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Original Article

Efficacy and safety of Shen-Qi Paste, a Traditional Chinese Medicine, in dialysis patients with sarcopenia: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: The lack of effective treatments for sarcopenia remains a major unmet medical need. Shen-Qi Paste (SQP), a Traditional Chinese Medicine (TCM) dietary formulation developed on the basis of the theory of "same origin of medicine and food," offers a novel therapeutic strategy. Unlike conventional approaches that are focused solely on nutrition and exercise, SQP targets the underlying TCM-defined etiologies (e.g., spleen-kidney deficiency) to address the root causes of muscle wasting. Studies have shown that the traditional herbal ingredients of SQP has anti-inflammatory, antioxidant, and muscle protein inhibition properties and can enhance muscle mass and strength.

Hypothesis/Purpose: This study aimed to assess the efficacy and safety of SQP in dialysis patients with sarcopenia by using a two-center, randomized, double-blind, placebo-controlled clinical trial.

Methods: A total of 128 dialysis patients (age: 45–89 years old) with sarcopenia (as identified by the Asian Sarcopenia Group for Sarcopenia 2019) were randomly allocated to either the SQP group or control group for intervention. Patients in the SQP group and control group were respectively administered oral SQP and placebo at 1 vial/15 g twice daily for 12 weeks. At the same time, all participants maintained low-intensity exercise for 20–30 min/d at a frequency of 3–4 d/wk during the trial. The indexes and scales were examined and evaluated before and after the intervention. The primary indicators were changes in sarcopenia measures, including skeletal muscle mass index (SMI), grip strength, and physical function by five-times sit-to-stand test (FTSST).

Results: A total of 163 patients aged 45–89 years were screened, and 128 patients were randomized to receive the study intervention. Some patients (SQP group, $n = 6$; control group, $n = 5$) stopped the intervention because of various reasons. A total of 117 patients (55.56 % of whom were male) completed the 12 weeks intervention. The statistical results of the study were as follows: (1) Intra-group comparison: compared to pre-intervention, SQP intervention significantly improved SMI (t, -0.248, [95 %CI, -0.37 to -0.127], $p < 0.001$), and decreased FTSST, myostatin levels, and serum uric acid levels ($P<0.05$). Both groups had significant changes in grip strength and 36-Item Short Form Health Survey (SF-36) scores post-intervention ($p < 0.05$). (2) Inter-group comparison: compared to the control group, SQP intervention improved the SMI (t, -0.384, [95 %CI, -0.66 to -0.109], $p = 0.007$); even though the grip strength of SQP group decreased, it was still significantly higher (t, -2.113, [95 %CI, -3.755 to -0.123], $p = 0.037$); the score for Mini Nutritional Assessment Short Form significantly increased ($p < 0.05$); Pittsburgh Sleep Quality Index, TCM syndrome score, C-reactive protein level, and blood urea nitrogen level significantly decreased ($p < 0.05$); and the change in the score of International Physical Activity

Abbreviations: AWGS, Asian Sarcopenia Group for Sarcopenia; BIA, Bioelectrical impedance analysis; BUN, Blood urea nitrogen; CRP, C-reactive protein; CKD, Chronic kidney disease; FTSST, Five Times Sit-to-Stand Test; IPAQ-SF, International Physical Activity Questionnaire-Short Form; ITT, Intention-to-treat; MNA-SF, Mini nutritional assessment-short form; MSTN, Myostatin; PP, Per protocol; PSQI, Pittsburgh sleep quality index; ROS, Reactive oxygen species; SQP, Shen-Qi Paste; SMI, Skeletal muscle mass index; SCr, Serun creatinine; SF-36, 36-Item Short Form Health Survey; SUA, Serum uric acid; TCM, Traditional Chinese Medicine; UPLC-Q-TOF-MS, Ultra-Performance Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry.

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Questionnaire-Short Form was statistically significant ($p = 0.026$). There were no notable differences between the two groups in terms of Fatigue, Resistance, Aerobic Capacity, Illnesses, and Loss of Weight scale score, FTSST scores, SF-36 score, Irisin level, serum creatinine level, hemoglobin level, and metabolic markers ($p > 0.05$). *Conclusion:* SQP has the potential to notably enhance muscle mass; therefore, it could be a viable option for treating sarcopenia. Further research should investigate its effectiveness in a broader group of patients and delve into its mechanism of action to offer more detailed evidence for SQP in treating sarcopenia.

Introduction

Chronic renal failure is marked by a glomerular filtration rate below 15 ml/min/1.73 m^2, which corresponds to stage 5 chronic kidney disease (CKD) (Klahr, 1991). Treatment options include renal transplantation, hemodialysis, peritoneal dialysis, or continuous renal replacement therapy, which are all aimed at extending patient survival (Bello et al., 2022; Klahr, 1991; Voora et al., 2019). Globally, over 3.5 million individuals are affected by chronic renal failure; in the United States, 540,000 require maintenance dialysis, with 90 % requiring hemodialysis (Flythe et al., 2024). Approximately 40 % of individuals live for five years once maintenance dialysis is initiated (Flythe et al., 2024).

Sarcopenia is marked by a reduction in muscle mass, strength, and/or physical function (Cruz-Jentoft et al., 2019). For individuals with CKD, sarcopenia is a notable complication, and it affects 24.5 % of patients globally (Duarte et al., 2024). The prevalence of sarcopenia in dialysis patients (including peritoneal dialysis and hemodialysis) was higher than that in patients not requiring dialysis treatment (26.2 % vs. 3.0 %); the prevalence of sarcopenia in dialysis patients was as high as 28.5 % (Duarte et al., 2024; Shu et al., 2022). It adversely affects prognosis; contributes to frailty, falls, disability, and depression; and is correlated with enhanced mortality risk (Ribeiro et al., 2022; Shu et al., 2022). The underlying causes of sarcopenia in dialysis patients are multifaceted, including metabolic disturbances such as insulin resistance, acid-base imbalances, and electrolyte abnormalities associated with renal failure; persistent chronic inflammation; dialysis-induced protein catabolism with protein synthesis suppression, which results in negative nitrogen balance; dietary restrictions; nutritional deficiencies; and decreased physical activity (Massini et al., 2023; Wang et al., 2023). Together, these aspects speed up the process of muscle atrophy.

As muscle loss-related diseases become more prevalent with aging, the demand for effective sarcopenia treatments continues to increase. Managing sarcopenia in connection with CKD primarily relies on nutritional support and exercise rehabilitation because no pharmacological treatment has been proven effective (Consensus Expert Group on Diagnosis et al., 2024). Patients undergoing dialysis treatment face dietary restrictions, nutritional deficiencies, and limited physical activity, which restrict the effectiveness of these interventions, leading to variable outcomes that fail to meet clinical demands (Lu et al., 2021; March et al., 2022; Massini et al., 2023). The contrast between theoretical gains and actual outcomes points to the critical need for improved treatment strategies in patients with sarcopenia undergoing dialysis treatment. Consequently, investigating alternative strategies, such as the use of Chinese herbal medicine, holds significant potential in addressing this condition.

For >2000 years, Traditional Chinese Medicine (TCM) has been an important part of Chinese cultural heritage and has been used for treating muscle disorders and supplementing dietary regimens. Emerging evidence suggests that some TCM compounds may improve muscle atrophy (Zhang et al., 2017; Zhu et al., 2017). A recent systematic review suggested that TCM compounds could address key sarcopenia pathways through multiple mechanisms, including skeletal muscle metabolism modulation, anti-inflammatory effects, mitochondrial modulation, and myocyte apoptosis reduction (Zhang et al., 2024). Although Chinese clinical practice often involves the use of TCM formulas to treat sarcopenia, the results have not been strictly verified; this gap is particularly evident in dietary treatment methods involving Shen-Qi Paste (SQP), which implement the concept of "same origin of medicine and food."

TCM theory posits that dialysis-related sarcopenia is fundamentally attributed to spleen-kidney deficiency, which is characterized by impaired nutrient transformation and essence distribution that ultimately manifests as muscle wasting (Wei et al., 2024). SQP is a TCM dietary formulation based on the theory of "same origin of medicine and food" in TCM. The SQP is composed of eight substances, all of which can be safely used in food. These substances include seven medicine and food-derived substances—Huang Qi (*Astragalus membranaceus*), Dang Shen (*Codonopsis pilosula*), Du Zhongye (*Eucommia ulmoides*), Huang Jing (*Polygonatum kingianum*), Shan Yao (*Dioscorea opposita*), Fu Lin (*Poria cocos*), Mai Ya (*Hordeum vulgare*), as well as Hong Qu (*Fermentum Rubrum*), which is used as a traditional food additive. All of these ingredients comply with the relevant national food safety regulations of China (Huang et al., 2022; Yan et al., 2023). These ingredients are soaked in water, extracted, precipitated, filtered, and concentrated; thereafter, the concentrate is boiled to make a paste. Supplemental Tables 1 and 2 show the scientific names, family names, parts used, reported bioactivities, isolated compounds, and identified bioactive compounds of the main ingredients of SQP. The National Food Products Administration approved the patent for SQP in 2023 (Approval No SC10633012713026). SQP is designed to tonify the spleen and kidneys, harmonize the stomach, promote digestion, build muscles, and strengthen bones. This formulation is indicated for the treatment of sarcopenia. Currently, traditional herbal ingredients in this SQP compound have been shown to have positive effects on muscle growth. Research indicates that *Astragalus* monomer can reduce peritoneal fibrosis and muscle wasting in mice with CKD through the androgen receptor/transforming growth factor beta 1 signaling pathway (Sheng et al., 2024). Active ingredients in *Eucommia* trigger the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway; suppress muscle-specific RING finger protein 1 (MuRF1), atrogin-1, and myostatin (MSTN), which are muscle degradation proteins; and effectively mitigate muscle loss and functional decline (Koo et al., 2024). Additionally, the key components of *Polygonatum sibiricum* have been demonstrated to reduce oxidative strain and issues with mitochondria in C2C12 myotubes, enhance muscle mass and strength, decrease reactive oxygen species (ROS) levels in skeletal muscle, and increase antioxidant enzyme activity (Chen et al., 2024). These results offer theoretical backing for SQP to postpone muscle cell atrophy and act as a protective and therapeutic measure for sarcopenia. Nevertheless, even with the application of SQP in TCM clinical settings, the absence of a comprehensive clinical efficacy evaluation remains a significant limitation. To address this gap, the present study conducted a two-center, randomized, double-blind, placebo-controlled trial to assess the effectiveness and safety of SQP in treating dialysis patients with sarcopenia. Furthermore, serum metabolite changes related to sarcopenia were examined to provide a foundation for optimizing sarcopenia treatment and investigating the underlying mechanisms that might account for the effects of SQP.

Methods and design

Study design and participants

The clinical trial was conducted as a randomized, double-blind, parallel-group, and placebo-controlled study, involved two centers and

focused on patients with sarcopenia undergoing dialysis treatment. This study recruited patients undergoing maintenance hemodialysis treatment from the blood purification centers of two tertiary hospitals in Hangzhou, China (Hangzhou Hospital of TCM and First People's Hospital of Xiaoshan Hangzhou) between April 1, 2024, and December 20, 2024. The intervention was offered to patients who satisfied the set inclusion and exclusion standards. The participants were patients with clinical signs of sarcopenia and spleen-kidney deficiency syndrome. The research was granted approval by the Institutional Review Boards of Hangzhou Hospital of TCM (No. 2024KLL087, March 20, 2024 [12 months]) and First People's Hospital of Xiaoshan Hangzhou (Xiaoyi Medical Lunjian-Zi 2024-Section No 30, March 4, 2024 [12 months]). The study followed the Declaration of Helsinki, and the protocol was listed on the national health protection information platform of China (No. MR-33–24–012,106). All individuals provided their written informed consent prior to being enrolled. Fig. 1 presents the study flow chart.

Inclusion and exclusion criteria

The inclusion criteria consisted of : (1) patients undergoing maintenance hemodialysis treatment aged 45 years or older and undergoing regular hemodialysis for $\geq$ 3 months regardless of gender; (2) individuals diagnosed with sarcopenia according to the Asian Working Group for Sarcopenia 2019 (AWGS 2019); (3) patients diagnosed with spleen-kidney deficiency syndrome on the basis of TCM syndrome differentiation (He, 2006; Wei et al., 2024); (4) patients with stable conditions for at least 2 weeks, with infection, hypertension, electrolyte imbalance, diabetes, and other factors adequately managed; and (5) patients who voluntarily consented to participate and signed the informed consent form. The diagnostic criteria for sarcopenia established by the AWGS 2019 (Chen et al., 2020) include (1) muscle mass assessment using bioelectrical impedance analysis (Inbody S110, Biospace, Korea) (a skeletal muscle mass index [SMI] < 7.0 kg/m^2 in men, $<$ 5.7 kg/m^2 in women indicates muscle loss), (2) muscle strength evaluation via the Xiangshan electronic hand grip dynamometer EH101 (for individuals with internal fistulas, grip strength should be measured with the non-fistula hand, whereas those with catheters should use their dominant hand; values $<$ 28 kg for men and $<$ 18 kg for women suggest diminished grip strength), and (3) physical function evaluation by the five-times sit-to-stand test (FTSST) (a completion time $\geq$ 12 s indicates impaired function). A diagnosis of sarcopenia is made if the subject meets at least two criteria from (a), (b), or (c). For chronic renal failure (spleen-kidney deficiency syndrome) diagnosis based on TCM criteria (Chen et al., 2015; He, 2006), the (a) main symptoms include mental fatigue, asthenia, a dull complexion, cold limbs, lumbar and knee pain, nausea, and poor appetite, and the (b) secondary symptoms include dizziness and vertigo, muscle wasting, alopecia, loose teeth, sexual dysfunction, diarrhea, nocturia or oliguria, and low body weight. (c) Tongue and pulse manifestations may respectively present as a pale, purple or swollen, teeth-marked tongue or a deep, thready, or weak pulse. To confirm a diagnosis, there must be either two primary symptoms or one primary symptom and two secondary symptoms, in addition to tongue and pulse evaluations (Chen et al., 2015; He, 2006).

The criteria for exclusion encompassed the following:: (1) patients with implanted metal or electronic medical devices, such as pacemakers, contraindicated for bioelectrical impedance analysis use; (2) pregnant or lactating women; (3) patients with mental disorders (e.g., schizophrenia, depression, and anxiety) who are unable to cooperate; (4) patients with malignancies, severe gastrointestinal bleeding, active pulmonary tuberculosis, or other conditions affecting nutritional status; (5) patients with physical disabilities who were either unwilling to participate or unable to complete follow-up; (6) patients with poor treatment adherence; and (7) patients currently enrolled in other clinical

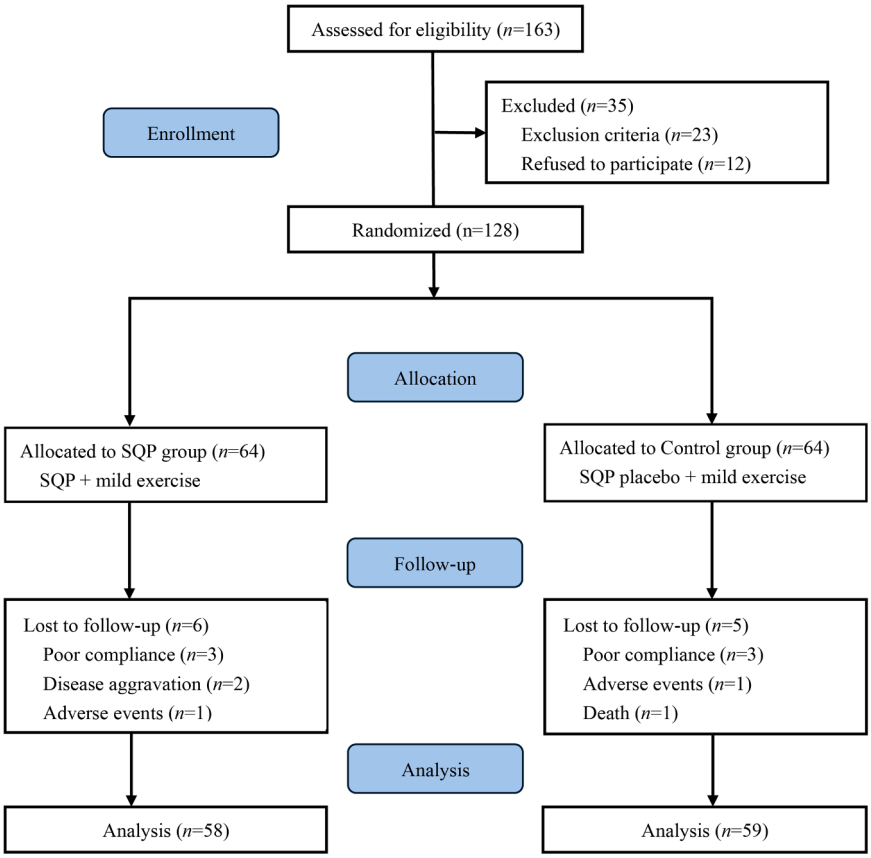

Fig. 1. Flow diagram of the selection of the study participants. SQP, Shen-Qi Paste.

trials or using TCM.

The withdrawal criteria included the following: (1) patients who cannot adhere to or cooperate with their prescribed treatment; (2) patients experiencing severe adverse reactions or complications during the trial, thus rendering continued participation unsuitable; and (3) individuals who were not tracked further, opted out, or deceased.

Sample size

The study utilized a randomized controlled trial design, referenced relevant literature, and applied the sample size formula $n = 2[(Z_\alpha + Z_\beta)\sigma/\delta]^2$ for comparing the means of two groups in a completely randomized framework (Woolson, 1987). The parameters were set as $\alpha = 0.05$, $\beta = 0.2$, and $1 - \beta = 0.8$, and a two-tailed test was used. The table presented $U_\alpha = 1.96$ and $U_\beta = 0.84$. The values of σ and δ estimated from the literature were 0.75 and 0.31, respectively, thus resulting in an initial sample size of approximately 92. To ensure an adequate number of valid cases, the sample size was increased by 20 %, thus bringing the total to 110 subjects, with 55 individuals in each group. Ultimately, 128 subjects participated in the intervention, and 117 subjects completed the entire intervention.

Randomization and blinding

Professional statisticians employed SPSS 27.0 software to simulate random number generation and create random grouping codes on the basis of case allocation numbers and ratios. Random code numbers were then assigned to eligible patients according to the order of medical visits to ensure a 1:1 allocation between the treatment and control groups. Both the researchers selecting the subjects and those performing the measurements were blinded to the random assignment process.

The study adopted a double-blind design and implemented the blinding process through a two-level coding system. The first level is the groups corresponding to each case number (Group A/Control Group, Group B/SQP Group), which is managed by independent statisticians. The second level involves the intervention measures corresponding to each group (SQP, placebo). The properties, appearance, smell, flavor, and specifications of the placebo are the same as those of the SQP, and they are kept by the paste management staff of the sub-centers. The researchers, participants and evaluators were blinded throughout the entire clinical trial process, meaning that they were unaware of the group allocation and intervention information.

Preparation of SQP and placebo

All intervention pastes in this trial were manufactured by certified preparation companies in compliance with national standards and food production quality management regulations. SQP is prepared by using extraction and purification processes. The *Astragalus membranaceus, Eucommia ulmoides, Codonopsis pilosula*, and other constituents undergoes the process of soaking, extraction, precipitation, concentration, boiling, and other processes. Thereafter, the concentrate is boiled down to make a paste. Supplementary Table 1 provides further details on this process. SQP and placebos were produced by Zhejiang Jing Cun-ren Technology Co., Ltd. (Zhejiang, China; NO. 20,231,229) in 15 g tubes of concentrated paste. To minimize potential biases from drug formulations and psychological factors of both patients and researchers, the placebos were prepared by mixing 1/30 of SQP with tremella and pear juice. The resulting product matched SQP in terms of appearance, packaging, odor, and specifications.

The quality of SQP was evaluated by the manufacturer, with assessments for thin layer identification, particle size, moisture content, solubility, filling volume variations, and microbial limits, all of which complied with industry standards. Nutritional content also met regulatory requirements, and tests revealed the absence of *Escherichia coli*, mold, yeast, or *Salmonella*. The SQP compound's components underwent analysis through ultra-performance liquid chromatography and quadrupole time-of-flight mass spectrometry, thus leading to the identification of 55 compounds through comparison with commercially available reference standards. Supplementary Table 2 and Fig. 2 listed the top 10 compounds ranked by intensity in both positive and negative ion modes. The paste was stored in a cool, ventilated area for subsequent use. Drug packaging, which was designed by the principal investigator, was distributed to each sub-center by an authorized distributor in accordance with subject enrollment numbers. The food quality inspection report of SQP is presented in the supplementary materials.

Intervention measures

Routine care that is tailored to the patient's underlying condition and hemodialysis requirements included targeted education on disease management, diet, exercise, psychology, and general health, along with standard care procedures such as vascular access maintenance. The observation record form was designed by the researcher to document follow-up data in a timely manner.

Participants in this study were placed in the SQP group or the control group. Along with routine care, subjects in the SQP group and control group were respectively administered oral SQP and placebo at 1 vial/15 g twice daily for 12 weeks. At the same time, all participants maintained low-intensity exercise (baduanjin or hand swing health exercises) for 20–30 min/d at a frequency of 3–4 d/wk (excluding dialysis days) during the trial. Both SQP and the placebo were provided in 15 g sticks and was intended for direct oral intake or mixed with 20–30 ml of warm water. Follow-up evaluations and paste distribution occurred every 2 weeks. To ensure adherence, the packaging of used pastes was collected for recycling after each distribution. All SQP and placebo were supplied by the sponsor and adhered to the blinding protocols and quality standards. At the conclusion of the trial, any remaining trial paste was collected and destroyed by the sponsor.

The intervention plan remained consistent throughout the trial, continuing until the trial concluded or until the withdrawal criteria were met. Prior to the intervention, patients were fully informed by the researcher that the use of any other Chinese medicine or drugs that could influence the outcome of the study was prohibited, except for medications that are routinely taken. In the event of withdrawal, the researcher should document the withdrawal thoroughly and complete the most recent assessment for each relevant indicator.

Outcomes

Patient assessments, including evaluations of primary and secondary outcomes, blood parameters, and safety indicators, were conducted before and after the intervention.

Primary outcomes

The primary outcomes was the variation in metrics related to sarcopenia from baseline to week 12, including muscle mass on the SMI, handgrip strength, and performance on the FTSST.

Secondary outcomes

The secondary outcomes included changes in the Mini Nutritional Assessment Short Form (MNA-SF); Fatigue, Resistance, Aerobic Capacity, Illnesses, and Loss of Weight (FRAIL) scale; International Physical Activity Questionnaire-Short Form (IPAQ-SF); Pittsburgh Sleep Quality Index (PSQI); 36-Item Short Form Health Survey (SF-36); and TCM syndrome score from baseline to week 12.

Serum biomarkers of aging and inflammation

MSTN and Irisin are muscle-specific biomarkers, whereas

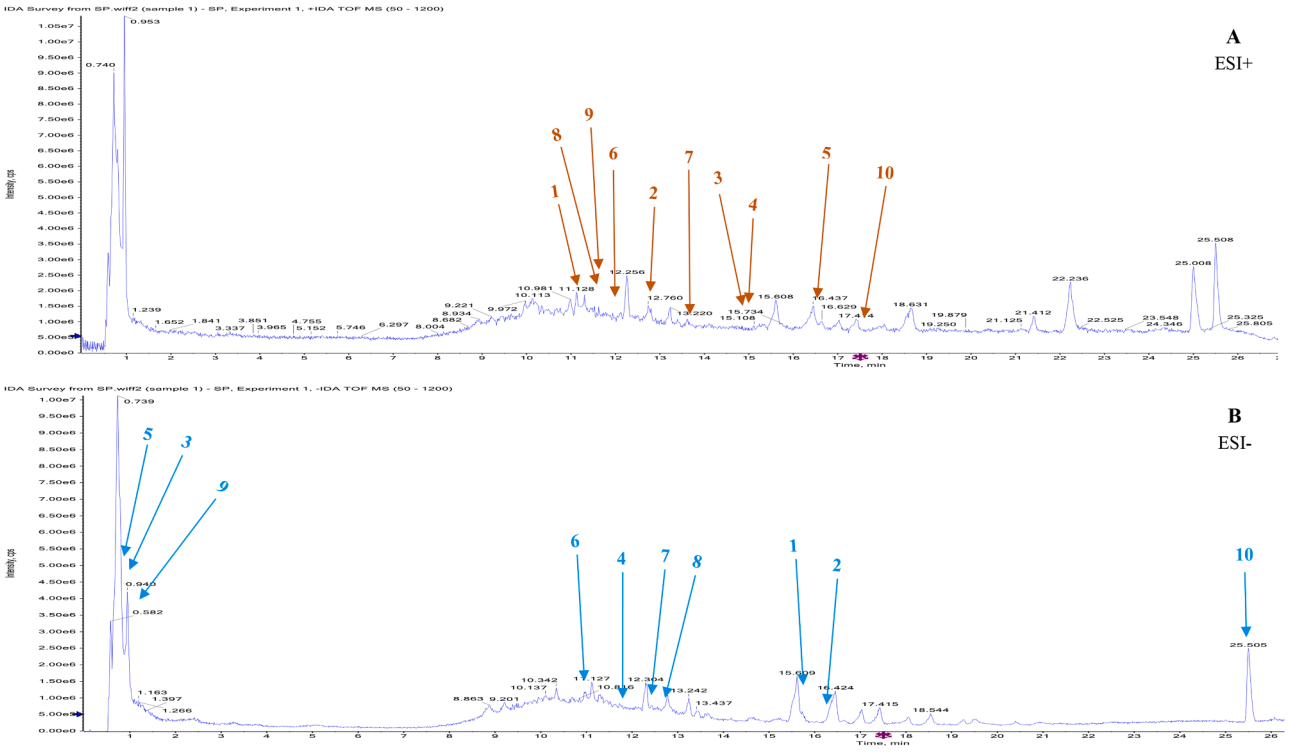

Fig. 2. UPLC-Q-TOF-MS chromatograms of extraction of Shen-Qi Paste. (A) Positive pattern. (B) Negative pattern.

inflammatory markers such as C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) are connected to sarcopenia. This prospective study involved collecting blood samples before and after the intervention, and conducting serum separation to assess changes in biomarkers. Each time blood is collected, after the patient fasting for 8 h, the clinical nurse takes the blood sample, which is then transported to the hospital and school laboratory by the designated personnel. CRP levels were measured using the same method across both sub-centers. For the other 3 biomarkers, 42 patients were selected for analysis, and enzyme-linked immunosorbent assay kits (Jiangsu Jingmei Biotechnology Co., Ltd.) were used to quantify the serum levels of MSTN, Irisin, and TNF-α. Statistical analysis was applied to all biomedical data, which are shown as the mean ± standard deviation from a minimum of three separate experiments. The comparison between the two groups was conducted using a *t*-test, considering a $p < 0.05$ as statistically significant.

Safety

The safety evaluation parameters in this study included general condition monitoring (body temperature, pulse, blood pressure, and respiration) and an adverse event reporting table, which was designed to record any adverse reactions during the trial, including vomiting and diarrhea. All patients with at least one efficacy assessment were included in the safety analysis. The incidence of adverse events, reactions, and withdrawal-related events was summarized. To assess the incidence of systems and symptoms/signs, a chi-square test was used to assess differences between groups. Additional safety assessments included laboratory parameters for drug safety evaluation, such as hemoglobin, serum creatinine (SCr), blood urea nitrogen (BUN), serum uric acid (SUA), glucose, cholesterol, triglycerides, and parathyroid hormone. These indicators were classified and subjected to statistical analysis on the basis of clinical relevance.

Statistical analysis

IBM SPSS Statistics 27.0 (IBM Corporation, Armonk, NY, USA) was used to carry out the statistical analysis on the total number of patients enrolled in both groups, demographic data, efficacy indicators, and safety measures. The analysis population consisted of patients who met the primary endpoint criteria. Efficacy was evaluated using both the intention-to-treat (ITT) set and per protocol (PP) set. The ITT approach included all randomized participants who received treatment and underwent baseline efficacy assessment and at least one post-baseline efficacy assessment. The PP set excluded subjects with significant protocol deviations from the ITT to ensure that the analysis focused on those who adhered to trial procedures and to provide a precise evaluation of intervention outcomes. Meanwhile, exploratory subgroup analyses by age were conducted for primary outcomes, with acknowledgment of their hypothesis-generating nature.

Categorical data were summarized as frequencies or proportions and compared between groups using the chi-square test. Continuous variables were first assessed for normality using the Shapiro-Wilk test and for homogeneity of variance using Levene's test. Normally distributed data with equal variances were expressed as mean ± standard deviation and analyzed using the independent samples *t*-test for between-group comparisons or the paired *t*-test for within-group comparisons (pre- vs. post-intervention). If normality was met but variances were unequal, the corrected *t*-test (Welch's *t*-test) was applied. Non-normally distributed data were presented as median (interquartile range) and analyzed using Mann-Whitney U test for between-group comparisons or Wilcoxon signed-rank test for within-group comparisons. The study compared primary and secondary efficacy measures within and between groups pre- and post-intervention and calculated the 95 % confidence interval for the differences in symptom scores. Adverse event occurrences across the groups were evaluated using the chi-square test, which was accompanied by a list of these events. Statistical significance was determined with a threshold of $p < 0.05$.

Results

Baseline features of the subjects

Among the dialysis patients, 163 were diagnosed with sarcopenia (45–89 years of age) were screened, and 128 participated in the intervention (Supplementary Table 3). The patients were allocated randomly to the SQP and control groups for intervention between April and December 2024, and all individuals were incorporated into the ITT analysis. In the SQP group, 2 patients exhibited poor compliance, 2 experienced disease exacerbation, and 2 reported adverse reactions, thus resulting in 58 participants (90.6 %) completing the trial. In the control group, 3 patients had poor compliance, 1 experienced adverse reactions, and 1 died from respiratory failure, thus resulting in 59 participants (92.2 %) completing the trial. Consequently, 117 participants completed the intervention, and efficacy was assessed using PP analysis. Fig. 1 shows the patient disposition. The results confirmed the success of randomization: both groups were comparable across most variables, and no notable differences were observed in the baseline traits (Table 1).

Primary outcomes

Regarding muscle mass, the SQP group exhibited a notably higher SMI index than the control group following 12 weeks by ITT analysis (*t*, −0.384, [95 %CI, −0.66 to −0.109], $p = 0.007$). Additionally, the SMI index in the SQP group increased significantly post-intervention in contrast to pre-intervention (*t*, −0.248, [95 %CI, −0.37 to −0.127], $p < 0.001$). Concerning muscle strength, both groups experienced a decrease in grip strength ($p < 0.01$), but ITT analysis revealed that the SQP group exhibited significantly greater grip strength compared to the control group after 12 weeks of intervention (*t*, −2.113, [95 %CI, −3.755 to −0.123], $p = 0.037$). Regarding physical function, improvement in FTSST was observed in both groups, and significant improvements were observed in the SQP group compared with their pre-intervention status (*t*, 2.336, [95 %CI, 0.257 to 3.297], $p = 0.023$) (Table 2 and Fig. 3).

Table 1
Baseline characteristics of the two study groups[1].

Variables	Intention-to-treat set			Per protocol set		
	SQP ($n = 64$)	Control ($n = 64$)	*P*	SQP ($n = 58$)	Control ($n = 59$)	*P*
Males	37 (57.8)	35 (54.7)	0.859	33 (56.9)	32 (54.2)	0.775
Age, year	65.89 ± 9.48	65.58 ± 8.65	0.846	65.76 ± 9.87	65.34 ± 8.87	0.809
Height, cm	162.97 ± 7.62	162.56 ± 8.14	0.771	163.19 ± 7.83	162.20 ± 7.82	0.497
Weight, kg	55.36 ± 7.90	54.24 ± 9.31	0.464	55.39 ± 8.05	54.01 ± 9.55	0.399
BMI, kg/m^2	20.86 ± 2.75	20.47 ± 2.78	0.432	20.82 ± 2.83	20.45 ± 2.83	0.491
Smoker	9 (14.1)	13 (20.3)	0.647	9 (15.5)	13 (22.0)	0.705
Alcohol	7 (10.9)	5 (7.8)	1.000	7 (12.1)	5 (8.5)	0.756
Fruit intake	32 (50.0)	27 (42.2)	0.379	27 (46.6)	24 (40.7)	0.524
Vegetable intake	60 (93.8)	61 (95.3)	0.700	55 (94.8)	56 (94.9)	0.983
Duration of dialysis, year	5.95 ± 5.83	6.87 ± 6.58	0.403	5.99 ± 5.89	6.83 ± 6.55	0.472
Polypharmacy	23 (35.9)	28 (43.8)	0.279	21 (36.2)	28 (47.5)	0.219
Comorbidity	43 (67.2)	43 (67.2)	1.000	40 (69.0)	41 (69.5)	0.951

[1] Values are mean ± SD or *n* (%); SQP, Shen-Qi Paste; BMI, Body Mass Index.

Secondary outcomes

Renal function index

In addition to SCr, several markers of renal injury showed improvement following the intervention (Supplementary Table 4). PP analysis indicated that the control group had higher BUN levels than the SQP group ($p = 0.01$). Additionally, SUA levels in the SQP group were significantly lower than the baseline ($p = 0.03$). However, The intervention led to no notable differences between the two groups ($p > 0.05$).

Nutritional status and frailty index

The MNA-SF, which serves as a quick anddependable method for evaluating nutritional status, particularly in elderly and chronically ill patients, indicated notable improvements in both groups. The SQP group showed a significant increase in MNA-SF scores post-intervention compared to the control group ($p < 0.05$) and also showed a substantial increase from pre-intervention levels ($p < 0.001$) (Table 2, Fig. 4).

The FRAIL scale was an easy-to-use tool for frailty assessment and showed a modest reduction in frailty scores in both groups after intervention. However, no significant statistical difference was detected ($p > 0.05$) (Table 2, Fig. 4).

Physical activity and sleep quality

The IPAQ-SF is a widely used tool for assessing physical activity and is suitable for evaluating the physical activity levels of adults over the past 7 d The results indicated an obvious improvement in physical activity energy expenditure (MET-min/wk) in both groups post-intervention. The IPAQ-SF score was significantly elevated in the SQP group compared with the control group ($p < 0.001$), and statistical significance was observed between the two groups of the difference in d-values (from baseline to post-intervention) ($p = 0.026$) (Table 2, Fig. 4).

The PSQI is a validated and effective tool for assessing sleep quality and is widely applied in clinical and research scenarios. The results indicated that the PSQI score and d-value for the SQP group were less than those of the control group ($P<0.01$) and before the intervention ($p < 0.001$) (Table 2, Fig. 4).

Serum muscle-specific biomarkers and inflammatory factors

Muscle-specific biomarkers are typically indicative of muscle mass and strength loss. This study revealed a considerable decrease in MSTN levels after SQP intervention compared with before the intervention ($p = 0.001$), but no notable differences were observed between the two groups. After the intervention, the SQP group showed a marginal decrease in Irisin levels, though no statistically significant difference was observed between groups ($p > 0.05$) (Table 2, Fig. 5).

Chronic low-grade inflammation is considered a potential pathophysiological factor in sarcopenia. PP analysis demonstrated a significant decline in CRP levels post-intervention in contrast to the control group ($p = 0.028$), with CRP levels in the SQP group showed a marked decrease from the pre-treatment levels ($p < 0.05$). The SQP group demonstrated a modest reduction in TNF-α levels after the intervention, while no significant differences between the two groups were observed ($p > 0.05$) (Table 2, Fig. 5).

Quality of life and TCM syndrome score

The SF-36 is a widely recognized tool for assessing quality of life and is frequently used in clinical evaluations of health status. SF-36 scores increased in both groups relative to baseline ($p < 0.05$), but no significant differences were observed between the groups ($p > 0.05$) (Table 2, Fig. 4).

Both groups demonstrated significant reductions in TCM syndrome scores post-treatment ($p < 0.01$), with notable differences observed between the groups. There was a notable decrease in the TCM syndrome score and d-value for the SQP group compared with the control group ($p < 0.05$) (Table 2, Fig. 4).

Table 2
Comparisons the primary and secondary outcomes after treatment between and within the two groups.

Outcomes	Intention-to-treat set			Per protocol set		
	SQP group ($n = 64$)	Control group ($n = 64$)	*P (Δbetween groups)	SQP group ($n = 58$)	Control group ($n = 59$)	*P (Δbetween groups)
Primary outcomes						
SMI (kg/m^2)						
Baseline	5.87 ± 0.69	5.72 ± 0.81	0.262	5.90 ± 0.69	5.68 ± 0.81	0.121
12 weeks	6.11 ± 0.80	5.73 ± 0.78	0.007	6.16 ± 0.79	5.73 ± 0.79	0.003
D-value	0.25 ± 0.49	0.01 ± 0.27	0.001	0.26 ± 0.51	0.04 ± 0.24	0.004
**P(ΔWithin group)	<0.001	0.68		<0.001	0.186	
Handgrip strength (kg)						
Baseline	20.81 ± 7.48	20.04 ± 8.61	0.593	20.79 ± 7.53	20.06 ± 8.90	0.635
12 weeks	18.83 ± 4.85	16.89 ± 5.52	0.037	18.59 ± 4.62	16.77 ± 5.64	0.058
D-value	−1.98 ± 5.23	−3.15 ± 5.13	0.201	−2.19 ± 5.41	−3.29 ± 5.30	0.270
**P(ΔWithin group)	0.004	<0.001		0.003	<0.001	
FTSST (s)						
Baseline	14.31 ± 6.98	15.13 ± 7.59	0.533	14.48 ± 7.26	15.36 ± 7.69	0.528
12 weeks	12.53 ± 4.17	14.08 ± 9.42	0.234	12.61 ± 4.30	14.19 ± 9.69	0.258
D-value	−1.77 ± 6.09	−1.05 ± 7.63	0.553	−1.87 ± 6.38	−1.17 ± 7.87	0.601
**P(ΔWithin group)	0.023	0.289		<0.001	0.186	
Secondary outcomes						
MNA-SF						
Baseline	11.56 ± 1.60	11.36 ± 1.95	0.520	11.53 ± 1.63	11.32 ± 1.99	0.528
12 weeks	12.34 ± 1.28	11.59 ± 1.39	0.002	12.31 ± 1.31	11.73 ± 1.26	0.016
D-value	0.78 ± 1.30	0.23 ± 1.96	0.065	0.78 ± 1.35	0.41 ± 1.91	0.231
**P(ΔWithin group)	<0.001	0.342		<0.001	0.108	
FRAIL score						
Baseline	2.34 ± 0.95	2.30 ± 0.83	0.766	2.38 ± 0.91	2.32 ± 0.84	0.725
12 weeks	2.22 ± 1.08	2.08 ± 1.01	0.448	2.24 ± 1.07	2.05 ± 0.97	0.314
D-value	−0.13 ± 1.18	−0.22 ± 1.20	0.656	−0.14 ± 1.24	−0.27 ± 1.22	0.557
**P(ΔWithin group)	0.398	0.15		0398	0.092	
IPAQ-SF						
Baseline	586.85 ± 646.28	721.14 ± 1099.77	0.402	597.88 ± 670.52	765.47 ± 1133.64	0.332
12 weeks	1377.49 ± 1442.65	1003.11 ± 1060.45	0.097	1462.75 ± 1487.19	1077.53 ± 1070.87	0.110
D-value	790.64 ± 1330.77	281.97 ± 1222.14	0.026	864.87 ± 1377.47	312.05 ± 1268.66	0.026
**P(ΔWithin group)	<0.001	0.07		<0.001	0.064	
PSQI						
Baseline	9.09 ± 4.12	9.36 ± 4.20	0.719	9.07 ± 4.11	9.25 ± 4.24	0.811
12 weeks	6.95 ± 3.55	9.31 ± 3.91	<0.001	6.84 ± 3.50	9.07 ± 3.82	0.001
D-value	−2.14 ± 4.01	−0.05 ± 4.05	0.004	−2.22 ± 4.19	−0.19 ± 4.17	0.010
**P(ΔWithin group)	<0.001	0.926		<0.001	0.733	
SF-36						
Baseline	58.23 ± 11.23	57.39 ± 12.70	0.696	58.29 ± 11.49	57.06 ± 12.74	0.585
12 weeks	62.71 ± 8.58	62.58 ± 9.90	0.940	63.34 ± 8.38	61.79 ± 8.76	0.332
D-value	4.48 ± 11.25	5.18 ± 14.56	0.759	5.05 ± 11.67	4.74 ± 14.16	0.896
**P(ΔWithin group)	0.002	0.006		0.002	0.013	
TCM syndrome score						
Baseline	16.34 ± 2.99	15.52 ± 2.56	0.095	16.38 ± 3.11	15.36 ± 2.57	0.054
12 weeks	8.91 ± 2.69	10.20 ± 2.87	0.009	8.34 ± 2.11	9.75 ± 2.46	0.001
D-value	−7.44 ± 3.33	−5.31 ± 2.87	<0.001	−8.04 ± 2.88	−5.61 ± 2.79	<0.001
**P(ΔWithin group)	<0.001	<0.001		<0.001	<0.001	
MSTN						
Baseline	-	-	-	388.63 ± 34.29	379.72 ± 36.97	0.428
12 weeks	-	-	-	377.21 ± 28.01	378.59 ± 32.90	0.885
D-value	-	-	-	−11.42 ± 14.16	−1.12 ± 18.99	0.055
**P(ΔWithin group)	-	-	-	0.001	0.795	
Irisin						
Baseline	-	-	-	288.07 ± 27.86	274.61 ± 22.95	0.099
12 weeks	-	-	-	282.78 ± 24.13	274.68 ± 20.38	0.254
D-value	-	-	-	−5.28 ± 12.74	0.07 ± 14.19	0.210
**P(ΔWithin group)	-	-	-	0.072	0.982	
CRP						
Baseline	5.97 ± 7.77	6.12 ± 6.65	0.908	6.12 ± 8.05	6.34 ± 6.82	0.875
12 weeks	3.89 ± 4.29	6.49 ± 8.79	0.042	3.50 ± 3.76	6.17 ± 8.03	0.028
D-value	−2.33 ± 7.19	0.47 ± 7.57	0.043	−2.52 ± 7.29	0.27 ± 10.14	0.096
**P(ΔWithin group)	0.015	0.643		0.011	0.939	
TNF-α						
Baseline	-	-	-	910.06 ± 84.19	911.94 ± 108.79	0.951
12 weeks	-	-	-	906.74 ± 51.71	914.53 ± 88.25	0.922
D-value	-	-	-	6.69 ± 56.51	2.59 ± 55.01	0.816
**P(ΔWithin group)	-	-	-	0.594	0.835	

Abbreviation: SQP, Shen-Qi Paste; SMI, Skeletal muscle mass index; FTSST, Five Times Sit to Stand Test; MNA-SF, Mini-nutritional Assessment Short Form; IPAQ, International Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form 36; MSTN, Myostatin; CRP, C-reactive protein; TNF-α, Tumor Necrosis Factor-α; IL, Interleukin.
D-value refers to the difference before and after intervention. *P was the compared values between the two groups; **P was the compared value of each group before and after intervention (baseline and 12 weeks).

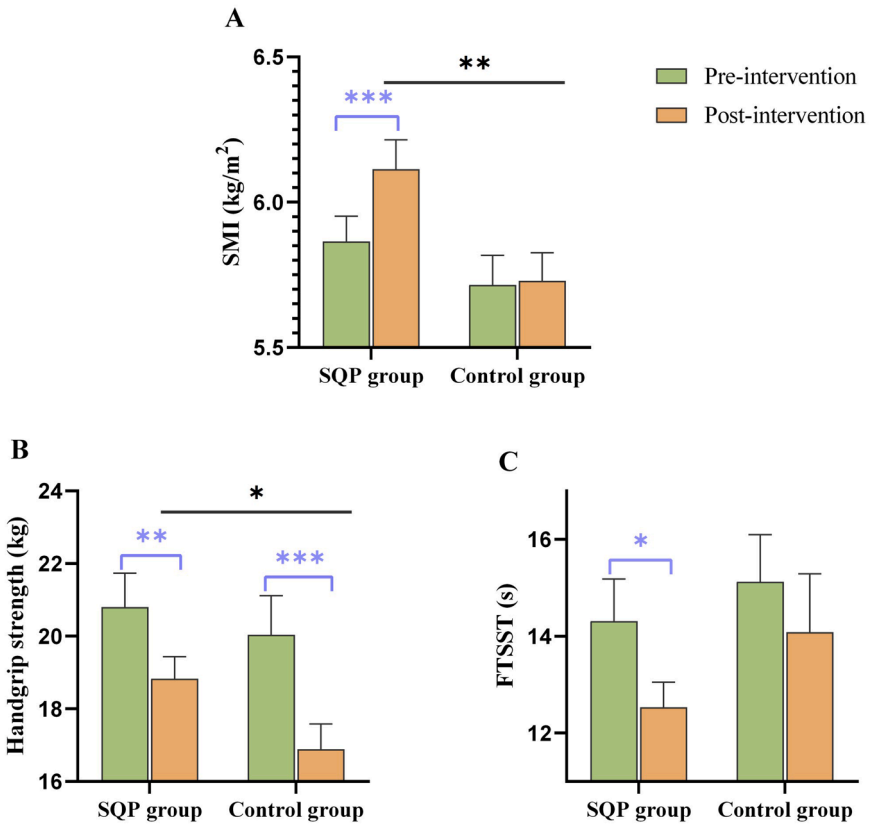

Fig. 3. The changes of SMI, handgrip strength and FTSTT were observed in SQP group and control group pre-intervention and post-intervention by ITT analysis. (A) changes in SMI; (B) changes in handgrip strength; (C) changes in FTSTT. SMI, skeletal muscle mass index; FTSST, Five Times Sit-to-Stand Test; SQP, Shen-Qi Paste; ITT, intention-to-treat.

Subgroup analysis for the primary outcomes by age

Sarcopenia, which is closely linked to aging, exhibits a significant increase in incidence with advancing age. The research concentrated on patients who are middle-aged and older. A subgroup analysis based on the latest World Health Organization age classification was conducted, and the subjects were divided into three groups: 45–59 years (middle aged), 60–74 years (young elderly), and 75–89 years (elderly). This analysis aimed to assess the effect of SQP on sarcopenia across different age groups. The results indicated improvements in SMI, handgrip strength, and FTSST in both groups across all age ranges following the intervention. Notably, a significant increase of SMI was observed in the middle-aged subgroup of the SQP group compared with the control group ($p = 0.017$), and the young-elderly subgroup of the SQP group had a significantly enhanced d-value of SMI compared with the control group ($p = 0.01$). However, handgrip strength and FTSST did not show significant variations across the age subgroups between the two groups ($p > 0.05$) (Table 3).

The SQP group showed significant improvement over the control group in terms of sarcopenia evaluation indicators. In the middle-aged and young-elderly subgroups, the SMI index in the SQP group significantly increased relative to its levels prior to the intervention ($p < 0.05$), but no significant change was observed in the elderly subgroup ($p > 0.05$). Grip strength decreased in both groups after intervention, and statistically significant differences were found between each age subgroup within both groups compared with the pre-intervention levels ($p < 0.01$). Notably, in the young-elderly subgroup, the SQP group had a lower reduction in grip strength (0.82 kg) than the control group (3.28 kg), but no significant differences were observed ($p > 0.05$). The other two subgroups did not exhibit this difference, thus this points to the need for additional research with a larger sample size to confirm the efficacy. The SMI index in the SQP group increased notably from pre-intervention levels ($p < 0.05$), but there were no significant changes in the FTSST among the age subgroups of both groups compared with the pre-intervention levels ($p > 0.05$) (Table 3). Some subgroup parameters differed significantly, but sample sizes were limited. This could be due to the limited sample size and the natural variability in the data. Therefore, these results should be interpreted carefully, and studies with larger sample sizes are needed for verification.

Safety and adverse events

A total of 128 individuals with at least one follow-up were part of the ITT analysis. A significant portion of patients in each group complied with the study protocol, and serious adverse reactions were absent in the reports. Most adverse events were typically mild and bearable, and their incidence was similar between groups. In the SQP group, 5 out of 64 patients (7.8 %) experienced adverse reactions, which were primarily mild oral and gastrointestinal discomfort (2 cases of oral ulcers, 2 of vomiting, and 1 of diarrhea). In the control group, 3 out of 64 patients (4.7 %) experienced adverse events, mainly mild gastrointestinal symptoms (2 cases of diarrhea and 1 of vomiting). Of the 8 adverse events reported, 3 participants (37.5 %) who took Chinese medicine for the first time were deemed to be possibly related to the intervention, including diarrhea. This is because certain herbal components in TCM may moderately enhance intestinal motility, which can lead to transient mild diarrhea in first-time users, typically resolving with physiological adaptation. One patient from each group withdrew because of adverse reactions, whereas the remaining participants completed the follow-up (Table 4). Secondary outcomes, including hemoglobin, glucose, cholesterol, triglycerides, and parathyroid hormone, demonstrated that there were no notable differences between or within the groups duration the study (Supplementary Table 4).

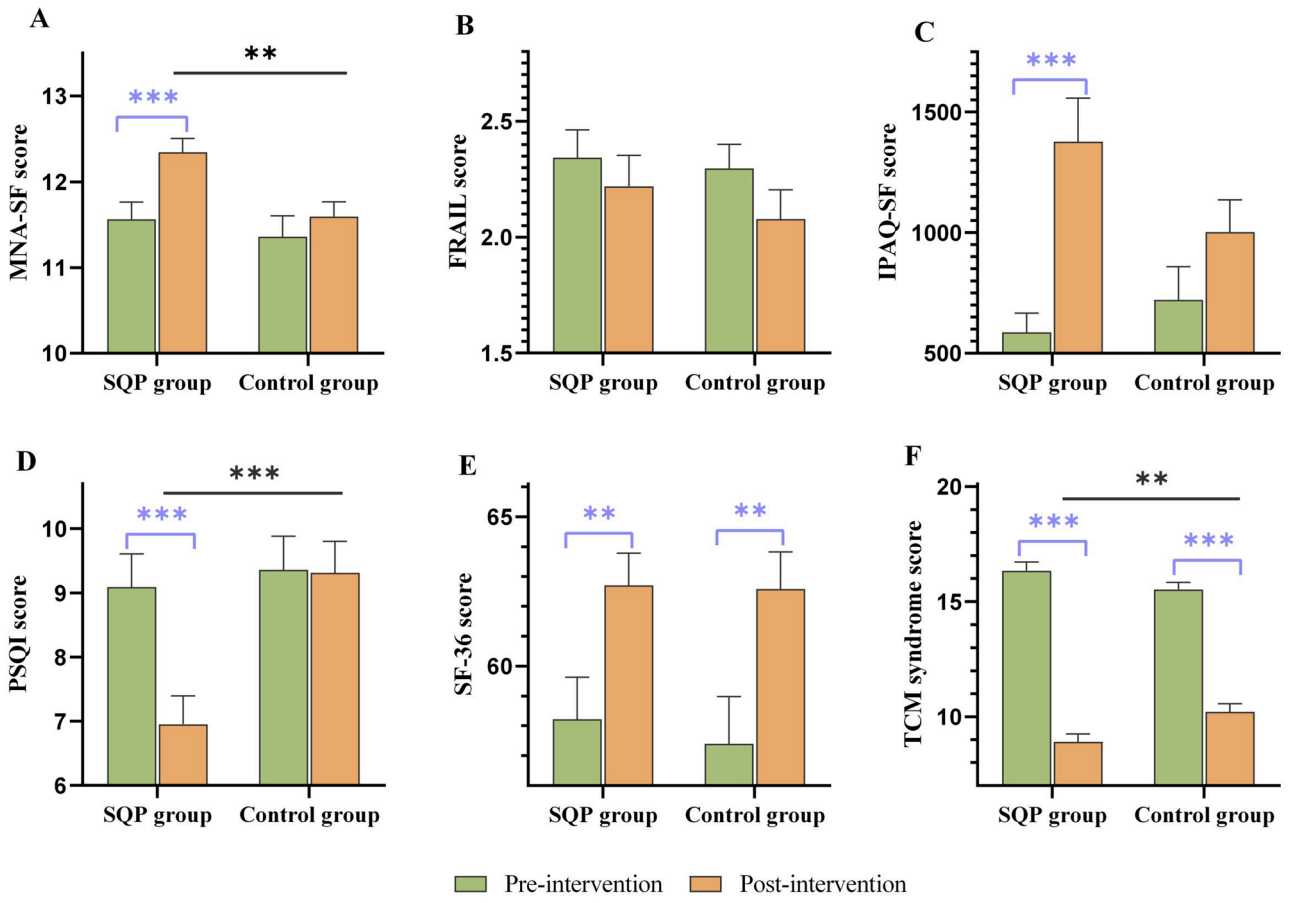

Fig. 4. The changes of MNA-SF score, FRAIL socre, IPAQ-SF score, PSQI score, SF-36 score and TCM syndrome score were observed in SQP group and control group pre-intervention and post-intervention by ITT analysis. (A) changes in MNA-SF score; (B) changes in FRAIL score; (C) changes in IPAQ-SF score; (D) chnges in PSQI score; (E) changes in SF-36 score; (F) changes in TCM syndrome score. MNA-SF, Mini Nutritional Assessment-Short Form; FRAIL, FRAIL Scale; IPAQ-SF, International Physical Activity Questionnaire-Short Form; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form Health Survey-36; TCM,Traditional Chinese Medicine; ITT, Intention-to-Treat.

Discussion

To the best of our knowledge, this is the first two-center, randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of a TCM dietary formulation (SQP) for sarcopenia. Although nutritional and exercise interventions have been widely studied in sarcopenia management-particularly in CKD patients-SQP uniquely combines TCM theory (same origin of medicine and food) to target the root pathology (spleen-kidney deficiency) rather than just the symptoms. Unlike pharmacological options with potential side effects, SQP offers a natural, well-tolerated alternative, particularly for patients undergoing dialysis treatment. Our research indicates that SQP has a robust and statistically significant protective effect in patients with sarcopenia undergoing dialysis treatment. Furthermore, the lack of serious side effects implies that SQP is a safe and potentially promising candidate for preventing the progression of sarcopenia.

Prior research utilizing nutritional interventions has discovered that protein (Nasimi et al., 2023), essential amino acids (Hey et al., 2024), vitamin D (Midttun et al., 2024), and oral nutrient supplements (Bear et al., 2019) can effectively treat sarcopenia. Nonetheless, there have been some contentious findings. Standardized criteria for nutritional intake in sarcopenia are currently absent, such as a protein intake recommendation of 1.2–1.5 g/kg (Chinese Society of Geriatric Medicine, 2019), while higher levels are suggested for those who are severely malnourished (McKendry et al., 2024). For elderly patients, adhering again to long-term nutritional supplement use can be difficult because of factors such as financial burden, unpleasant taste, or swallowing challenges (Bai et al., 2023). Concurrently, research has shown that the combination of nutritional supplements and exercise interventions, including resistance training, is more effective than implementing a single intervention, but the effectiveness of the combined treatment is compromised in practice because of patients' low compliance with exercise routines (Cuyul-Vásquez et al., 2023; Hsu et al., 2019). In line with these findings, our results indicate that SQP is particularly effective in boosting muscle mass and preventing grip strength decline while maintaining high safety and compliance. Drugs and herbs that prevent sarcopenia, such as SQP, are a highly promising choice.

SQP is a TCM dietary formulation based on the theory of "same origin of medicine and food." SQP is designed to tonify the spleen and kidney, harmonize the stomach, enhance digestion, build muscles, and strengthen bones, thus positioning it as a promising option for treating sarcopenia. Recent pharmacological and clinical studies have shown that SQP contains traditional herbal ingredients such as *Astragalus membranaceus, Eucommia ulmoides*, and *Polygonatum kingianum*, which possesses anti-muscle atrophy properties. The potential mechanisms of SQP in combating sarcopenia may be attributed to its multi-component and multi-target effects. *Astragalus membranaceus* is rich in saponins, flavonoids, and polysaccharides, which have anti-inflammatory, antioxidant, metabolic regulation, and muscle cell proliferation-promoting effects (Chen et al., 2023; Dong et al., 2023). *Eucommia ulmoides* and its active ingredients exhibit various pharmacological properties, such as enhancing liver and kidney function; reinforcing tendons and bones; decreasing blood pressure; and anti-inflammatory, antioxidant, immune-regulating, and anti-aging benefits (He et al., 2014; Yu et al.,

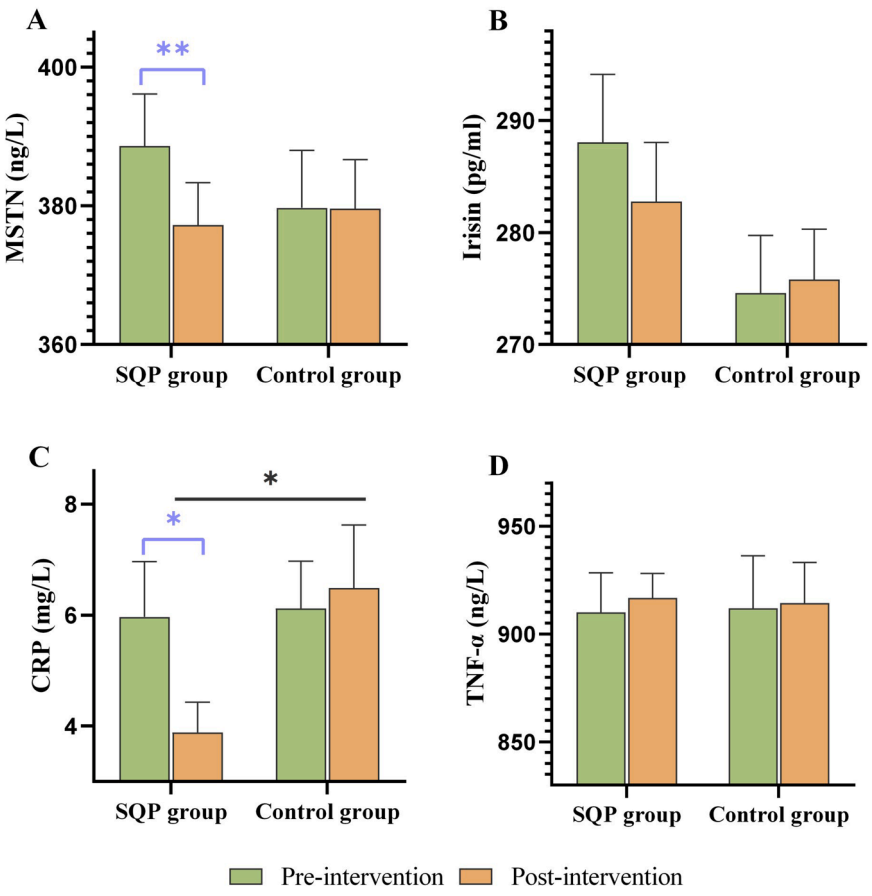

Fig. 5. The changes of MSTN level, Irisin level, CRP level, and TNF-α level were observed in SQP group and control group pre-intervention and post-intervention by PPS analysis. (A) changes in MSTN level; (B) changes in Irisin level; (C) changes in CRP level; (D) chnges in TNF-α level. MSTN, Myostatin; CRP, C-Reactive Protein; TNF-α, Tumor Necrosis Factor-alpha; PPS, Per Protocol Set.

2024). Previous investigations using animals have explored the potential mechanisms through which these ingredients influence muscle function. One study (She et al., 2023) demonstrated that a compound (Ast-Dio) composed of *Astragalus* and *Dioscorea* enhanced the expression of the muscle protein myogenin while reducing the levels of muscle degradation proteins atrogin-1 and MuRF1. This compound effectively mitigated sarcopenia in aged mice with type 2 diabetes by activating the Ras-related protein Rab-5A/mammalian target of rapamycin (mTOR) pathway and modulating mitochondrial quality (She et al., 2023). Research has shown that a blend of *Eucommia ulmoides* and *Cervus elaphus* (KGC01CE) increased muscle mass and grip strength in both C2C12 cells and elderly rats (Koo et al., 2024). By activating the PI3K/Akt pathway and blocking proteins that degrade muscle, this treatment stopped muscle loss and functional decline (Koo et al., 2024). *Polygonatum* polysaccharides suppress the senescence-associated secretory phenotype; by the activation of the PI3K/Akt/mTOR signaling pathway and reducing ROS activity, these polysaccharides considerably ameliorate the aging process, atrophy, and mitochondrial problems in skeletal muscles (Li et al., 2025). Nonetheless, these studies focused solely on the effects of individual components within the herbal compounds, leaving the specific mechanism of how these components combine (i.e., SQP) to prevent muscle atrophy undetermined (Fig. 6). It should be emphasized that the proposed molecular mechanisms of SQP remain exploratory and hypothesis-generating, requiring further in-depth experimental validation. Extensive research indicates that chronic low-grade inflammation is a common underlying factor in both hemodialysis and sarcopenia, thus contributing to the emergence and evolution of sarcopenia by influencing inflammatory markers, hormone regulation, and protein turnover (de Resende et al., 2024; Leng et al., 2025; Margiotta et al., 2021; Yasar et al., 2022).

Our study confirms that SQP is a safe and well-tolerated intervention for dialysis-associated sarcopenia. The SQP group showed clinical efficacy, with baseline differences not being significant in factors such as age, gender, disease duration, medication use, and comorbidities between the two groups, thus minimizing potential confounding biases. SQP paired with light exercise was more successful in boosting skeletal muscle mass than a placebo paired with light exercise. The SMI index in the SQP group increased significantly post-intervention, surpassing both its baseline levels and concurrent control measurements. This effect was significant in the middle-aged and young-elderly subgroups, whether it's between intra-group comparison or inter-group comparison. The subgroup analysis based on age was exploratory rather than prespecified, and thus was underpowered. These results should be regarded as hypothesis-generating and should be interpreted with caution. They need to be verified in future studies.

Although the muscle mass of both groups increased, the grip strength of both groups decreased. This paradox primarily stems from acute post-dialysis fatigue, which intradialytic hypoperfusion may induce transient muscle dysfunctionapproximately, and two-thirds of the tests were completed within two hours post-treatment; uremic toxins (e.g., elevated IL-6 and β2-microglobulin) potentially impair excitation-contraction coupling and disrupt calcium handling in sarcoplasmic reticulum, as shown in CKD models (Molfino et al., 2023; Shroff et al., 2019). Furthermore, although both groups experienced a decrease in grip strength, but inter-group comparison showed that the SQP group exhibited significantly greater grip strength compared to the control group post-intervention. Furthermore, inter-group comparison showed that physical function improved more significantly in the SQP group

Table 3
Subgroup analysis by age for primary outcomes after intervention by ITT analysis.

Subgroups and outcomes	SQP group	Control group	*P (Δ between groups)
Middle-aged	***n* = 18**	***n* = 13**	
SMI (kg/m^2)			
Baseline	5.95 ± 0.70	5.47 ± 0.80	0.051
12 weeks	6.24 ± 0.88	5.49 ± 0.84	0.017
D-value	0.29 ± 0.51	0.02 ± 0.26	0.172
**P (Δ Within group)	0.026	0.299	
Handgrip strength (kg)			
Baseline	24.77 ± 6.09	21.85 ± 6.24	0.204
12 weeks	20.86 ± 3.29	18.38 ± 4.49	0.086
D-value	−3.91 ± 4.93	−3.48 ± 3.87	0.796
**P (Δ Within group)	<0.001	<0.001	
FTSST (s)			
Baseline	10.82 ± 3.07	13.34 ± 6.45	0.157
12 weeks	9.68 ± 2.21	12.36 ± 6.61	0.119
D-value	−1.14 ± 2.42	−0.98 ± 3.89	0.893
**P (Δ Within group)	0.063	0.382	
Young-elderly	***n* = 34**	***n* = 42**	
SMI (kg/m^2)			
Baseline	5.80 ± 0.72	5.80 ± 0.80	1.000
12 weeks	6.06 ± 0.79	5.83 ± 0.78	0.223
D-value	0.26 ± 0.49	0.03 ± 0.22	0.010
**P (Δ Within group)	0.005	0.326	
Handgrip strength (kg)			
Baseline	19.11 ± 7.74	20.02 ± 9.12	0.645
12 weeks	18.29 ± 5.24	16.74 ± 5.56	0.220
D-value	−0.82 ± 5.57	−3.28 ± 5.68	0.630
**P (Δ Within group)	<0.001	<0.001	
FTSST (s)			
Baseline	15.16 ± 5.84	14.74 ± 7.43	0.790
12 weeks	13.35 ± 4.12	13.52 ± 8.30	0.915
D-value	−1.82 ± 5.20	−1.23 ± 8.41	0.725
**P (Δ Within group)	0.05	0.362	
Elderly	***n* = 12**	***n* = 9**	
SMI (kg/m^2)			
Baseline	5.93 ± 0.63	5.82 ± 0.82	0.748
12 weeks	6.08 ± 0.73	5.66 ± 0.60	0.171
D-value	0.16 ± 0.48	−0.17 ± 0.44	0.128
**P (Δ Within group)	0.273	0.293	
Handgrip strength (kg)			
Baseline	19.68 ± 6.86	17.53 ± 9.34	0.551
12 weeks	17.33 ± 5.01	15.44 ± 6.71	0.470
D-value	−2.35 ± 3.92	−2.09 ± 4.18	0.885
**P (Δ Within group)	<0.001	0.004	
FTSST (s)			
Baseline	17.14 ± 11.44	19.94 ± 9.10	0.569
12 weeks	14.51 ± 4.62	19.71 ± 16.09	0.299
D-value	−2.63 ± 10.97	−0.23 ± 8.79	0.612
**P (Δ Within group)	0.424	0.943	

Abbreviations: ITT, Intention-to-treat; SQP, Shen-Qi Paste; SMI, Skeletal muscle mass index; FTSST, Five Times Sit to Stand Test.
D-value refers to the difference before and after intervention.
* *P* was the compared values between the two groups; ***P* was the compared value of each group before and after intervention (baseline and 12 weeks).

Table 4
Summary of adverse events by ITT analysis [1].

Items	SQP group (*n* = 64)	Control group (*n* = 64)	*P*
Adverse effect			0.465
Yes	5 (7.8)	3 (4.7)	
No	59 (92.2)	61 (95.3)	
Severe adverse effect			1.000
Yes	0 (0.0)	0 (0.0)	
No	64 (100.0)	64 (100.0)	
Discontinued owing to adverse effect			1.000
Yes	1 (1.6)	1 (1.6)	
No	63 (98.4)	63 (98.4)	
Complete treatment course			0.752
Yes	58 (90.6)	59 (92.2)	
No	6 (9.4)	5 (7.8)	

[1] Values are *n* (%); ITT, Intention-to-treat; SQP, Shen-Qi Paste.

than in the control group, even though statistical significance was not achieved.

Sarcopenia is classified as a nutrition-related disorder, with nutritional support being a key component of treatment aimed at increasing muscle protein and improving physical function (Robinson et al., 2023). This study inter-group comparison demonstrated that after 12 weeks of intervention, the SQP group had a significantly higher MNA-SF score, thus indicating that the nutritional status of the SQP group was superior to that of the control group. Furthermore, inter-group comparison demonstrated that significant improvements in PSQI scores and TCM syndrome scores were observed in the SQP group post-intervention. The inter-group comparison data imply that SQP might improve motor function, as seen in the slower decrease in grip strength and enhanced physical activity. However, larger sample sizes in future studies are essential to verify these results. Although some indicators statistical significance was not observed in the differences among the groups, both groups exhibited improvements in these parameters compared with the baseline.

The effective clinical evaluation of sarcopenia requires a comprehensive assessment of anthropometric indicators, serum biochemical markers, and imaging modalities and the acknowledgment of the limitations of current clinical practice. The AWGS 2019 guidelines highlight the importance of improving clinical indicators while also focusing on specific biochemical markers in blood, which may serve as valuable references for future sarcopenia interventions (Chen et al., 2020). Prior investigations have identified substantial differences in serum metabolites between those affected by sarcopenia (Baczek et al., 2020; Guo et al., 2023; Verzola et al., 2019). In this context, the present study investigated changes in the serum levels of MSTN, Irisin, CRP and TNF-α before and after SQP intervention. Intra-group comparison showed that this intervention measure resulted in a significant decrease in MSTN levels in the SQP group compared to the pre-intervention levels, and inter-group comparison showed that the CRP level in the SQP group decreased significantly than that in the control group. The results indicate that SQP can reduce the levels of myostatin and pro-inflammatory cytokines in the muscles, alleviate the inflammatory response in the participants' bodies, and promote muscle growth. Even though changes in Irisin and TNF-α levels showed no significant difference between the groups. These results suggest that SQP's primary mechanism likely operates through MSTN downregulation and CRP reduction, potentially independent of TNF-α pathways; and Irisin non-response may reflect assay sensitivity limits or tissue-blood gradient differences, as muscle FNDC5 mRNA increased 2.1-fold in rodent models (Guo et al., 2023). Critically, MSTN reduction remains the central driver of observed functional gains, warranting future studies with muscle biopsy-based biomarker validation. Given that SQP increases muscle mass and mitigates grip strength decline, it may exert an anti-inflammatory effect through exercise; further investigations are needed to confirm this finding.

This study also examined changes in several conventional biochemical markers. Inter-group comparison showed that a significant reduction in BUN level was observed in the SQP group compared to the control group. Additionally, PP analysis of inter-group comparison after the intervention demonstrated a substantial decrease in SUA levels for the SQP group, whereas no major differences in SCr levels were found between the two groups. SQP contains ingredients such as *Eucommia* leaf

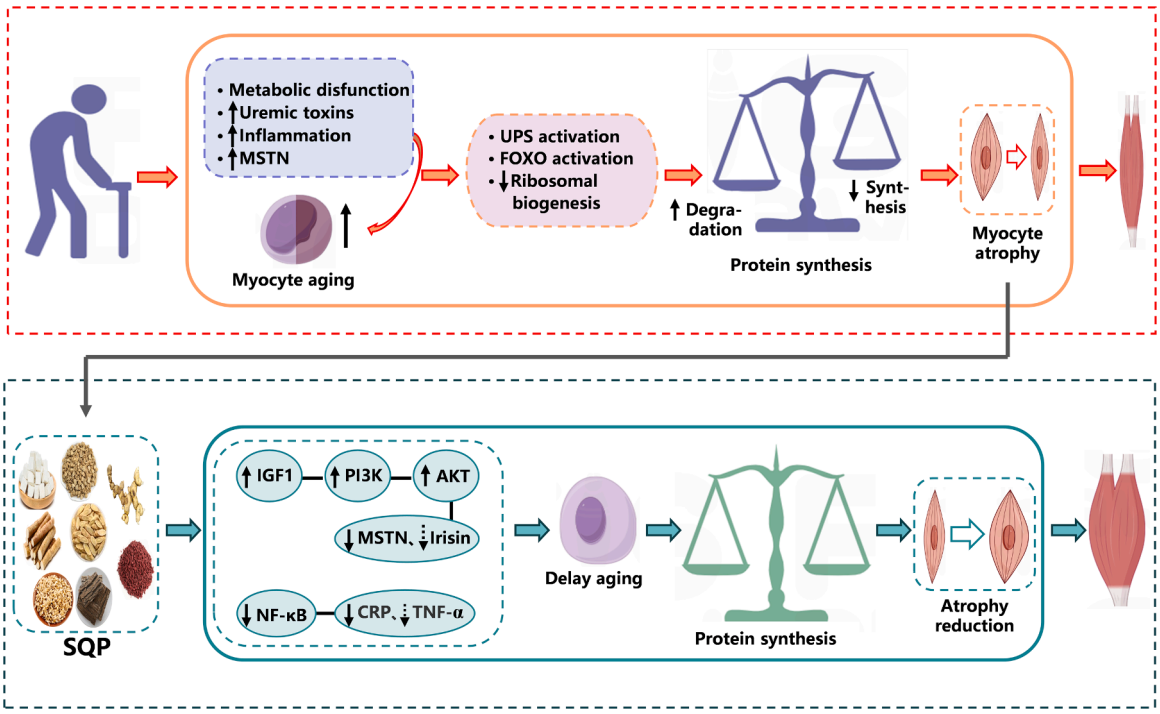

Fig. 6. The potential mechanism by which Shen-Qi Paste (SQP) delays sarcopenia or muscle atrophy. Sarcopenia associated with hemodialysis primarily results from enhanced catabolism, driven by metabolic dysfunction, uremic toxins, inflammation, and myostatin. These pathological alterations impair insulinlike growth factor 1 (IGF-1) and insulin signaling in skeletal muscle, a critical pathway for maintaining protein homeostasis by promoting protein synthesis and suppressing the ubiquitin-proteasome system (UPS). In hemodialysis patients, reduced AKT (also known as protein kinase B) activity leads to forkhead box class O (FOXO) transcription factor activation and mammalian target of rapamycin (mTOR) signaling inhibition, resulting in increased protein degradation and decreased synthesis, ultimately causing muscle atrophy. PI3K, Phosphoinositide 3-Kinase. Solid arrows stands for significant, dashed arrows stands for insignificant.

and poria, which have demonstrated protective effects on kidney function in multiple studies. A study (Lin et al., 2024) reported that *Eucommia ulmoides* extract significantly reduced BUN and SCr levels in mice with acute renal injury and alleviated the renal histopathological damage caused by cisplatin. Another study (Niu et al., 2016) demonstrated that *Eucommia ulmoides* reduced BUN and SCr levels while also improving renal fibrosis in rats with type 1 diabetic nephropathy. Fang et al. (Fang et al., 2019) reported that *Eucommia ulmoides* significantly lowered blood uric acid levels. Recent research has further demonstrated that poria extract can decrease the levels of SUA, BUN, and SCr; inhibit the activity of xanthine oxidase; and alleviate renal damage (Wang et al., 2025). However, the current study's results revealed that SQP did not notably affect metabolic indices such as blood glucose and lipids; this finding could be attributed to the exclusion of individuals with comorbid diabetes and the unstable use of statins. Given that the baseline blood glucose and lipid levels of most participants were within the normal range, the potential effects of SQP on metabolic parameters might not have been fully captured. Therefore, further studies are needed to evaluate how effective SQP is for patients with sarcopenia who are undergoing dialysis and have irregular blood glucose or lipid levels.

The clinical efficacy of the TCM dietary formulation SQP in treating sarcopenia was evaluated. Results indicated that SQP consistently alleviated the clinical symptoms of sarcopenia, thus improving subjective symptoms related to nutritional status, sleep quality, physical activity, and urogenital function. These effects align with the TCM syndrome score for spleen-kidney deficiency. SQP also demonstrated a favorable safety profile and was well tolerated. The occurrence of adverse events in the SQP group was comparable to that in the control group. In the treatment group, the predominant side effects experienced were vomiting and diarrhea. In each group, one patient discontinued participation because of adverse events.

While these findings demonstrate statistically significant effects, their clinical meaningfulness should be interpreted cautiously through comparison with existing benchmarks, as statistical significance does not inherently reflect clinical relevance. To contextualise our findings, we compared the observed changes against published minimal clinically important differences (MCIDs). The mean reduction in PSQI scores (Δ = 2.22 points) in the SQP group aligns closely with the widely accepted MCID of 2.5–2.7 points for adults with sleep disturbances (Qin et al., 2024), suggesting that the benefit, while trending toward clinical relevance, may not yet reach a threshold that patients would perceive as meaningful. For the SMI, no formally established MCID is currently available; the mean improvement in SMI scores (Δ=0.24 points) in SQP group comparable to gains reported after protein and fish oil supplementation in older adults at risk of sarcopenia (Murphy et al., 2022), suggesting a tangible benefit for muscle mass preservation. Finally, the mean reduction in TCM syndrome scores (Δ = 2.22 points) in SQP group was roughly equivalent the 2–3 point MCID proposed by similar study (Zhu et al., 2024), indicating a clinically relevant improvement in traditional Chinese medicine-defined symptom burden. Collectively, the PSQI improvement borders on the MCID, the SMI change is encouraging, and the TCM score improvement appears clinically meaningful; longer follow-up and patient-reported global ratings are warranted to corroborate these inferences.

This research has a few limitations. First, the study cohort, which comprised individuals over 45 years of age who are self-sufficient, may not represent the broader population. Besides, the study population was foused on Chinese dialysis patients, so these findings may not generalize to non-Chinese populations due to ethnic differences in genetics, comorbidities, or dialysis practices, or to non-dialysis CKD patients. Further studies in diverse cohorts are needed. Additionally, as participants are able to participate in consistent exercise, such as walking for 20 to 30 min for >3 times per week, the results may not be generalizable to individuals with limited mobility. Finally, due to the absence of specific sarcopenia drugs and the lack of standard positive controls, we

used a placebo-controlled design to evaluate the efficacy and safety of SQP, and used a multidimensional evaluation system to comprehensively evaluate the effects of SQP. But this may potentially reduce the clinical relevance and interpretability of the study findings. Despite these limitations, the study remains valuable owing to several strengths. To the best of our knowledge, this study is the first well-designed clinical trial that assessed the combined effects of SQP consumption and regular low-intensity exercise on muscle mass and strength in patients with dialysis-associated sarcopenia. Moreover, the investigation of sarcopenia-specific serum biomarkers further strengthens the study's contributions.

Conclusion

In conclusion, this study is the first to implement SQP for managing sarcopenia in dialysis patients according to the theory of "same origin of medicine and food" and by adopting a double-center, randomized, double-blind, placebo-controlled design. SQP shows potential in increasing skeletal muscle mass; mitigating grip strength reduction; and improving non-motor symptoms such as nutritional status, sleep quality, and overall quality of life. It also appears to enhance motor function through increased grip strength and physical activity levels, with a favorable safety and tolerability profile, thus indicating its potential for long-term clinical use. Furthermore, the efficacy of SQP is correlated with reduced MSTN and CRP levels, thus supporting its promise as a therapeutic intervention. However, this research has some limitations, such as a limited sample size and a brief 12-week period, thus potentially affecting generalizability. The mechanisms of SQP, particularly its microbiological effects, remain unclear. Future studies should include more samples, conduct a longer follow-up, and investigate the mechanisms of SQP to confirm long-term efficacy and clinical value.

Ethics and dissemination

This study has been approved by Hangzhou Hospital of Traditional Chinese Medical (No. 2024KLL087, March 20, 2024, 12 months), and First People's Hospital of Xiao-shan Hangzhou (Xiaoyi Medical Lunjian-Zi 2024-Section No 30, March 4, 2024, 12 months). We will obtain written informed consent from all participants. Research results will be presented at academic conferences and published in peer-reviewed publications.

Trial registration number

This trial is registered at China National Health Insurance Information Platform and the registration number is MR-33-24-012106.

CRediT authorship contribution statement

Xiaoyan Li: Writing – original draft, Investigation, Funding acquisition, Formal analysis. **Rongyun Wang:** Writing – review & editing, Conceptualization. **Keda Lu:** Methodology, Formal analysis. **Luchen He:** Methodology, Investigation. **Lin Li:** Methodology, Investigation. **Rulin Yong:** Methodology. **Ting Liu:** Investigation. **Lijiangshan Hua:** Investigation. **Zhuoer Hou:** Investigation. **Qiuhua Sun:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

There is no conflict of interest between the participants, authors, and paste manufacturing company.

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Founding

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2025.157190.

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