaoshe promote blood circulation and unblock meridians. Shenggancao is used to harmonize the effects of various herbs, and the insect components are selected for their swift and capable action in expelling blockages in qi and blood. The entire formula works synergistically to tonify the kidneys, detoxify the body, and open meridians.

Prior studies have validated that BSJDTL can improve joint symptoms in patients with RA and possesses strong anti-inflammatory, anti-angiogenic, and immune-regulatory effects. The research team found that combining this formula with conventional Western treatments resulted in significantly better outcomes in alleviating clinical symptoms, suppressing inflammatory responses in RA, and preventing vascular proliferation and bone destruction than Western medicine alone.[3,4] This formula, alongside TCM external treatment, notably improves joint symptoms during active RA, lowers inflammatory markers, and reduces adverse drug reactions.[5,6] Basic research has shown that BSJDTL significantly alleviates inflammatory responses in CIA rats and improves synovial tissue damage through mechanisms related to the inhibition of TLR4/NF-κB signaling pathway activation.[7] These studies indicate that BSJDTL is effective in treating RA and possesses strong anti-inflammatory, anti-angiogenic, and immunoregulatory properties. Thus, this decoction has distinct advantages in RA treatment, warranting its clinical promotion.

Therefore, this study aimed to provide high-level evidence for the use of TCM in the treatment of RA. Under the guidance of the Kidney-Tonifying, Detoxifying, and Meridian-Passing Methods, we will conduct a multi-center, randomized, double-blind, placebo-controlled study, utilizing assessment of RA activity and imaging techniques (musculoskeletal ultrasound and X-ray) to scientifically evaluate the clinical efficacy and safety of BSJDTL for active RA.

Methods/Design

Methods

This 24-week follow-up exploratory study was conducted in a multi-center, randomized, double-blind, and controlled manner from August 2024 to July 2026. Written informed consent was obtained from all the participants (Figure 1).

Sample Size Calculation

Referencing statistical methods for calculating the sample size for a superiority trial:

Using the Disease Activity Score 28 - erythrocyte sedimentation rate (DAS28-ESR) as the primary indicator, this study involved two groups of independent samples. Previous research has indicated that the decrease in DAS28-ESR score (units: points) for MTX treatment of RA is 2.8, with a standard deviation of 0.55.[2] The decrease in DAS28-ESR score for the combination treatment of BSJDTL with MTX was 2.2, with a standard deviation of 0.49.[2] Given $\alpha = 0.05$, test power $1-\beta = 0.80$, two-tailed test $Z0.05 = 1.96$, $\beta = 0.1$, power = 0.9, $Z\beta = 1.28$, and standard deviation $\sigma = 0.27$, the calculated sample size was $n = 96$, with 48 subjects per group. Considering a 20% dropout rate, the planned randomized sample size was increased to 120 participants. The expected recruitment was 40 eligible RA subjects from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 20 from Shanghai Pudong Hospital, 20 from

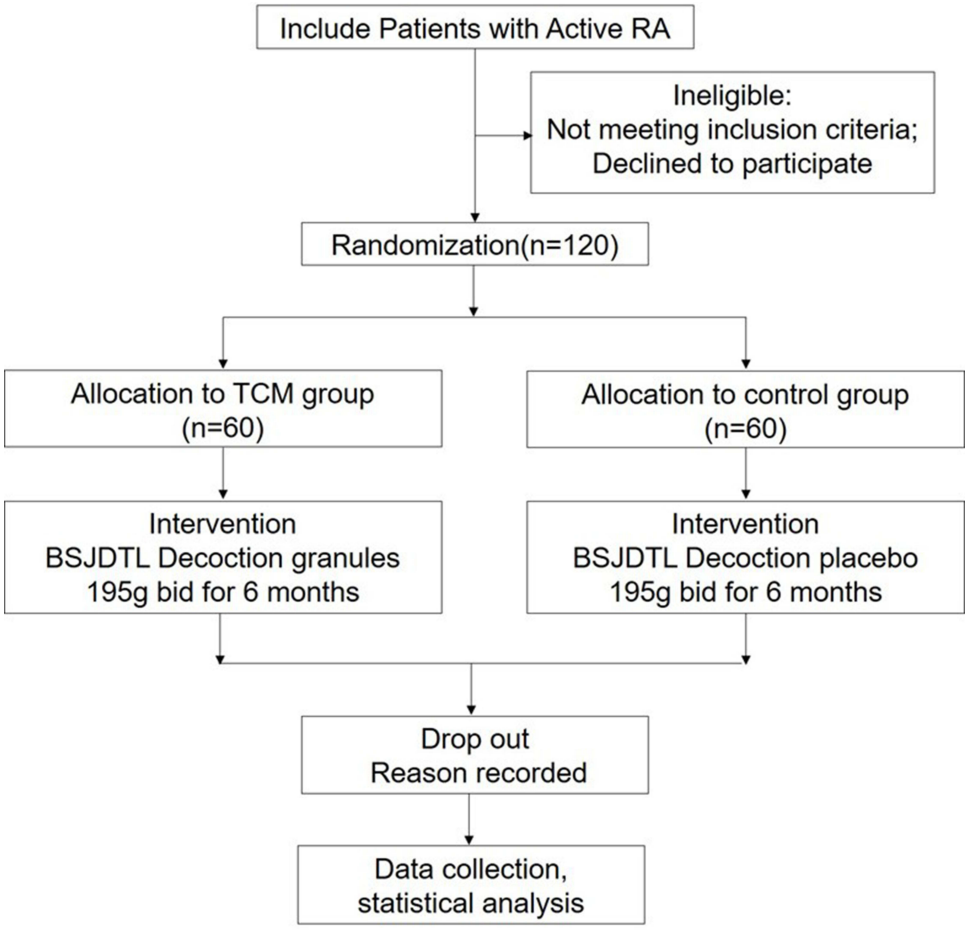

Figure 1 Study flow chart.

Shanghai Punan Hospital of Pudong New District, 20 from Shanghai Nanmatou Community Health Service Center, and 20 from Shanghai Sanlin Kangde Community Health Service Center. The reference formula is as follows:

$$n = \frac{\left(Z_\alpha + Z_\beta\right)^2 \cdot 2\sigma^2}{\delta^2}$$

Diagnostic Criteria for RA

According to the 2010 classification criteria proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), a score of 6 or higher confirms the diagnosis of RA.[8]

Diagnostic Criteria for Active RA

The diagnosis of active RA is based on DAS28-ESR, as formulated by EULAR.[9] This study focuses on active RA. According to EULAR's diagnostic criteria for RA activity, the DAS28-ESR of active RA is greater than 2.6.

Diagnostic Criteria for TCM Syndrome Differentiation

The diagnosis of "Kidney Qi Deficiency with Phlegm and Blood Stasis" diagnosis standard outlined in the 2002 "Guiding Principles for Clinical Research of New Chinese Medicines (Trial)",[10] in conjunction with the 1997 "Clinical Terminology of Traditional Chinese Medicine – Syndromes":[11]

Main Symptoms

Joint soreness, numbness, heaviness, difficulty in flexion and extension, and severe cases may have swollen, hot, and deformed joints, often accompanied by weakness in the lower back and knees.

Secondary Symptoms

Fatigue, low-grade fever, weight loss, poor appetite.

Tongue and Pulse

Dark red tongue with greasy coating, thin and rapid pulse.

A diagnosis can be made when a subject exhibits three or more of the above seven main and secondary symptoms, in combination with tongue and pulse characteristics.

Inclusion Criteria

1. Meet the diagnostic criteria for RA; meet the diagnostic criteria for active RA; meet the diagnostic criteria for traditional Chinese medicine.
2. Subjects aged 18–80 years;
3. Subjects receiving steroid treatment must maintain s dosages for at least 30 days prior to entering the trial and must continue with the same dosages throughout. Additionally, participants on other DMARDs must discontinue these medications for a minimum of 30 days before the trial.
4. Sign the informed consent form for participation in the clinical study.

Exclusion Criteria

1. Subjects who do not meet the above inclusion criteria;
2. Pregnant or lactating women, or women planning to conceive within six months;
3. Subjects allergic to the study medication or those with allergic constitutions;
4. Subjects with severe primary diseases of the heart, liver, kidneys, brain, endocrine system, hematopoietic system, or psychiatric disorders;
5. Subjects with interstitial lung disease or severely elevated liver enzymes (ALT≥3 times the upper limit of normal)
6. Subjects with overlapping rheumatic diseases such as systemic lupus erythematosus, Sjögren's syndrome, and myositis.

Rejection Criteria

1. Cases mistakenly included that do not meet the inclusion criteria;
2. The subjects who did not adhere to the medication protocol during the trial affected the efficacy assessment.
3. Subjects who took other prohibited traditional Chinese medicines during the trial made it impossible to accurately assess efficacy and safety.

Randomized and Blind Review

Participants were stratified by study center and baseline DAS28-ESR score (≤5.1 vs >5.1). Permuted block randomization (block size = 4) was applied within each stratum using SPSS 26.0 (SPSS version 26.0; IBM, NY, USA). An independent statistician generated the sequence, which was concealed in sealed opaque envelopes until assignment. Randomization was performed using the SPSS software (SPSS version 26.0; IBM, NY, USA) by an independent statistician. Participants were randomly assigned in a 1:1 ratio to either the BSJDTL or placebo group. After screening, participants who consented to join the study signed an informed consent form. An independent research physician then assigned them a random sequential number. This physician was not involved in the recruitment, treatment, or assessment processes.

Blinding Methodology

This trial will utilize a double-blind placebo-controlled methodology. Both BSJDTL and placebo granules were identical in size, shape, color, and packaging. An independent statistician will categorize BSJDTL and placebo drugs into two types (A and B), sealing this information at the bottom of the packaging based on the randomization results.

This blinding method will be applied to all participants and researchers, including physicians, investigators, coinvestigators, and pharmacists. The drugs are distributed according to the sequence of subject visits. Unblinding will follow the Contract Research Organization (CRO) standard operating procedure (SOP).[10] In the event of adverse events during the trial, the principal investigator will have access to an emergency envelope containing backup information and a secondary blinding method will be employed. The principal investigator must report this process to an independent safety-monitoring board.

Upon trial completion, an independent statistician will secure the data to prevent any modifications. The same statistician who sealed the information will then perform the first level of unblinding, immediately informing another statistician of the corresponding group number for each participant. This statistician will conduct a statistical analysis of all the collected data. After the analysis is complete, the blinding information will be fully disclosed, revealing which participants correspond to group A or B by an independent statistician.

Intervention

Basic Therapy and Drug Specification

According to the 2018 "Chinese Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis" issued by the Chinese Medical Association Rheumatology Branch,[12] it is recommended to supplement folic acid should be supplemented during MTX treatment (a dose of 5 mg per week may be considered) to reduce gastrointestinal side effects, liver function damage, and other adverse reactions. Therefore, the basic Western medication treatment regimens for both groups were as follows.

Methotrexate (MTX): Taken once a week, 15 mg orally per dose (specification: 2.5 mg per t, 16 ts per bottle, manufactured by Shanghai Xinyi Pharmaceutical Co., Ltd., National Drug Approval Number: H31020644).

Folic acid: Once a week, 5 mg orally per dose (specification: 5 mg per tablet, 100 tablets per bottle, manufactured by Shanghai Xinyi Pharmaceutical Co., Ltd., National Drug Approval Number: H31022233).

Test Drug Name and Specification

BSJDTL granules comprised *Rhizoma Curculiginis* (Xianmao,12g), *Herba Epimedii* (Yinyanghuo,12g), *Dipsacales* (Xuduan,15g), *Sarcandrae Herba* (Zhongjiefeng,30g), *Caulis Sinomenii* (Qingfengteng,15g), *Lonice Raejaponicae* Caulis (Rendongteng,30g), *Radix Paeoniae Rubra* (Chishao,9g), *Curcuma zedoaria* (Ezhu,30g), *Cortex Moutan* (Danpi,9g), *Rhizoma Wenyujin Concisum* (Pianjianghuang,15g), *Scorpio* (Quanxie,3g), *Zoacys dhumnades* (Wushaoshe,9g) *Radix Glycyrrhizae* (Shenggancao,6g).

The placebo consisted of starch, dextrin, and a bitter agent, containing one-tenth of the active ingredients of BSJDTL granules. Preliminary sensory testing confirmed comparable taste and odor between placebo and BSJDTL granules.

Both BSJDTL granules and placebo were prepared under Good Manufacturing Practice (GMP) standards by Jiangyin Tianjiang Pharmaceutical Co., Ltd. Quality control included raw material authentication via macroscopic/microscopic examination and HPLC fingerprinting, standardization of active compounds, placebo sensory validation (taste/smell similarity confirmed by pilot testing), and batch testing for contaminants (microbial, heavy metals) per the Chinese Pharmacopoeia (2020 Edition). The labels on the packaging (such as medication instructions, storage methods, etc). are expressed in Chinese (Box 1).

A summary of the composition and therapeutic properties of each herb in BSJDTL granules can be found in Table 1.

Box 1 Labeling (in Chinese)

Efficacy of Bushen Jiedu Tongluo Decoction in Treating Active Rheumatoid Arthritis: A Randomized, Double-Blind, Controlled Trial (For Clinical Trial Only)
Package No.: XXXX
[Package] 56 bags in each box (28-d dosage for one subject) [Usage and dosage] 1 bag per time, bid [Batch No.] xxxx [Expiration date] xxxx [Storage] Packaged drugs should be stored in a dry place away from children.
"Science and Technology Innovation Action Plan" Medical Innovation Research Special Project of Science and Technology Commission of Shanghai Municipality in 2023 (No. 23Y11920200), the Shanghai Municipal Health Commission for Traditional Chinese Medicine Research Project (No. 2024QN016) and Technology Innovation Action Plan and the Science and Technology Development Fund of Shanghai University of Traditional Chinese Medicine (No. 23KFL100).
Please follow doctors' advices and receive follow-up visits at hospital on appointed day. Thank you for your cooperation.

Table 1 Composition and action of BSJDTL granules in Chinese herbal medicine

Ingredients	Granule Dose	Efficacy (TCM)	Efficacy (Pharmaceutical study)
Rhizoma Curculiginis (Xianmao)	12g	Tonifying kidney yang, strengthening muscles and bones, dispelling cold and dampness	1. Anti-inflammatory; 2. Antioxidant; 3. Anti osteoporosis; 4. Immune regulation.
Herba Epimedii (Yinyanghuo)	12g	Tonifying the kidney and promoting yang, dispelling wind and dampness	1. Immune regulation; 2. Bone metabolism regulation; 1. Anti-tumor.
Dipsacales (Xuduan)	15g	Nourish the liver and kidneys, promote blood circulation, and strengthen muscles and bones	1. Anti osteoporosis; 2. Anti-inflammatory; 3. Antioxidant; 4. Promoting bone injury healing; 5. Immune regulation.
Sarcandrae Herba (Zhongjiefeng)	30g	Clear heat and cool blood, promote blood circulation and eliminate spots, dispel wind and unblock collaterals	1. Anti-inflammatory; 2. Immune regulation.
Caulis Sinomenii (Qingfengteng)	15g	Dispelling wind and dampness, promoting meridian circulation, and facilitating urination	1. Anti-inflammatory; 2. Immune regulation; 3. Analgesic.
Lonice Raejaponicae Caulis (Rendongteng)	30g	Clearing away heat and toxic material; Smooth the meridians	1. Anti-inflammatory; 2. Anti-tumor; 3. Antiviral.
Radix Paeoniae Rubra (Chishao)	9g	Clearing heat, cooling blood, promoting blood circulation, and relieving pain	1. Anti-inflammatory; 2. Analgesic; 3. Antioxidant; 4. Anti-tumor.

(*Continued*)

Table 1 (Continued).

Ingredients	Granule Dose	Efficacy (TCM)	Efficacy (Pharmaceutical study)
Curcuma zedoaria (Ezhu)	30g	Promote qi circulation, eliminate blood stasis, relieve pain, and eliminate blood stasis	1. Anti-inflammatory; 2. Antioxidant; 3. Anti-tumor; 4. Inhibit platelet Aggregation; 5. Improve microcirculation.
Cortex Moutan (Danpi)	9g	Clearing heat and cooling blood, promoting blood circulation and dispersing stasis	1. Anti-inflammatory; 2. Antipyretic; 3. Anti platelet aggregation; 4. Anti thrombotic; 5. Improves blood rheology; 6. Anti-tumor.
Rhizoma Wenyujin Concisum (Pianjianghuang)	15g	Breaking blood, promoting qi circulation, and relieving pain through meridian circulation	1. Anti-inflammatory; 2. Analgesic; 3. Antioxidant; 4. Anti platelet aggregation.
Scorpio (Quanxie)	3g	Relieve wind and spasm, dispel wind and relieve pain, detoxify and disperse nodules	1. Analgesia; 2. Anti-inflammatory; 3. Antipyretic.
Zoacys dhumnades (Wushaoshe)	9g	Dispelling wind and dampness, unblocking meridians, and stopping spasms	1. Analgesia; 2. Anti-inflammatory.
Radix Glycyrrhizae (Shenggancao)	6g	Tonifying Qi and Tonifying the Middle, Clearing Heat and Detoxifying, Removing Phlegm and Coughing, Relieving Acute Pain, and Harmonizing Medicinal Properties	1. Immune regulation; 2. Anti-tumor; 3. Anti-inflammatory.

Medication Method

- Control Group: Basic Western medication regimen plus placebo, administered once daily, divided into two oral doses.
- Treatment Group: Basic Western medication regimen plus BSJDTL granules, taken once daily, divided into two oral doses.
- Each subject will last for 6 months.

Combination of Drugs

- Permitted concomitant medication: Medications that must be continued in conjunction with other diseases may remain unchanged. The drugs necessary for treating comorbidities must be recorded in detail in case report forms (CRFs).
- In accordance with ethical guidelines, subjects who cannot tolerate pain may concurrently use NSAIDs. However, if the increased dosage is used continuously for more than two weeks, the subject will be considered to have withdrawn from the study. For subjects already using NSAIDs before the trial, the dosage must have been stable for at least four weeks. The name of the combined medication (such as NSAIDs), medication time, and total medication amount will be recorded for the subsequent summary and analysis.

Outcomes

General Information

The subjects' general information, such as demographic details, results from general medical examinations, and overall clinical data, will be collected at baseline.

Demographic Information

Age, gender, occupation, and contact information. General medical examination include respiration, body temperature, pulse, blood pressure, height, weight, tongue coating, and pulse condition.

General Clinical Data

History of comorbid diseases, medication history, allergy history, and family history.

Outcome Variables

Primary Outcome

DAS28: The DAS28 is a measure of disease activity in patients with RA. It evaluates 28 specific joints in the body for tenderness and swelling and includes the patient's assessment of their own health.[9] The DAS28 includes tender joint count (TJC28) and swollen joint count (SJC28) of 28 joints (bilateral wrists, elbows, shoulders, knees, proximal interphalangeal joints, and metacarpophalangeal joints), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, and the subject's global health (GH) assessment on a 100 mm visual analog scale (VAS). These parameters were used in the following formula to calculate the final score:

$$\text{DAS28-ESR} = 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \ln\text{ESR} + 0.014 \times \text{GH}$$

Secondary Outcomes

VAS Scores: VAS is a commonly used tool to measure pain intensity. VAS is presented on a 10-cm line with anchor statements on the left (no pain) and right (extreme pain) from the subject's marking.[13] 0 cm: No pain;1–3 cm: Mild pain;4–6 cm: Moderate pain;7–9 cm: Severe pain;10 cm Worst Severe Pain.

ACR20/50/70: ACR20, ACR50, and ACR70 are criteria established by the ACR to measure improvement in patients with RA. These criteria are widely used in clinical trials to evaluate the treatment efficacy. Numbers 20, 50, and 70 represent the percentage of improvement.[14] ACR20/50/70 Criteria: Patient's global assessment; Physician's global assessment; Patient's pain scale; Patient's physical function (disability index). Acute phase reactant (CRP or ESR): ACR20:20% improvement in TJC, SJC, and three of the five other criteria; ACR50:50% improvement in TJC, SJC, and three of the five other criteria; ACR70:70% improvement in TJC, SJC, and three of the five other criteria.

RAPID3: The RAPID3 is a patient-reported outcome measure used to assess disease activity in patients with RA. Unlike other indices that require laboratory tests or joint counts, RAPID3 is derived solely from the patient's perspective, and is therefore quicker and easier to administer in clinical settings.[15] RAPID3 includes three patient-reported measures: Physical Function, Pain, Patient Global Assessment. Each component (physical function, pain, and global patient assessment) was scored from 0 to 10, giving a total possible score of 30. The total scores yield the RAPID3 score, categorized into four levels of disease activity: High (12–30), Moderate (6.1–12), Low (3.1–6), and Remission (0–3).

Health Assessment Questionnaire Disability Index (HAQ-DI): The HAQ-DI is divided into eight dimensions and consists of 20 items, each scored on a scale of 0–3. Each dimension represents a specific aspect of self-care ability: dressing and grooming, raising, eating, walking, hygiene, reach, grip, and Activities.[16,17] For each dimension, the highest score for any item within that dimension was taken as the score for that dimension. If assistance or devices were not required, the highest score in each category determined the score for that category. If assistance or devices are necessary, the score for that category is increased to reflect the dependency on help or devices. If a patient provided fewer than six categories of answers, the HAQ-DI score was not calculated.

TCM Symptoms: To facilitate the evaluation of treatment outcomes, we will employ the measurement scale for Traditional Chinese Medicine (TCM) symptoms as recommended by the "Guidelines for Clinical Research of Chinese Medicine (New Drug)".[10] This scale assesses patients based on four major symptoms and seven minor symptoms, with

each symptom rated on a 4-point scale: none (0 points), light (1 point), medium (2 points), and heavy (3 points). The total symptom score was calculated by summing the scores for each symptom. The efficacy indicator (EI) is then calculated using the following formula:

$$\mathrm{EI} = \frac{(\text{Total symptom score at baseline} - \text{Total symptom score post treatment})}{\text{Total symptom score at baseline}} \times 100\%$$

Based on the EI, treatment outcomes are categorized as follows: Full recovery: EI ≥ 90%; Good recovery: 70% ≤ EI < 90%; Modest recovery: 30% ≤ EI < 70%; No recovery: EI < 30%. This standardized scale allows for systematic and quantitative assessment of treatment efficacy in patients receiving TCM therapies.

The US7 Score by musculoskeletal ultrasound: The US7 score is a comprehensive ultrasonographic scoring system used to assess the disease activity in patients with RA. It evaluates seven joints in the dominant hand and foot and provides detailed information on synovitis, tenosynovitis, and erosions.[18] The joints to be assessed included the dominant side (if both sides were affected, the more symptomatic side was selected): the wrist, second metacarpophalangeal joint (MCP2), third metacarpophalangeal joint (MCP3), second proximal interphalangeal joint (PIP2), third proximal interphalangeal joint (PIP3), second metatarsophalangeal joint (MTP2), and fifth metatarsophalangeal joint (MTP5). Each joint is evaluated for synovitis, tenosynovitis, and bone erosion in three aspects, with a maximum score of 94 points.

The Sharp score by X-ray: Sharp score is a radiographic scoring system used to assess joint damage in patients with RA. It measures the extent of joint space narrowing (JSN) and erosion in specific joints of the hands and feet, and provides a detailed quantification of structural damage over time. The Sharp score evaluates the two main types of joint damage.[19] Erosions: Erosions are assessed across 16 areas in each hand and wrist, and 6 areas in each foot, providing a comprehensive evaluation of joint damage. Each area is scored from 0 to 5, where 0 indicates no erosion and 5 indicates severe erosion. The maximum erosion score for hands and wrists is 160, and for feet it is 120, giving a total maximum erosion score of 280. Joint Space Narrowing (JSN): JSN is assessed in 15 areas in each hand and wrist and in six areas in each foot. Each area is scored from 0 to 4, where 0 indicates no narrowing and 4 indicates a complete loss of joint space. The maximum JSN score for hands and wrists is 120, and for feet it is 48, giving a total maximum JSN score of 168.

Study Procedure

The primary outcome was DAS28-ESR. Secondary outcomes included changes in joint symptoms and signs (VAS, ACR20/50/70 reaction standard, RAPID3, HAQ-DI, and TCM symptoms), ESR, CRP, Macrophage Migration Inhibitory Factor (MIF), Matrix Metalloproteinase 2 (MMP2), CD147, Intercellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1), and Hypoxia-Inducible Factor 1 Alpha (HIF-1α) levels, and joint evaluation via musculoskeletal ultrasound and X-ray. Joint symptoms and signs were evaluated every four weeks. Laboratory tests and musculoskeletal ultrasound examinations were compared with those before treatment. Composite outcomes will encompass the incidence rates of all potential safety events observed in both treatment groups. Adverse Event (AEs) will be monitored throughout the trial, and several biological indicators (blood, urine, and stool tests; routine liver and kidney function tests; and ECG tracings) will also be closely monitored every two months. The measured items and time points of data collection are found in Table 2.

Multicenter Coordination and Quality Assurance

To maintain consistency across multiple centers, the study will implement standard operating procedures (SOPs) for patient enrollment, data collection, intervention administration, and outcome evaluations. All site investigators and research staff will receive centralized training prior to recruitment to ensure uniform understanding of the protocol. Regular monitoring visits, audits, and inter-site communication (eg, teleconferences) will further ensure that trial procedures are followed consistently and that any discrepancies are promptly addressed.

Table 2 Schedule of Study Procedures

		STUDY PERIOD								
	Enrolment (day)	**Allocation (day)**	**Post-Allocation (Months)**							**Close-out**
TIMEPOINT**	***-T0d***	***-T0d***	***T0m***	***T1m***	***T2m***	***T3m***	***T4m***	***T5m***	***T6m***	
ENROLMENT:										
Patients with active RA	X									
diagnosis and investigation of the distribution of TCM syndrome types	X									
Informed consent	X									
General information	X									
General physical examination	X									
Allocation		X								
INTERVENTIONS:										
Western medicine as well as TCM placebo combined group				X	X	X	X	X	X	
Western medicine as well as TCM combined group				X	X	X	X	X	X	
ASSESSMENTS:										
Joint symptoms and signs [a]			X	X	X	X	X	X	X	
TCM symptoms			X	X	X	X	X	X	X	
ESR, CRP			X	X	X	X	X	X	X	
MIF, ICAM-1, VCAM-1, and HIF-1α			X						X	
Musculoskeletal ultrasonography			X						X	
X-ray			X						X	
Blood test [b]			X		X		X		X	
Urine test [c]			X		X		X		X	
Stool routine			X		X		X		X	
Liver function [d]			X		X		X		X	
Kidney function [e]			X		X		X		X	
ECG			X		X		X		X	
Adverse events			X		X		X		X	

Notes: [a]Joint symptoms and signs include VAS, ACR20/50/70 reaction standard, RAPID3, HAQ-DI. [b]Blood test consists of white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), platelets (PLT). [c]Urine test consists of e WBC, RBC, protein. [d]Liver function consists of alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), gamma glutamyl (γ-GT), alkaline phosphatase (AKP). [e]Kidney function consists of serum creatinine (Scr), blood urea nitrogen (BUN).

Protection of the Subjects' Rights

The informed consent form was prepared in accordance with the requirements of the "Declaration of Helsinki" and the "Management Practices for Drug Clinical Research". It is the responsibility of both the project leader and the research team to obtain informed consent. We will provide subjects with comprehensive information about the clinical study, including the research objectives, methods, processes such as treatment measures, grouping and testing, the expected benefits, and any potential risks and inconveniences.

Participants' personal information will be kept strictly confidential to protect their privacy. Participation in the clinical study was entirely voluntary, and subjects may withdraw from the study at any time without facing any discrimination or retaliation. Their rights and interests are not affected. If any harm or injury related to clinical research occurs, the subjects will be appropriately compensated.

The clinical study can proceed only once the informed consent form is signed and dated by the subject or their legal representative/guardian. If a subject or their legal representative/guardian is unable to read, a witness should be present during the process. After a thorough explanation of the informed consent form, the subject or their legal representative/guardian can provide consent, and the witness will then sign and date the form.

Details about the participant' involvement in the study will be recorded in the study's medical records or case report forms. All study results, including personal information and lab notes, found in the original medical records will be kept confidential to the fullest extent permitted by the law. Subjects' names will not be included in the case report forms (CRFs); instead, only their initials and assigned study numbers will be utilized. Drug regulatory authorities, ethics committees, and funding agencies may require access to the participants' data. However, they will not use the data and biological specimens for any other purposes or disclose them to other groups without permission.

Any changes to the protocol that may impact the conduct of the study, the potential benefit to the patient, or patient safety, including changes to study objectives, design, patient population, sample sizes, procedures, or significant administrative aspects, will require a formal amendment. Such amendments must be agreed upon by the project leader and research team, approved by the Ethics Committee of Shuguang Hospital affiliated with Shanghai University of Traditional Chinese Medicine, and notified by the Shanghai Science and Technology Commission. The participants will be informed of these modifications.

Intervention Protocols and Procedures for Monitoring Adherence

Face-to-face adherence reminder sessions will be held during the initial product dispensing and at each follow-up study visit. These sessions will cover the following points.

Adherence Importance: Emphasizing the importance of strictly following the study guidelines for taking once-daily study medications.

Medication Instructions: Detailed instructions on how to use traditional Chinese medicine granules or colchicine, including proper dose timing, storage guidelines, the importance of adherence to the medication schedule, and what to do if a dose is missed.

Drug Packaging: Information on the purpose, usage, care, and recycling of drug packaging.

Medication Count: Notification that there will be a count of study medications at each study visit to ensure adherence.

Contacting the Physician: Stressing the importance of contacting the physician if any issues arise that may be related to the study medication, such as experiencing symptoms or losing pill.

Research Questions: Providing information on how to reach the physician for any research-related questions, either via WeChat or telephone.

AEs/Serious Adverse Events (SAEs)

Throughout the trial, we will closely monitor AEs associated with each treatment, such as acute pain and gastrointestinal discomfort. Any adverse events or reactions suspected to be linked to the intervention will be documented, addressed, and communicated to the study coordinator. SAEs will be reported to the ethics committee within 24 hours.

Data Quality Control

All participating staff will undergo training on the trial protocol, use of the randomization process, and data management systems, among other relevant topics. The principal investigator will monitor the trial's progress at least once per month. An ethics committee will review the trial's conduct, focusing particularly on participant safety, rights, and well-being at the midpoint and conclusion of the trial. The Clinical Evaluation Center of the China Academy of Chinese Medical Sciences will conduct audits at the beginning, midpoint, and conclusion of the trial.

Data Collection and Management

The Data and Safety Monitoring Committee (DSMC) is composed of professional statisticians. They will be involved in the entire process, from study design and implementation to analysis and summary. They will perform statistical analyses throughout the trial. A statistical analysis plan will be developed following the completion of the study program and case report forms. Statistical analysis reports will be generated with necessary modifications to data analysis as required during the study. EpiData 3.1a software will be used to establish the data entry procedure and set the logical examination criteria at the time of entry. The database will be piloted to create a dedicated database system for this experiment. The

signed case report forms and audit statements were handed over to the data administrator. The data administrator then reviewed the date, group criteria, culling criteria, shedding criteria, and missing values to ensure data integrity.

If there is any uncertainty regarding the data query form, it is returned to the monitor. The researcher addresses the query in writing, signs it, and returns it to the data administrator. The data query form must be securely stored to ensure confidentiality before, during, and after the trial. The data administrator entered the data utilizing a two-person entry method to ensure accuracy. Each item in the database was verified using the verification function in the EpiData 3.1a software, and any discrepancies were reported. The original CRFs were checked item by item, and a random sample of 10 CRFs was manually compared with the data in the database to ensure consistency. All original CRFs and related records will be archived for 5 years.

An interim analysis will be conducted on the primary endpoint once 50% of the subjects have been randomized and have completed follow-up. This analysis will be performed by an independent statistician who is blinded to treatment allocation. The statistician then reports the findings to the independent DSMC. The DSMC will have unblinded access to all the data and will discuss the interim analysis results with the steering committee in a joint meeting. The steering committee is responsible for deciding whether to continue the trial and report their decisions to the ethics committee. The trial will not be stopped for futility unless advised otherwise by the DSMC, based on safety monitoring. In such cases, the DSMC will discuss the potential for stopping the trial due to futility with the steering committee.

Statistical Analysis

In accordance with the per-protocol (PP) principle, all patients who completed the study and adhered to the protocol are included in the analysis. Statistical analysis was conducted using SPSS software (SPSS version 26.0; IBM, NY, USA).

Measurement Data Analysis

If the data will follow a normal distribution, t-tests will be used, and the results are presented as means ± standard deviation ($\overline{x} \pm s$).

If the data do not follow a normal distribution, Mann–Whitney *U*-tests will be used, with the results shown as medians and quartiles M (P25-P75).

For measurement data at multiple time points (>2) following a normal distribution, repeated-measures ANOVA variance will be applied.

A generalized estimation equation (GEE) was used for measurement data at multiple time points (>2) that do not follow a normal distribution.

Categorical Data Analysis

Chi-square (χ^2) tests will be employed for categorical data.

Mann–Whitney *U*-tests will be used for ordinal data.

The GEE was used for ordinal data at multiple time points (>2).

A significance level of $P<0.05$ will be considered statistically significant.

Handling of Missing Data

Last Observation Carried Forward (LOCF): In cases where the entire treatment process cannot be observed, the last observation data will be carried forward to the final results of the trial. Intention-to-treat (ITT) analysis was conducted to evaluate the efficacy and safety of the main indicators.

Imputation for Missing Data

Numeric Data: Missing numeric values were imputed using the average of the other values under the same variable.
Non-Numeric Data: Missing non-numeric values are imputed using the mode of other values under the same variable.

Additional Analysis

Stratified analysis will be performed, if necessary, to control for confounding factors. All data analyses will be conducted by statisticians, who are independent of the research team.

Ethics and Dissemination

This trial protocol adhered to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Shuguang Hospital, affiliated with the Shanghai University of Traditional Chinese Medicine (approval no. 2024–1524-107-01). It was also registered in International Traditional Medicine Clinical Trial Registry (ITMCTR2025000194). A qualified doctor will serve as the principal investigator of this study. All personal information of the subjects and data collected during the trial will be kept confidential and will not be disclosed to any third party. Subjects will be enrolled in the study only after receiving detailed information about the study and signing an informed consent form. The research findings will be published in peer-reviewed journals with an emphasis on open-access dissemination. The results will be shared through oral and poster presentations at domestic conferences. In addition, all resources and findings will be uploaded to an online knowledge management platform. Plans are in place to ensure that any important protocol modifications are communicated to researchers in a timely manner.

Discussion

According to statistics, the global prevalence of RA is between 0.2% and 1%, while the incidence rate in China is approximately 0.3% to 0.6%. As of October 2021, there are about 5 million RA patients in the country.[20] This disease is a chronic, highly disabling autoimmune disorder, with joint swelling and pain as the most common clinical manifestations. In addition to joint lesions, RA can also affect multiple organs and systems throughout the body, and the condition often relapses and gradually worsens, ultimately leading to joint structural damage. This results in physical disabilities, loss of work capacity, and reduced life expectancy for patients, creating a significant economic burden for individuals, families, and society. Research indicates that 33% to 39% of patients become disabled and lose their ability to work within 5 to 10 years of diagnosis.[21] Therefore, controlling immune inflammation in RA patients, delaying bone destruction, and preventing the loss of joint function are currently key challenges that need to be addressed in the treatment process.

Currently, there is no cure for RA. The goal of treatment is to achieve target therapy, alleviate symptoms, control disease activity, and improve function and prognosis. NSAIDs reduce joint swelling symptoms through their anti-inflammatory and analgesic effects, but they cannot control disease progression when used alone and must be combined with DMARDs. DMARDs can delay bone erosion and reduce disease activity by suppressing the immune response, and they are recommended in guidelines both domestically and internationally.[8,22] However, DMARDs have many side effects and limited efficacy, while biological agents are expensive and carry a risk of serious infections. Glucocorticoids are commonly used anti-inflammatory drugs in clinical practice; they can effectively alleviate inflammatory symptoms in patients, but they also have notable side effects, such as moon facies, buffalo hump, and osteoporosis.[20]

According to the fundamental theories of TCM and in combination with the clinical manifestations of patients, TCM emphasizes treating according to the syndrome, achieving clear efficacy and addressing both the symptoms and the root causes. The combination of TCM and Western medicine can enhance efficacy while reducing toxicity and dosage, showcasing unique advantages. Our research group has previously confirmed that BSJDTL can improve joint symptoms in RA patients and exhibits strong anti-inflammatory, anti-angiogenic, regulate bone metabolism and immune-regulatory effects.[2–7] This has practical significance for the development of TCM in the treatment of RA and provides guidance for clinical applications, offering optimized treatment options and new references for clinical medication in RA management.

Currently, high-quality randomized controlled trials (RCTs) are needed to support the effectiveness and safety of BSJDTL in the treatment of RA. Therefore, this study aims to provide high-level evidence from evidence-based medicine. Guided by the Kidney-Tonifying and Detoxifying method for RA, we will employ a multicenter, randomized, double-blind, placebo-controlled trial design. The study will assess disease activity in RA patients using both clinical evaluation and imaging techniques (musculoskeletal ultrasound and X-ray examination) to scientifically evaluate the clinical efficacy and safety of BSJDTL in active RA. We propose the following scientific hypothesis:

> The Bushen Jiedu Tongluo Decoction can significantly improve the clinical treatment target rate in RA patients, control disease activity, alleviate symptoms and enhance the quality of life, regulate the immune environment, and protect joint function, all of which can be validated through imaging studies, while also demonstrating good safety.

The implementation of this study will provide new insights for exploring clinical treatment options for RA and will offer evidence-based medical evidence to confirm the advantages of traditional Chinese medicine in the treatment of RA.

Data Sharing Statement

After the completion of the study, the datasets generated and analyzed during the study will be available from the corresponding author upon reasonable request. The data will be made available in accordance with the principles of data sharing and open access, while ensuring participant confidentiality.

Ethics Approval and Consent to Participate

This study has been approved by the ethics committee of hospital. The international review board of Shuguang Hospital affiliated with Shanghai University of Traditional Chinese Medicine (approval no. 2024-1524-107-01). Written informed consent will be obtained from all participants.

Trial Status

The protocol version number is V2.0, and the research strategy and study protocol were developed from August 2024 to July 2026. The follow-up visits and data analysis will take place from August 2026 to December 2026.

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Disclosure

Dr Yikun He reports a patent A traditional Chinese medicine preparation for treating rheumatoid arthritis with royalities paid to Guanghui Yang; Yikun He; Yueqi Zheng; Xin Pan; Xiaofang Xu; Huihui Wu. Dr Xin Pan reports a patent China National invention patent licensed to Guanghui Yang, Yikun He, Yueqi Zheng, Xin Pan, Xiaofang Xu, Huihui Wu. The authors declare that they have no other competing interests.

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