

METHOD

Study to evaluate the effect of Tangshen Fang combined with guideline-directed medical treatment on the quality of life and clinical outcomes in patients with diabetic nephropathy: A clinical trial on constructing a novel paradigm of integrated traditional Chinese and Western medicine in the treatment of diabetic nephropathy

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Abstract

Background: Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus and has become the primary cause of end-stage renal disease in China. In patients with severe renal insufficiency, Western medical treatments often yield unsatisfactory results. Preliminary studies have indicated that the Chinese herbal formula Tangshen Fang improves estimated glomerular filtration rate (eGFR) in patients with DKD.

Methods/design: This is a multicenter, randomized, open-label, controlled clinical trial. DKD patients with eGFR levels between 25 and 75 mL/min (1.73 m²) and urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g, or eGFR level between 25 and 60 mL/min (1.73 m²) and UACR <30 mg will be included. A total of 144 participants will be randomly allocated to the treatment group (Tangshen Fang plus standard Western medicine with or without other traditional Chinese medicine [TCM]) and the control group (standard Western medicine with or without other TCM) at a 1:1 ration. The study duration will be 24 weeks and the follow-up period will be extended to 96 weeks. The primary endpoint will be the change in eGFR from baseline to week 24. Secondary endpoints will include changes in UACR, body weight, waist circumference, blood pressure, lipid levels, fasting plasma glucose, glycosylated hemoglobin A_{1c} (HbA_{1c}), and improvement in TCM symptoms and quality of life. Adverse events will also be evaluated.

Abbreviations: ADA, American Diabetes Association; AE, adverse event; ALT, alanine transpeptidase; AST, aspartate transpeptidase; CKD, chronic kidney diseases; Cr, creatinine; CRF, case report form; DBIL, direct bilirubin; DBP, diastolic blood pressure; DKD, diabetic kidney disease; ECG, electrocardiogram; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; GGT, gamma-glutamyl transpeptidase; HbA_{1c}, glycosylated hemoglobin A_{1c}; QOL, quality of life; SAE, severe adverse event; SBP, systolic blood pressure; T2DM, type 2 diabetes; TBIL, total bilirubin; TCM, traditional Chinese medicine; UACR, urinary albumin-to-creatinine ratio.

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Discussion: This study will provide evidence of the effectiveness and safety of Tangshen Fang in treating patients with DKD. It will also form the clinical pathway and expert consensus on integrating traditional Chinese and Western medicine for DKD and provide clinical evidence for the rational use of hospital preparations of Tangshen Fang.

Trial registration: Chinese Clinical Trials Registry, ChiCTR2300069269. Registered March 10, 2023.

KEYWORDS

diabetic kidney disease (DKD), glomerular filtration rate (eGFR), Tangshen Fang, traditional Chinese medicine (TCM)

BACKGROUND

The latest epidemiological data shows that the prevalence of diabetes in China is 11.2% [1]. Among the chronic kidney diseases (CKD) that lead to end-stage renal disease (ESRD), Diabetic kidney disease (DKD) has become the main cause of ESRD in China [2–4]. For patients with severe renal insufficiency (CKD 3b or below), Western medicine treatment has certain limitations [3, 5, 6]. Recent studies have shown that certain Chinese herbs exert renoprotective effects on CKD [7]. In this study, we aim to clarify the therapeutic effect of the Chinese herbal medicine Tangshen Fang combined with Western medicine on DKD and form a standardized treatment scheme of integrated traditional Chinese and Western medicine that can be promoted and applied in clinical practice. Tangshen Fang is an effective herbal formulation for treating diabetic nephropathy, developed from the expertise of renowned traditional Chinese medicine (TCM) practitioners and refined by Professor Li Ping and his team at the China-Japan Friendship Hospital. Because of the integration of clinical research and field practice, along with a solid foundation of preliminary work, it is now prepared for broader application and promotion. In previous studies, a combination of Chinese and Western medicine has shown significant advantages in the treatment of CKD [8–11]. Previous clinical and basic studies from our research group have confirmed that standardized treatment with Western medicine combined with TCM could further reduce the urinary protein excretion rate of patients with DKD, slow down the decrease in the evaluated estimated glomerular filtration rate (eGFR), relieve patients' discomfort, improve their quality of life (QOL), and delay the progression of the disease [12]. According to academician Tong Xiaolin's "State Target Theory," DKD is characterized by "Qi and Yin deficiency and Collaterals stasis" [13, 14]. The efficacy of Tangshen Fang in improving eGFR and reducing proteinuria will be assessed, building upon a solid foundation of preliminary research. The optimized combination treatment scheme integrating traditional Chinese and Western medicine holds promise for nationwide demonstration and promotion.

This study aims to investigate the effectiveness and safety of Tangshen Fang combined with integrated traditional Chinese and Western medicines in the management of DKD. Ultimately, the goal of this study is to establish a clinical pathway and expert consensus for integrating traditional Chinese and Western medicine in the treatment of DKD as well as to provide clinical evidence to support the rational use of Tangshen Fang Hospital preparations.

METHODS/DESIGN

Ethics, consent, and permissions

The protocol (version identifier: 4.0 (20230212)) has been approved by the Ethics Committee of the China-Japan Friendship Hospital (Ethical Review No. 2022-KY-117-2) and is registered with the Chinese Clinical Trial Registry under registration number ChiCTR 2300069269. The study will be conducted in accordance with the principles of good clinical practice, specifically following the Declaration of Helsinki (2004 version). The trial will adhere to reporting guidelines outlined in the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) (see Supporting Information S1: Additional file 1). Prior to entry into the trial, all participants will receive comprehensive information regarding the purpose, risks, and benefits and provide informed consent (version identifier: 4.0 (20230212)) (see Supporting Information S2: Additional file 2). All visits will be meticulously documented in a case report form (CRF) (version identifier: 3.0 (20230212)) (see Supporting Information S3: Additional file 3).

Study design and setting

It will be a multicenter, randomized, open-label, controlled clinical trial with two parallel groups. The study will be unblinded to investigators, the statistician, and participants. The trial flow is depicted in Figure 1.

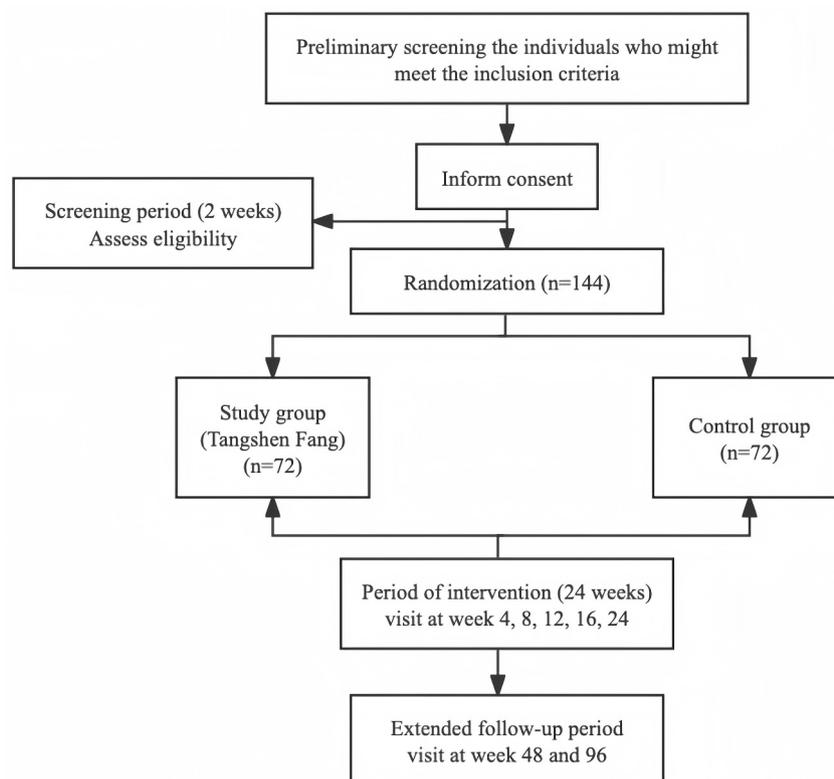


FIGURE 1 Flow diagram of the study.

Outpatients diagnosed with DKD who meet the admission and discharge criteria were enrolled in the study. Participants will be recruited from five hospitals in Beijing, China: the Department of Endocrinology of China-Japan Friendship Hospital; the Diabetes Department of Integrated Traditional Chinese and Western Medicine of China-Japan Friendship Hospital; the Xiyuan Hospital of China Academy of Chinese Medical Sciences; the Guang'anmen Hospital of China Academy of Chinese Medical Sciences; the Beijing Hospital of TCM; and the Fang Shan Hospital of Beijing University of Chinese Medicine.

Eligibility criteria

Diagnostic criteria

The diagnosis of type 2 diabetes (T2DM) will be based on the American Diabetes Association criteria and DKD will be defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K-DOQI) guidelines [15, 16].

TCM syndrome pattern differentiation

The Chinese syndrome pattern differentiation type of deficiency of both qi and yin with blood stasis will be based on guidelines delineated in Clinical Research of

New Investigational Drugs in TCM [17]. The diagnostic standards are as follows:

- Primary signs and symptoms encompass fatigue, listlessness, weakness, and soreness of the low back and knees; sensation of heat in the palms and soles; as well as dryness of the mouth and throat.
- Secondary signs and symptoms encompass heightened susceptibility to respiratory infections, pallor, irritability, numbness, edema, nocturia, constipation, and hematuria.

Participants will be diagnosed with deficiency of both qi and yin with blood stasis syndrome if they have two or more of the primary signs/symptoms and at least two of the secondary signs/symptoms.

Participants who meet the inclusion criteria and do not meet the exclusion criteria (Table 1) will undergo screening and be randomly allocated to the treatment group.

Interventions

Eligible participants will be randomized to two groups according to a 1:1 ratio, with 72 cases in the study group and 72 cases in the control group. A total of 144 cases will be included in the trial. The study groups will be treated with Tangshen Fang plus standard Western medicines with or without other TCM. The control group

TABLE 1 Eligibility criteria and criteria for midway exit.

Inclusion criteria	Exclusion criteria	Criteria for midway exit
<ul style="list-style-type: none"> Aged 18–75 years old, no gender limitation 	<ul style="list-style-type: none"> Patients with the history of severe diabetic complications or major vascular events within 6 months 	<ul style="list-style-type: none"> Reach the exploratory endpoint, such as creatinine level doubling or the need for renal replacement therapy
<ul style="list-style-type: none"> Diagnosed with T2DM, HbA_{1c} ≤ 11% 	<ul style="list-style-type: none"> Patients with the history of various infections within 4 weeks 	<ul style="list-style-type: none"> Those who are unwilling to continue participating in this study
<ul style="list-style-type: none"> Diagnosed with diabetic nephropathy; eGFR between 25–75 mL/min (1.73 m²) with UACR ≥30 mg/g, or eGFR between 25 ~ < 60 mL/min (1.73 m²) with UACR <30 mg; and these last for more than 3 months 	<ul style="list-style-type: none"> Those who use Niaoduqing granules or Shenshuaining capsules 	<ul style="list-style-type: none"> Those who are unable to follow up for other reasons
<ul style="list-style-type: none"> TCM syndrome differentiation diagnose is “Qi and Yin Deficiency and Collateral Stasis” 	<ul style="list-style-type: none"> Pregnant women, lactating women, or those who are allergic to test drugs 	<ul style="list-style-type: none"> Those who are unsuitable for this study judged by the investigators
<ul style="list-style-type: none"> Those who sign informed consent and can cooperate with follow-up 	<ul style="list-style-type: none"> Combined with other serious diseases such as hematological diseases, malignant tumors, severe heart failure, obvious liver diseases 	
	<ul style="list-style-type: none"> Uncontrolled hypertension (systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg) 	
	<ul style="list-style-type: none"> Patients with mental illness or unable to follow up 	
	<ul style="list-style-type: none"> Kidney disease caused by non-diabetes 	
	<ul style="list-style-type: none"> Hyperkalemia (blood potassium >5.5 mmol/L) 	

will be treated with standard Western medicines with or without other TCM.

Tangshen Fang is light brown to brown granules, and every 1 g is equivalent to 1.77 g of Chinese herb piece. Tangshen Fang consists of seven natural herbs: astragalus root (*Astragalus membranaceus* (Fisch.) Bge.), rehmannia root (*Rehmannia glutinosa* (Gaertn.) Libosch.), notoginseng root (*Panax notoginseng* (Burk.) F. H. Chen), winged burning bush twig (*Euonymus alatus* (Thunb.) Sieb.), Asiatic cornelian cherry fruit (*Cornus officinalis* Sieb. Et Zucc.), rhubarb root and rhizome (*Rheum palmatum* L.), and bitter orange (*Citrus aurantium* L.).

Tangshen Fang (Lot NO. 2210001) were manufactured by the Beijing Asia East Biopharmaceutical Co. LTD. The manufacturing process was quality controlled for physical characteristics, purity, microbial content, and weight consistency of the packets. The certificate of quality for the manufacturing of Tangshen Fang has been provided by the manufacturer (Supporting Information S4: Additional file 4). The main components in Tangshen Fang were validated and quantified by thin-layer chromatography and high-performance liquid chromatography.

The product is packed in a polyester/aluminized polyester/polyethylene medical composite film, with 8 g in each bag, and 12 bags in each box. Participants in

the study group will be instructed to consume two bags at a time, three times daily, with warm water after their morning and evening meals. It is contraindicated in children, pregnant women, and lactating women, and should be used with caution in patients with a bleeding tendency.

Concomitant treatments

In this study, standard Western medicine treatment refers to the standardized management of blood sugar, blood pressure, and blood lipids following the Chinese guidance of the diagnosis and treatment of DKD [1, 2]. The study and control groups will be treated using the standard Western medicine. Both groups will also be permitted to add TCM decoction according to the participants' conditions, except for the Niaoduqing granules and Shenshuaining capsules, due to numerous references in the literature indicating their potential for reducing serum creatinine levels and slowing the progression of renal dysfunction.

The participants will also receive guidance on managing their diabetes through dietary adjustments and regular exercise. The attending physician investigator will have discretion in administering other medications to ensure that they do not interfere with the

outcome assessments. Investigators are also required to accurately document any additional or alternative drugs or therapies in the CRF, including details such as the name, dosage, and duration of administration.

Study visits and assessment

Screening period (week –2 to week 0) and allocation (week 0)

The enrolled participants will receive continuous treatment for 24 weeks. The following data will be collected during the screening period and allocation: baseline demographic characteristics, medical history, vital signs (height, weight, blood pressure, pulse, respiration, and waist circumference), laboratory examination (routine blood examination, blood biochemistry, routine urine examination, eGFR, HbA_{1c}, urinary albumin-to-creatinine (UACR), 24-h urine protein quantification, and urine pregnancy test [if necessary]), extra blood samples (approximately 10 mL of venous blood from the participants), electrocardiogram (ECG), TCM symptom assessment scores, QOL evaluation, and safety index assessment.

Period of intervention (week 4 to week 24)

The enrolled participants will undergo follow-up assessments at week 4, 8, 12, 16, and 24. During each subsequent follow-up, the following data points will be gathered: vital signs (height; weight; blood pressure; pulse; respiration; and waist circumference), laboratory examinations (HbA_{1c} and 24-h urine protein quantification are not required at week 4, 8, and 16, and the rest are the same as the screening period and baseline), ECG (only at week 24), TCM symptom assessment score, QOL evaluation, safety index assessment, drug combination, and adverse events (AEs) of the participants. Extra blood samples (approximately 10 mL of venous blood from the participants) will be collected at week 24 for subsequent omics studies.

Extended follow-up period

The follow-up period will be extended to 48 and 96 weeks. The visit data of the participants will be collected as the same manner as during the intervention period, and we will focus on the evaluating changes in serum creatinine, urine protein, and exploratory endpoints.

The eGFR levels at week 0 and week 24 will be assessed at China-Japan Friendship Hospital, while other blood and urine tests will be conducted at the

clinical laboratories of each affiliated hospital. The extra blood samples collected at week 0 and week 24 will be centrifuged and stored in the refrigerator at –70°C in the biological sample bank of China-Japan Friendship Hospital for further research. An overview of specific measurements and time points of data collection can be found in Table 2.

Outcome measurements

Through statistical analysis, we will evaluate and assess the following changes under treatment with Tangshen Fang combined with the integrated treatment of TCM and Western medicine: the extent of delay in the progression of renal function, influence on clinical parameters (such as urine protein, blood lipid, and blood pressure), TCM symptom assessment and QOL, the influence of creatinine doubling, and the hard end point of renal replacement therapy.

Primary endpoint

The alteration in eGFR (calculated using the CKD-EPI creatinine equation) from week 0 to week 24.

Secondary endpoints

- The change in UACR from week 0 to week 24.
- The changes in body weight, waist circumference, blood pressure, lipid, fasting plasma glucose, and HbA_{1c} from week 0 to week 24.
- The improvement in TCM symptoms (evaluated by TCM symptom assessment score) from week 0 to week 24.
- The improvement in QOL (evaluated by QOL) from week 0 to week 24.

Exploratory endpoints

- The incidences of serum creatinine level doubling at week 24, 48, and 96.
- The incidences of renal replacement therapy at week 24, 48, and 96.

Safety endpoints

- The occurrence of liver insufficiency at any visit.
- The occurrence of AEs at any visit: including vital signs, clinical chemistry/hematology parameters and significant abnormality of ECG.
- Meeting the exit criteria.

TABLE 2 Schedule of enrollment, allocation, visits, and assessments.

	Study period						
	Enrollment	Allocation	Intervention				
Time point (week)	≤-2	0	4	8	12	16	24
Time point (day)	≤-14	0	28	56	84	112	168
Visit time window (day)		±5	±3	±3	±3	±7	±7
Written informed consent	√						
Eligibility screen	√						
Assessment of inclusion/exclusion criteria	√	√					
Demographic data	√						
Medical history	√						
Concomitant medications	√	√	√	√	√	√	√
Vital signs	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√
Height, weight, and waist circumference	√	√	√	√	√	√	√
Laboratory inspection ^a	√	√	√	√	√	√	√
Serum Cr, eGFR	√	√*	√	√	√	√	√*
UACR	√	√	√	√	√	√	√
24-h urinary protein quantity		√			√		√
HbA1c	√				√		√
Urine pregnancy test	√	√	√	√	√	√	√
Extra blood samples		√*					√*
ECG	√						√
QOL		√	√	√	√	√	√
TCM symptom		√	√	√	√	√	√
Assignment of random number		√					
Drug distribution		√	√	√	√	√	√
AE	√	√	√	√	√	√	√
Assessment of diet and exercise	√	√	√	√	√	√	√
Assessment of whether creatinine level doubling or dialysis occurred	√	√	√	√	√	√	√

Note: √ = Action items; √* = Tested or collected in the central laboratory (Clinical Laboratory Department of China-Japan Friendship Hospital).

Abbreviations: AE, Adverse events; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A_{1c}; QOL, Quality of Life; serum Cr, serum creatinine; TCM, traditional Chinese medicine; UACR, urinary albumin-to-creatinine ratio.

^aLaboratory inspections include blood routine (white blood cell, neutrophil, percentage of neutrophils, red blood cell, hemoglobin, and platelet), blood biochemistry (ALT, AST, GGT, TBIL, DBIL, fasting blood glucose, cystatin, urea nitrogen, uric acid, total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, plasma albumin, total protein, blood potassium, blood sodium, blood chloride, blood calcium, and blood phosphorus), and urine routine (red blood cells, white cells, glucose, ketone body, and protein).

Adverse events

AEs may occur during the treatment of participants, and once AEs (including severe adverse events [SAEs]) occur, the time of the occurrence, clinical manifestations, the treatment process and duration, the outcome of AEs, and the relationship with drugs should be recorded in detail on the CRF. Laboratory abnormalities must be followed until they returned to normal or to

premedication levels or determined to be unrelated to the trial drug. SAE forms should be completed and reported to the sponsor and ethics committee within 24 h.

Quality control of laboratory specimens

To standardize the processing and testing of laboratory samples across multiple centers, serum samples for the

detection of serum creatinine will be collected at week 0 and 24 from five participating medical centers, transported under cold-chain conditions to the central laboratory (Clinical Laboratory of China-Japan Friendship Hospital). Serum levels of serum creatinine will be analyzed by an automated biochemistry analyzer (Beckman Coulter AU5800, US) using validated commercial kit. Subsequently, the test results will be promptly communicated to the principal investigators at each center. Extra blood samples (about 10 mL of venous blood of the participants) will also be collected at week 0 and 24. The serum of each blood sample will be separated by centrifugation (4000 rpm, 15 min, 4°C). Extra blood samples will be centrifuged and stored in the China-Japan Friendship Hospital Biobank refrigerator at -70°C .

Sample size estimation

It was found that the eGFR level of “Tangshen Fang” group ($N = 57$) was 6.15 mL/min (1.73 m^2) higher than that of the placebo group ($N = 64$) in 24-week in the per-protocol set of the previous clinical trial [12]. Type I error α was set to 0.05 (bilateral), and the power ($1-\beta$) was 80%. The standard deviation of the Tangshen Fang group and the placebo group was 11.77 and 12.16, respectively. The ratio of the sample between the groups was 1:1. PASS 15.0 was used to calculate the sample size with 60 cases of each group. Considering the possibility of shedding and elimination, the sample size is enlarged by 20%, that is, 72 patients will be included in each group, and a total of 144 patients will be included.

Randomization and concealment

Randomization will be performed by an independent statistician from the Information Center of China-Japan Friendship Hospital. The statistician will utilize R software to generate random sequences using a randomized block randomization method. The random sequences will be ultimately enclosed in light-tight sealed envelopes. Participants will be randomly assigned to either the study or control group in a 1:1 ratio. The drug administrator at each participating medical center will enroll patients sequentially based on the consultation order. To ensure concealment, the block sizes will not be disclosed.

Blinding

This study is conducted in an open-label manner, without the blinding of participants, implementers, and outcome measures or data analysts.

Statistics and analysis of research data

The Shapiro–Wilk test will be used to assess the normality. Measurement data following a normal distribution will be presented as mean \pm standard deviation, whereas data not conforming to the normal distribution will be presented as median and interquartile range. Categorical variables will be reported as absolute numbers and relative frequencies (%). Continuous variables following a normal distribution will undergo t -tests, whereas those deviating from the normal distribution will undergo nonparametric tests. Comparisons between groups of categorical variables will involve chi-square or exact probability tests. Correlation analyses will be performed using Pearson or Spearman correlation coefficients. The significance level is set at a p -value less than 0.05 with bilateral testing.

The review of the Ethics Committee

The protocol, written informed consent, and the data directly related to the participants must be submitted for review by the Ethics Committee. Formal research can only commence upon obtaining written approval from the Ethics Committee. Researchers are required to submit an annual report to the Ethics Committee at least once a year (if applicable). Upon discontinuation or completion of the study, researchers must provide written notification to the Ethics Committee; any changes in the study process (such as project revisions and/or informed consent) must be promptly reported to and approved by the Ethics Committee before implementation, unless necessary to eliminate obvious and direct risks to participants, in which case researchers will notify the Ethics Committee.

The informed consent

The researcher is required to furnish the participant or his/her legal representative with a clear and Ethics Committee-approved informed consent, allowing sufficient time for consideration. Enrollment of the participants may only proceed upon receipt of a signed written informed consent form. Throughout their participation, participants will be provided with all updated versions of informed consent and written information. The informed consent should be maintained as a crucial document for clinical trials.

Confidentiality measures

The results of this study are intended for publication in medical journals, with strict adherence to legal requirements to ensure the confidentiality of the patient

information. The personal data will not be disclosed unless required by applicable laws. The patient data may be accessed as necessary by governmental administrative departments, hospital ethics committees, and their authorized personnel in accordance with regulations.

DISCUSSION

TCM is a medical practice with a rich history based on syndrome pattern differentiation and is widely utilized in China for the managing various diseases. Its notable advantages include minimal side effects, a multitarget, multilink approach for treating diabetes, and the ability to delay the progression of diabetic complications. In recent years, there has been extensive exploration and research on TCM for the treatment of DKD, both domestically and internationally. This has led to the discovery that TCM exhibits promising therapeutic effects on DKD. TCM has demonstrated varying degrees of efficacy in improving glucose and lipid metabolism in DKD, inhibiting inflammatory reactions, reducing oxidative stress, decreasing ECM accumulation, alleviating renal fibrosis, and reducing urinary protein excretion. This demonstrates its potential for kidney protection and the prevention and delay of DKD. Therefore, TCM is widely used by physicians in China as either a primary or complementary therapy for kidney diseases. Tangshen Fang is commonly used to address the deficiency of both qi and yin, which is a prevalent symptom among patients with DKD. Previous studies have indicated that Tangshen Fang may improve renal function [18–20]; therefore, further investigation into its efficacy and safety in treating DKD is warranted.

We aim to investigate the effectiveness and safety of Tangshen Fang using multicenter, randomized, and controlled research methods. Rigorous study design, sample size estimation, and randomization will be conducted by experts in each field. Detailed protocol training will be provided at each site prior to trial implementation.

The results of this study may provide an adjuvant or alternative treatment option for patients with DKD who have decreased creatinine clearance. Additionally, it may provide a scientific basis for the using of Tangshen Fang in treating patients with DKD who have severe renal insufficiency (DKD 3b or below).

AUTHOR CONTRIBUTIONS

Xian Jin: Investigation. **Yanmei Wang:** Investigation. **Ping Li:** Investigation. **Lili Wu:** Investigation. **Na Wang:** Investigation. **Jun Duan:** Investigation. **Qinyu Jiang:** Investigation. **Yangxi Li:** Investigation. **Zhuo Yin:** Investigation. **Xiai Wu:** Investigation. **Xiaoping Chen:** Investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The study results will be available as the manuscripts, and no additional unpublished data are available.

TRIAL STATUS

This trial is currently ongoing, and 21 participants have been enrolled.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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