Integrative Medicine Research 14 (2025) 101143

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Original Article

Traditional Vietnamese herbal medicine TD0015 in Knee Osteoarthritis: A Phase-II randomized controlled trial

Nguyen Thi Thu Ha [a,1], Duong Trong Nghia [b,1], Ha Thi Viet Nga [b], Trinh Thi Lua [a], Nguyen Thi Bich Hong [b], Nguyen Thi Hanh [c], Nguyen Kim Ngoc [a], Nguyen Lam Vuong [d,*]

[a] Faculty of Traditional Medicine, Hanoi Medical University, Hanoi, Vietnam
[b] National Hospital of Traditional Medicine, Hanoi, Vietnam
[c] Thai Binh Medical University Hospital, Thai Binh, Vietnam
[d] Department of Medical Statistics and Informatics, Faculty of Public Health, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh, Vietnam

ARTICLE INFO

Keywords:
Traditional medicine
Herbal
Knee
Osteoarthritis

ABSTRACT

Background: Knee osteoarthritis (KOA) is a leading cause of disability among older adults worldwide. Traditional medicine offers a promising treatment for KOA with fewer side effects compared to current treatments such as non-steroidal anti-inflammatory drugs and corticosteroids. This study aimed to evaluate the safety and efficacy of TD0015, a herbal formulation based on the Duhuo Jisheng decoction, in treating KOA.

Methods: This randomized, double-blind, placebo-controlled trial enrolled 108 patients with KOA. Participants were randomly assigned in a 1:1:1 ratio to receive TD0015 5 g, TD0015 7.5 g, or placebo daily for 60 days. Efficacy endpoints included changes in Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), Visual Analogue Scale (VAS), Lequesne index, heel-buttock distance, and knee flexion and extension range of motion. Safety was assessed by adverse events (AEs).

Results: The mean age was around 60 years, and >80 % were females. Both TD0015 treatment groups significantly improved the WOMAC, VAS, Lequesne score, heel-buttock distance, and knee flexion and extension during the treatment period. At the 90-day follow-up, the mean percentage improvement in WOMAC scores was 74.5 % ± 13.4 %, 83.9 % ± 14.8 %, and 7.4 % ± 31.5 % in the TD0015 5 g, TD0015 7.5 g, and placebo groups, respectively, which corresponds to a 67.1 % (95 % CI: 56.3–77.9) and 76.5 % (95 % CI: 65.6–87.4) improvement in the TD0015 5 g and TD0015 7.5 g groups, compared to placebo. No AEs were reported in any group.

Conclusions: The Vietnamese herbal medicine TD0015 is safe, efficacious, and well-tolerated in treating KOA. Further studies are required to confirm the long-term efficacy and safety of TD0015.

Trial registration: ClinicalTrials.gov, NCT06657495.

1. Introduction

Knee osteoarthritis (KOA) is a prevalent degenerative joint disease characterized by pain, swelling, stiffness, and functional impairment.[1] With the global aging population and rising obesity rates, the prevalence of KOA is increasing, posing a significant burden on individuals and healthcare systems.[2-4] KOA is a leading cause of disability and a substantial source of societal costs, particularly among older adults, as highlighted by the 2019 Global Burden of Disease Study.[5] This condition significantly diminishes quality of life and contributes substantially to healthcare expenditures.[2-4]

The complex pathogenesis of KOA involves a multifaceted interplay of factors, including inflammation, oxidative stress, apoptosis, and altered energy metabolism.[6] Current treatment strategies, such as non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids, primarily target symptom management but often have limitations, including potential adverse effects, such as gastrointestinal and cardiovascular disorders, particularly with long-term use, and limited capacity to modify disease progression.[7,8] While intra-articular corticosteroid injections can provide short-term pain relief, concerns exist regarding their long-term impact on joint health, including the

* Corresponding author at: University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang, Ward 11, District 5, Ho Chi Minh City, Vietnam.
E-mail address: nguyenlamvuong@ump.edu.vn (N.L. Vuong).
[1] These authors contributed equally as co-first authors.

https://doi.org/10.1016/j.imr.2025.101143
Received 27 November 2024; Received in revised form 7 March 2025; Accepted 31 March 2025
Available online 31 March 2025

potential for accelerated KOA progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction.[9] These limitations underscore the urgent need for more effective and safer KOA treatments. Traditional medicine, with its long history of use and potentially fewer side effects, offers a promising avenue for addressing this unmet need.[10,11] Furthermore, herbal therapies have demonstrated potential in slowing KOA progression through various mechanisms.[12]

Duhuo Jisheng decoction (DJD), a well-known traditional Chinese medicine formula comprising 15 herbs, has demonstrated efficacy in osteoarthritis (OA) treatment.[13] Its use in treating KOA has been documented in various countries, including Vietnam.[14] However, preparing DJD using the classical formulation requires traditional medicine practitioners, limiting its broader applicability. TD0015 was developed from the DJD formulation as a commercially available drug, representing an improvement on the classical preparation and broadening its potential use. Preclinical studies have shown promising anti-inflammatory and analgesic effects of TD0015.[15-17] This phase II clinical trial was therefore designed to evaluate the safety and optimal dosage of TD0015 in patients with KOA.

2. Methods

2.1. Study design

This was a double-blind randomized, placebo-controlled phase-II trial to assess the safety and optimal dose of oral TD0015 in adults with KOA. The trial was conducted at the National Hospital of Traditional Medicine (Hanoi, Vietnam) between March and June 2022. Ethical approval was obtained from the Ministry of Health ethics committee (No. 107/CN–HDDD, dated July 19, 2021). Written informed consent was obtained from all participants. The trial adhered to the Declaration of Helsinki and Good Clinical Practice guidelines and was registered at ClinicalTrials.gov (NCT06657495). For the reporting of the trial, we referred to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (Supplement 1).

2.2. Patients

The study enrolled men and women aged 18 years or above with a confirmed diagnosis of KOA according to the American College of Rheumatology Clinical classification criteria for knee osteoarthritis, experiencing knee joint pain,[18] and with a Kellgren and Lawrence grade below 4.[19,20] Patients with Kellgren-Lawrence grade 4 were excluded because non-operative treatments are often ineffective at this stage, and surgical intervention is typically required. Exclusion criteria included: (i) contraindication to NSAIDS; (ii) known allergy or intolerance to any of the product ingredient; (iii) pregnancy or breastfeeding; (iv) planned surgery within six months of screening; (v) concomitant severe infections, malignant diseases, coagulation disorders, or uncontrolled or unmanageable systemic diseases; (vi) presence of other types of arthritis besides OA; (vii) intra-articular injection of hyaluronic acid or corticosteroid in the preceding two months; and (viii) inability to comply with study procedures or ensuring compliance with study drug administration as assessed by investigators.

2.3. Investigational product

TD0015, based on the DJD formulation, was developed as a 5 g and 7.5 g oral dosage form. Each pill contained a fine powder of 22 herbal ingredients extracted using water as the solvent (Table 1). Both TD0015 and the placebo were manufactured according to Good Manufacturing Practice (GMP) standards by the Sao Thai Duong Joint Stock Company (Sunstar JSC), a company with 25 years of experience in herbal product manufacturing. The two products were identical in appearance (color, shape, size, and smell) to ensure blinding.

2.4. Randomization and intervention

Eligible participants were randomly assigned in a 1:1:1 ratio to receive TD0015 5 g, TD0015 7.5 g, or placebo. The dose selection for TD0015 was based on preclinical studies in mice.[15-17] Block randomization with a block size of six was generated using the PROC PLAN statement in SAS version 9.4. Randomization codes were placed in sequentially numbered, sealed envelopes. Treatment allocation was known only to one study team member responsible for generating the randomization sequence until the database was locked on June 24, 2023. All participants, outcome assessors, and other study personnel were blinded to treatment assignment. Participants were allocated to treatment groups sequentially and received either TD0015 5 g, TD0015 7.5 g, or placebo one pill twice daily for 60 days (total of 120 pills).

Table 1
Composition of herbal mixture in a TD0015 pill.

No.	Latin name	Content (mg) in a TD0015 5 g pill	Content (mg) in a TD0015 7.5 g pill
1	Plastrum Testudinis	2.97	4.45
2	Cortex Phelodendri	2.26	3.38
3	Radix Paeoniae lactiflorae	0.77	1.16
4	Radix Rehmanniae glutinosae	0.71	1.06
5	Animal bone extract	0.70	1.06
6	Salix alba extract	0.50	0.75
7	Cortex Eucommiae	0.47	0.71
8	Poria	0.47	0.71
9	Radix Codonopsis pilosulae	0.34	0.50
10	Radix Angelicae sinensis	0.34	0.50
11	Rhizoma Anemarrhenae	0.31	0.46
12	Flos Pruni	0.26	0.39
13	Radix Saposhnikoviae divaricatae	0.24	0.35
14	Herba Loranthi Gracifilolii	0.24	0.35
15	Radix Gentianae	0.24	0.35
16	Pericarpium Citri reticulatae perenne	0.22	0.33
17	Radix Angelicae pubescentis	0.17	0.25
18	Rhizoma Ligustici wallichii	0.17	0.25
19	Radix Glycyrrhizae	0.12	0.18
20	Ramulus Cinnamomi	0.08	0.13
21	Radix et Rhizoma Asari	0.08	0.13
22	Radix Achyranthis bidentatae	0.03	0.04
23	Sodium benzoat	0.0025	0.0038
24	Excipient (amidon, NaCMC, HPMC E15, Black 952 colorant)	-	-

2.5. Assessments

Assessments were conducted at baseline (T0), 15, 30, 45, and 60 days post-randomization (T1, T2, T3, and T4 respectively), and a 90-day follow-up (T5). Clinical assessments included physical examinations, the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), Lequesne index, knee range of motion, and Visual Analogue Scale (VAS) for pain intensity. Laboratory tests, including blood chemistry and hematology, were performed at baseline (T0) and at the end of treatment (T4). Baseline X-ray and ultrasound imaging were conducted to confirm and assess the severity of KOA.

2.6. Outcomes

The primary efficacy endpoint was the change in WOMAC score from baseline to the end of treatment (T4) and the 90-day follow-up (T5). The WOMAC is a widely used self-administered questionnaire in patients with OA. It consists of 24 items divided into three subscales: pain (5 items), stiffness (2 items), and physical function (17 items).[21] The score ranges from 0 to 96, with higher scores indicating greater symptom severity and functional impairment.

Secondary efficacy endpoints included the VAS for pain intensity, Lequense index score for overall disease severity, heel-buttock distance, and knee flexion and extension range of motion to evaluate functional limitations. The VAS is a 10-cm visual analog scale, with higher scores indicating greater pain intensity (0 represents no pain, and 10 represents worst pain imaginable). The Lequesne index is an 11-item questionnaire divided into three sections: pain or discomfort (5 items), maximum distance walked (2 items), and activities of daily living (4 items). The score ranges from 0 (no pain, no disability) to 24 (maximum pain and disability).[22] Heel-buttock distance and knee range of motion are objective measures by study physicians. Improvement rates for each efficacy endpoint were calculated as the percentage change from baseline to T4 and T5, except for the knee extension which was the absolute change.

For all the primary and secondary efficacy endpoints, except for the knee extension, the percentage change was calculated for each individual patient as follows: Percentage change at T4 or T5 = (Score at T4 or T5 – Score at T0) / Score at T0 * 100 %.

Safety was assessed by monitoring adverse events (AEs), serious adverse events (SAEs), and routine laboratory tests, including complete blood count and blood chemistry (hepatic and renal functions tests, and glucose tests). Concomitant medications were recorded throughout the study period.

2.7. Statistical analysis

As this is the first study to explore the efficacy and safety of TD0015 on patients with KOA, we decided to recruit a convenient sample of 30 participants in each treatment group. Considering a dropout rate of 15 %, we recruited 36 patients for each group.

All efficacy analyses were performed on an intention-to-treat (ITT) basis, including all randomized patients regardless of their protocol adherence and continued participation in the study. Patients were analyzed according to their randomized group. Safety analyses were on an as-treated basis, including all patients who received at least one dose of the study drugs. Patients were analyzed according to their actual treatment group.

Continuous data with a normal distribution, including all the efficacy endpoints, were summarized using mean and standard deviation. Non-normally distributed continuous data, such as laboratory parameters, were summarized using median and interquartile range (25th, 75th percentiles). Categorical data were summarized using frequencies and percentages.

Kruskal-Wallis test was used to assess overall differences in the change from baseline to T4 or T5 for each endpoint. Where significant differences were identified, Dunn's non-parametric all-pairs test was used for post-hoc pairwise comparisons. In addition, linear regression models were used to further assess the change from baseline to T4 or T5 for each endpoint. The models included treatment group (TD0015 5 g, TD0015 7.5 g, or placebo) as the sole independent variable. Mean differences (MDs) and 95 % confidence intervals (CIs) were calculated for pairwise comparisons between each TD0015 group and placebo, and between the two TD0015 groups. Linear regression was selected to facilitate pairwise comparisons, estimate effect sizes using mean differences, and because of its ease of interpretation.

For non-normally distributed continuous variables, such as laboratory parameters, the Kruskal-Wallis test was used to compare differences between groups. Fisher's exact test was used to compare categorical variables, including safety endpoints. All statistical tests were two-sided. To account for multiple comparisons, statistical significance was defined as a p-value < 0.01.

There were missing data on the endpoints due to discontinuation of the study. We therefore performed a sensitivity analysis with imputation using the last observation carried forward (LOCF) method for the efficacy endpoints. This approach was chosen because the primary reason for dropout was loss to follow-up (presumed missing at random), and a smaller proportion of patients discontinued due to perceived lack of improvement. LOCF assumes that patients who were lost to follow-up would have maintained their last observed value, which is a conservative assumption in the context of an intervention aimed at improving symptoms. All the analyses were done using statistical software R version 4.1.0.

3. Results

Participant enrollment began on March 21, 2022 and concluded on June 23, 2022. Participants attended clinic visits at baseline (randomization), at 15-day intervals for 60 days during the treatment period, and at a final follow-up visit 90 days after randomization. The last follow-up visit for the final participant occurred on September 24, 2022. Between March and June 2022, 123 patients were screened, of whom 108 were eligible for randomization. Thirty-six patients were randomly assigned to each treatment group: placebo, TD0015 5 g, and TD0015 7.5 g. A total of 17 patients discontinued participation in the study: 8 in the placebo group, 4 in the TD0015 5 g group, and 5 in the TD0015 7.5 g group. The primary reason for dropout was loss to follow-up (13/17 patients), where investigators were unable to contact the participants. Four patients (2 in the placebo group, 1 in the TD0015 5 g group, and 1 in the TD0015 7.5 g group) withdrew due to perceived lack of improvement. All randomized patients were included in the ITT analysis (Fig. 1).

Baseline demographic and clinical characteristics were balanced among the three groups (Table 2). The mean age of patients in the placebo, TD0015 5 g, and TD0015 7.5 g groups was 61.8, 61.9 and 57.9 years, respectively. The majority of patients in all groups were female (83.3 %, 80.6 %, and 86.1 %, respectively). Symptoms, including pain and limited range of motion, were present in both knees for 44.4 %, 30.6 %, and 33.3 % of patients, respectively. For analysis, the knee with more severe symptoms was selected, with the right knee being more common. Most patients were categorized as Kellgren-Lawrence grade 2. All efficacy endpoints were non-significantly different between the three groups at baseline.

The mean number of study drug pills used was similar across all three groups: 111 in the placebo group, 115 in the TD0015 5 g group, and 115 in the TD0015 7.5 g group. One patient in the placebo group, two patients in the TD0015 5 g group, and no patients in the TD0015 7.5 g group required rescue medication (NSAIDs) (Supplementary Table S1).

Fig. 2 illustrates the progression of all efficacy endpoints over time. Both TD0015 treatment groups (5 g and 7.5 g) demonstrated greater improvements in WOMAC, VAS, Lequesne scores, and heel-buttock distance compared to the placebo group. Additionally, the higher-dose TD0015 group showed a slightly better improvement than the lower-

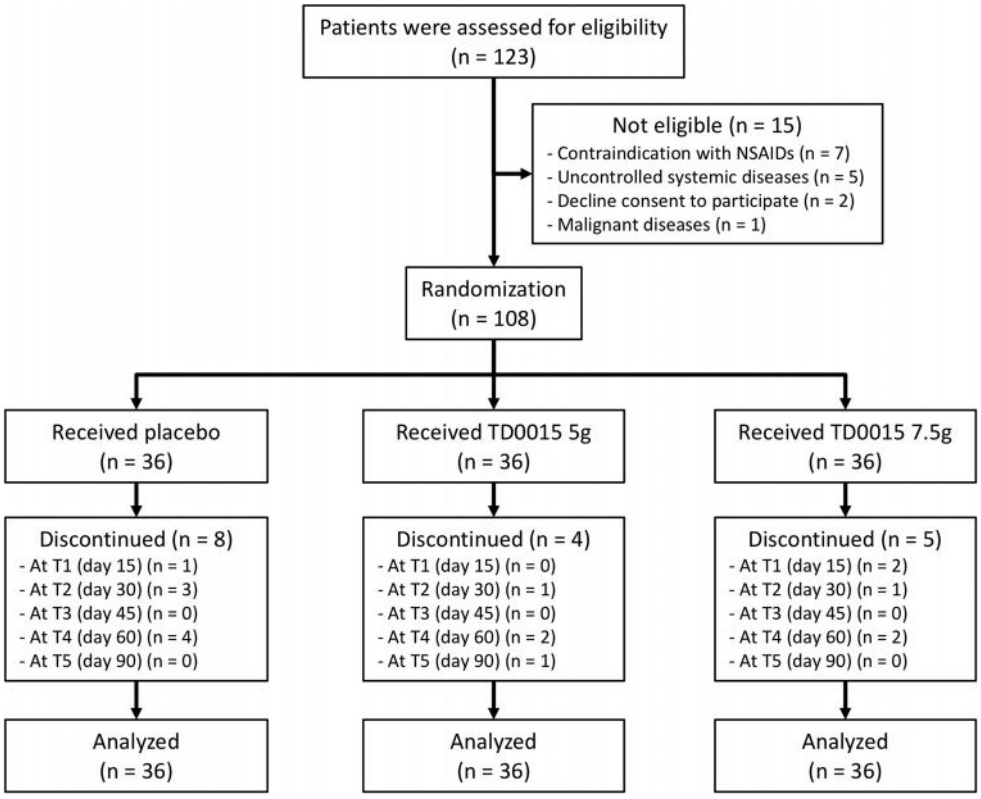

Fig. 1. Flowchart of patient selection and follow-up NSAIDS, nonsteroidal anti-inflammatory drugs.

Table 2
Baseline clinical and demographic characteristics.

	Placebo (N = 36)	TD0015 5 g (N = 36)	TD0015 7.5 g (N = 36)
Age (years)	61.8 ± 12.1	61.9 ± 11.2	57.9 ± 11.3
Sex, female	30 (83.3)	29 (80.6)	31 (86.1)
Hypertension	6 (16.7)	7 (19.4)	4 (11.1)
Diabetes	3 (8.3)	3 (8.3)	1 (2.8)
Postmenopause	23/30 (76.7)	24/29 (82.8)	22/31 (71.0)
Side with pain and limited range of motion			
Left	10 (27.8)	9 (25.0)	10 (27.8)
Right	10 (27.8)	16 (44.4)	14 (38.9)
Both sides	16 (44.4)	11 (30.6)	12 (33.3)
Side with more severe symptoms			
Right	24 (66.7)	25 (69.4)	23 (63.9)
Left	12 (33.3)	11 (30.6)	13 (36.1)
Body mass index (kg/m^2)	23.4 ± 3.1	23.6 ± 1.8	23.4 ± 2.4
Kellgren–Lawrence grade			
Grade 1	0 (0.0)	1 (2.8)	0 (0.0)
Grade 2	33 (91.7)	35 (97.2)	34 (94.4)
Grade 3	3 (8.3)	0 (0.0)	2 (5.6)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Knee joint effusion on ultrasound	25 (69.4)	26 (72.2)	29 (80.6)
WOMAC score	40.0 ± 8.3	43.9 ± 8.1	45.1 ± 10.4
VAS score	4.2 ± 0.9	4.4 ± 0.9	4.4 ± 0.9
Lequense score	13.9 ± 2.7	14.8 ± 2.7	15.0 ± 2.6
Heel-buttock distance (cm)	16.6 ± 4.5	15.4 ± 3.7	15.0 ± 3.7
Knee flexion (degree)	102.9 ± 10.2	105.6 ± 10.1	103.1 ± 10.8
Knee extension (degree)	−6.8 ± 5.5	−8.2 ± 3.2	−6.9 ± 5.2

Summary statistics are mean ± standard deviation and n (%).
VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

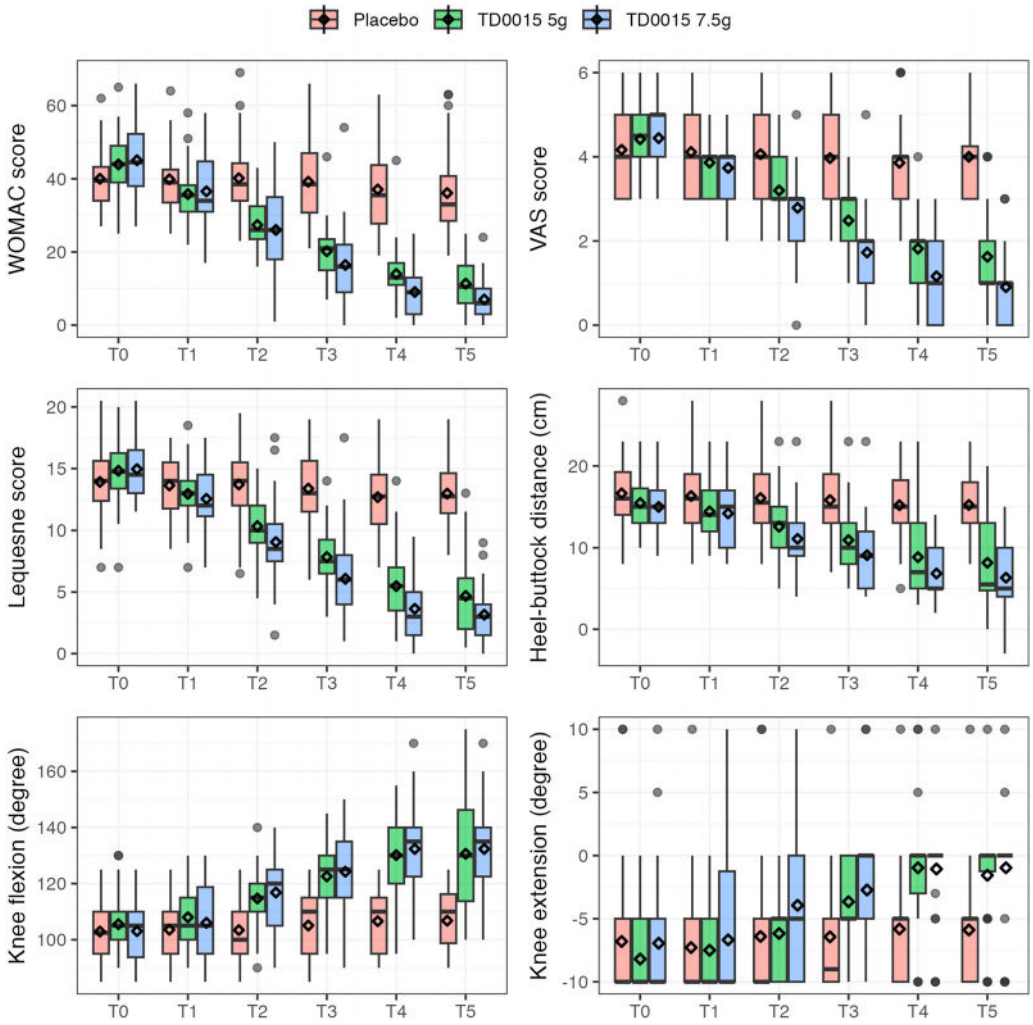

Fig. 2. Progression of the efficacy endpoints by treatment groups The line inside each box is the median, the upper and lower margins of each box represent the interquartile range (25th; 75th percentiles), and the diamond inside each box is the mean of the corresponding endpoint. VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

dose group. Regarding knee flexion and extension, both treatment groups improved compared to the placebo group, with similar effects between the two TD0015 doses.

Tables 3 and 4 present the improvement rates (percentage change from baseline) for the primary and secondary efficacy endpoints. Both TD0015 treatment groups demonstrated significant improvements in WOMAC, VAS, Lequesne scores, heel-buttock distance, and knee flexion and extension at both T4 and T5 compared to placebo. At T5, the mean percentage improvement in WOMAC scores was 74.5 % ± 13.4 % in the TD0015 5 g group, 83.9 % ± 14.8 % in the TD0015 7.5 g group, and 7.4 % ± 31.5 % in the placebo group. This corresponds to a 67.1 % (95 % CI: 56.3–77.9) and 76.5 % (95 % CI: 65.6–87.4) improvement in the TD0015 5 g and TD0015 7.5 g groups, respectively, compared to placebo. Similar trends were observed for WOMAC at T4, and VAS and Lequesne scores at both T4 and T5. While the improvements in heel-buttock distance and knee flexion/extension were smaller in magnitude, they were still statistically significant in both TD0015 groups. Sensitivity analysis using last observation carried forward imputation confirmed the primary findings, although the magnitude of the differences between the two TD0015 groups was slightly reduced (Supplementary Table S1, Table S2).

In the primary analysis, the higher-dose TD0015 group showed a slightly greater improvement in WOMAC, VAS, Lequesne score, heel-buttock distance, and knee flexion and extension compared to the lower-dose group at T4 and T5. However, this difference was not statistically significant in the sensitivity analysis using LOCF imputation (Supplementary Table S1, Table S2).

No AEs or SAEs were reported in any of the treatment groups. Routine laboratory tests, including hematology and blood chemistry, showed no significant abnormalities or treatment-related adverse effects (Supplementary Table S2, Figure S1, Table S3).

4. Discussion

This prospective, randomized, double-blind, placebo-controlled trial demonstrated the safety and efficacy of oral TD0015 in managing KOA. Over a 3-month period, both TD0015 treatment groups showed significant improvements in pain, stiffness, and physical function compared to the placebo group, as assessed by the WOMAC score, VAS, and Lequesne Index. The higher-dose TD0015 group exhibited slightly greater improvements in pain and functional limitations compared to the lower-dose group. Importantly, TD0015 was well-tolerated, with no AEs reported.

Traditional medicine in Vietnam has a long history of treating bone disorders, including OA. In traditional Chinese and Vietnamese medicine, OA is often classified as “Bi syndrome” or “flaccidity syndrome”.[23] TD0015 was developed from DJD, which is a well-known traditional Chinese medicine formula comprising 15 herbs, includ-

Table 3
Percentage change of the efficacy endpoints by treatment groups.

	Placebo		TD0015 5 g		TD0015 7.5 g					
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	$P_{overall}$	P_{01}	P_{02}	P_{12}
Percentage change of WOMAC score (%)										
At T4	28	6.2 ± 23.6	33	68.3 ± 14.8	31	79.8 ± 15.5	<0.001	<0.001	<0.001	0.099
At T5	28	7.4 ± 31.5	32	74.5 ± 13.4	31	83.9 ± 14.8	<0.001	<0.001	<0.001	0.140
Percentage change of VAS score (%)										
At T4	28	5.5 ± 19.9	33	59.1 ± 18.1	31	73.3 ± 22.4	<0.001	<0.001	<0.001	0.190
At T5	28	−0.6 ± 28.6	32	63.2 ± 27.1	31	80.1 ± 19.5	<0.001	<0.001	<0.001	0.093
Percentage change of Lequesne score (%)										
At T4	28	7.7 ± 15.4	33	63.0 ± 15.7	31	75.4 ± 15.5	<0.001	<0.001	<0.001	0.110
At T5	28	3.7 ± 24.6	32	68.5 ± 19.1	31	78.7 ± 14.3	<0.001	<0.001	<0.001	0.270
Percentage change of heel-buttock distance (%)										
At T4	28	5.3 ± 16.8	33	43.7 ± 23.8	31	54.6 ± 17.8	<0.001	<0.001	<0.001	0.380
At T5	28	4.0 ± 15.5	32	47.0 ± 36.4	31	58.2 ± 22.8	<0.001	<0.001	<0.001	1
Percentage change of knee flexion (%)										
At T4	28	2.8 ± 5.4	33	24.0 ± 18.5	31	29.9 ± 17.1	<0.001	<0.001	<0.001	0.490
At T5	28	3.1 ± 8.1	32	24.8 ± 23.1	31	30.2 ± 21.5	<0.001	<0.001	<0.001	0.710
Absolute change of knee extension (degree)										
At T4	28	0.6 ± 3.9	33	7.1 ± 5.3	31	5.5 ± 4.9	<0.001	<0.001	<0.001	1
At T5	28	0.5 ± 4.8	32	6.6 ± 4.5	31	5.6 ± 5.9	<0.001	<0.001	0.002	1

$P_{overall}$ values are from the Kruskal-Wallis test. P_{01}, P_{02}, and P_{12} values are from Dunn's post-hoc test, representing comparisons between placebo vs. TD0015 5 g, placebo vs. TD0015 7.5 g, and TD0015 5 g vs. TD0015 7.5 g, respectively.
SD, standard deviation; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4
Mean differences of the efficacy endpoints between treatment groups.

	At the end of treatment (T4)		At 90-day follow-up (T5)	
	MD (95 % CI)	P	MD (95 % CI)	P
Percentage change of WOMAC score (%)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	62.2 (52.9; 71.4)		67.1 (56.3; 77.9)	
TD0015 7.5 g vs. Placebo	73.6 (64.3; 83.0)		76.5 (65.6; 87.4)	
TD0015 7.5 g vs. TD0015 5 g	11.5 (2.5; 20.5)		9.4 (−1.1; 19.9)	
Percentage change of VAS score (%)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	53.6 (43.3; 63.9)		63.8 (50.8; 76.8)	
TD0015 7.5 g vs. Placebo	67.9 (57.4; 78.3)		80.7 (67.6; 93.8)	
TD0015 7.5 g vs. TD0015 5 g	14.2 (4.2; 24.3)		16.9 (4.2; 29.5)	
Percentage change of Lequesne score (%)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	55.3 (47.4; 63.3)		64.8 (54.7; 74.9)	
TD0015 7.5 g vs. Placebo	67.7 (59.7; 75.8)		75.0 (64.9; 85.2)	
TD0015 7.5 g vs. TD0015 5 g	12.4 (4.7; 20.1)		10.2 (0.4; 20.0)	
Percentage change of heel-buttock distance (%)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	38.5 (28.3; 48.6)		43.0 (29.3; 56.8)	
TD0015 7.5 g vs. Placebo	49.4 (39.0; 59.7)		54.3 (40.4; 68.1)	
TD0015 7.5 g vs. TD0015 5 g	10.9 (1.0; 20.8)		11.2 (−2.2; 24.6)	
Percentage change of knee flexion (%)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	21.2 (13.4; 28.9)		21.7 (11.8; 31.5)	
TD0015 7.5 g vs. Placebo	27.1 (19.2; 34.9)		27.1 (17.1; 37.0)	
TD0015 7.5 g vs. TD0015 5 g	5.9 (−1.7; 13.4)		5.4 (−4.2; 15.0)	
Absolute change of knee extension (degree)		<0.001		
				<0.001
TD0015 5 g vs. Placebo	6.5 (4.0; 8.9)		6.0 (3.4; 8.6)	
TD0015 7.5 g vs. Placebo	4.9 (2.5; 7.4)		5.1 (2.5; 7.7)	
TD0015 7.5 g vs. TD0015 5 g	−1.5 (−3.9; 0.9)		−0.9 (−3.5; 1.6)	

CI, confidence interval; MD, mean difference; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

ing *Angelica pubescens, Taxillus chinensis, Gentiana macrophylla, Saposhnikovia divaricata, Asarum sieboldii, Ligusticum chuanxiong, Angelica sinensis, Rehmannia glutinosa, Paeonia lactiflora, Cinnamomum cassia, Poria cocos, Eucommia ulmoides, Achyranthes bidentata, Panax ginseng*, and *Glycyrrhiza uralensis*. This formula is traditionally used to treat arthralgia, promoting blood circulation, and nourishing the liver and kidneys.[24] Modern research has supported the traditional use of DJD. Studies have demonstrated its potential to promote chondrocyte proliferation, inhibit apoptosis, and regulate the expression of key inflammatory factors like vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α).[25-28] Clinical trials have demonstrated the efficacy of DJD in managing OA symptoms, showing significant improvement in total WOMAC scores and pain compared to control groups.[13] These studies suggest that DJD treatment should be administered for at least four weeks. TD0015, a formulation based on DJD, incorporates additional herbs such as *Plastrum Testudinis, Cortex Phelodendri*, Animal bone extract, and *Salix alba* extract. These additions are believed to further enhance the formula's bone-strengthening and pain-relieving properties.[29]

Several preclinical studies have investigated the potential effects of TD0015 in models of OA. A 2018 study compared the effects of oral TD0015 (1.2 g/kg and 3.6 g/kg twice daily) with oral diclofenac (3 mg/kg twice daily) in rats with monosodium iodoacetate-induced KOA over six weeks.[15] Both doses of TD0015, as well as diclofenac, reduced knee mobility impairment, improved articular cartilage structure, and decreased levels of the pro-inflammatory cytokines IL-1β and TNF-α. The higher dose of TD0015 demonstrated greater analgesic, anti-inflammatory, and anti-degenerative effects.[15] A 2022 study evaluated the anti-inflammatory effects of oral TD0015 (at the same doses) compared to oral aspirin (200 mg/kg) in rat models of carrageenan-induced paw edema and peritonitis.[17] In a separate arm of this study, TD0015 (2.4 g/kg and 7.2 g/kg twice daily) was compared to oral methylprednisolone (10 mg/kg) in a rat model of asbestos-induced granuloma. TD0015 demonstrated anti-inflammatory effects in both acute and chronic models.[17] Another 2022 study examined the analgesic activity of TD0015 compared to oral aspirin (150 mg/kg) in three different pain models (heat, mechanical, and chemical).[16] TD0015 exhibited analgesic effects in the mechanical and chemical pain models, but not the heat pain model. These preclinical studies provide evidence of the anti-inflammatory and analgesic properties of TD0015 and support its potential for the treatment of KOA.

Apart from TD0015 and DJD, numerous herbal medicines have been used to treat KOA, both orally and topically. A meta-analysis involving 2362 patients demonstrated the safety and efficacy of Chinese herbal medicine in alleviating pain, improving function, and promoting overall health in KOA patients.[30] Similarly, a systematic review of 56 high-quality randomized controlled trials involving 5350 KOA patients provided strong evidence for the safety and efficacy of Chinese herbal medicine.[31] Traditional herbal medicine has been used in various forms in the treatment of KOA.[32,33] Traditional herbal medicines, including those used in Vietnam, often target specific symptoms and mechanisms of disease. For example, TD0015, derived from the DJD formula, is believed to exert its therapeutic effects through analgesic, anti-inflammatory, and blood circulation-promoting properties.[15-17] The increasing global interest in traditional medicine, particularly in Asia, reflects its potential to provide safe and effective treatments for chronic conditions like KOA.

This study has several limitations. Firstly, the relatively short follow-up period of 90 days limits our ability to assess long-term efficacy and safety. Secondly, the sample size was relatively small with a dropout rate of 16 %, which may have impacted the statistical power of the study. Therefore, the findings should be interpreted with caution. A larger, longer-term phase III trial is needed to confirm the benefits of TD0015. Finally, the primary and secondary outcomes were primarily patient-reported, which may be subject to bias. However, these measures are widely used in KOA research and repeated assessments over time can mitigate potential bias.[7,8,31]

In conclusion, this trial phase-II randomized controlled trial demonstrated the safety and efficacy of TD0015, a Vietnamese herbal medicine, in managing KOA. Both TD0015 treatment groups showed significant improvements in pain, stiffness, and physical function compared to placebo. The higher-dose TD0015 group exhibited slightly greater improvements in several outcomes. Importantly, TD0015 was well-tolerated, with a favorable safety profile. While these findings are promising, further larger-scale, long-term studies are needed to confirm the long-term efficacy and safety of TD0015. Additionally, further studies, including mechanistic investigations, are required to elucidate the underlying mechanisms of action of this herbal formulation and to evaluate its potential as a disease-modifying osteoarthritis drug.

CRediT author statement

Conceptualization: NTTH, DTN, HTVN, TTL, NTBH. Methodology: NTTH, DTN, NLV, HTVN, TTL, NTBH, NTH, NKN. Formal Analysis: NLV. Investigation: NTTH, DTN. Data Curation: HTVN, TTL, NTBH, NTH, NKN. Writing - Original Draft: NTTH, DTN. Writing - Review & Editing: NLV, HTVN, TTL, NTBH, NTH, NKN. Project Administration: HTVN, TTL.

Declaration of competing interest

All authors confirm that they have no conflict of interest to declare.

Acknowledgements

We acknowledge all the patients who participated in this study and the medical staff who looked helped in their management at the National Hospital of Traditional Medicine (Hanoi, Vietnam).

Funding

This work was funded by the Sunstar Joint Stock Company (Sao Thai Duong JSC, Hanoi, Vietnam). The funding body had no role in the design of the study, collection, analysis, and interpretation of data, and writing the manuscript.

Ethical statement

Ethical approval was obtained from the Ministry of Health ethics committee (No. 107/CN–HDDD, dated 19 July 2021). Written informed consent was obtained from all participants. The trial adhered to the Declaration of Helsinki and Good Clinical Practice guidelines and was registered at ClinicalTrials.gov (NCT06657495).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2025.101143.

Table S1. Percentage change of the efficacy endpoints by treatment groups after imputation using the last observation carried forward method.
Table S2. Mean differences of the efficacy endpoints between treatment groups after imputation using the last observation carried forward method.
Table S3. Follow-up status, use of study drugs and rescue drugs, and adverse events.
Table S4. Percentage change of routine laboratory tests after treatments.
Figure S1. Routine laboratory tests before and after treatments.
Supplement 1. CONSORT 2010 reporting checklist.

References

1. Herrero-Beaumont G, Pérez-Baos S, Sánchez-Pernaute O, Roman-Blas JA, Lamuedra A, Largo R. Targeting chronic innate inflammatory pathways, the main road to prevention of osteoarthritis progression. *Biochem Pharmacol.* 2019;165:24–32.
2. Dulay GS, Cooper C, Dennison EM. Knee pain, knee injury, knee osteoarthritis & work. *Best Pract Res Clin Rheumatol.* 2015;29(3):454–461.
3. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393(10182):1745–1759.
4. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2163–2196.
5. GBD 2019 Diseases and Injuries CollaboratorsGlobal burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study. *Lancet 2020.* 2019;396(10258):1204–1222.
6. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. *Nat Rev Rheumatol.* 2015;11(1):35–44.
7. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *Bmj.* 2021;375:n2321.

8. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2019;2(2):Cd013273.
9. Guermazi A, Neogi T, Katz JN, Kwoh CK, Conaghan PG, Felson DT, et al. Intra-articular corticosteroid injections for the treatment of hip and knee osteoarthritis-related pain: considerations and controversies with a focus on imaging-radiology scientific expert panel. *Radiology*. 2020;297(3):503–512.
10. Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev*. 2014;2014(5):Cd002947.
11. Cameron M, Gagnier JJ, Little CV, Parsons TJ, Blümle A, Chrubasik S. Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. Part I: osteoarthritis. *Phytother Res*. 2009;23(11):1497–1515.
12. Wang A, Leong DJ, Cardoso L, Sun HB. Nutraceuticals and osteoarthritis pain. *Pharmacol Ther*. 2018;187:167–179.
13. Zhang W, Wang S, Zhang R, Zhang Y, Li X, Lin Y, et al. Evidence of Chinese herbal medicine Duhuo Jisheng decoction for knee osteoarthritis: a systematic review of randomised clinical trials. *BMJ Open*. 2016;6(1):e008973.
14. Hou PW, Fu PK, Hsu HC, Hsieh CL. Traditional Chinese medicine in patients with osteoarthritis of the knee. *J Tradit Complement Med*. 2015;5(4):182–196.
15. Ha NTT, Huong NTTG. Effect of TD0015 on knee osteoarthritis treatment on experimental models. *Med Res J [Vietnamese]*. 2018;113(4):1–9.
16. Ha NTT, Trang TQ, Anh PTV, Lien NTH. Analgesic activity of TD0015 on experimental models. *Med Res J [Vietnamese]*. 2022;157(9):90–97.
17. Ha NTT, Trang TQ, Anh PTV, Lien NTH. Anti-inflammatory effect of TD0015 in experimental animals. *Med Res J [Vietnamese]*. 2022;157(9):82–89.
18. Altman RD. Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl*. 1991;27:10–12.
19. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: kellgren-Lawrence classification of osteoarthritis. *Clin Orthop Relat Res*. 2016;474(8):1886–1893.
20. Schiphof D, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Ann Rheum Dis*. 2008;67(7):1034–1036.
21. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833–1840.
22. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. *J Rheumatol*. 1997;24(4):779–781.
23. Wang X, Wei S, Liu T, Pang J, Gao N, Ding D, et al. Effectiveness, medication patterns, and adverse events of traditional chinese herbal patches for osteoarthritis: a systematic review. *Evid Based Complement Alternat Med*. 2014:343176 2014.
24. Ma Y, Cui J, Huang M, Meng K, Zhao Y. Effects of Duhuojisheng Tang and combined therapies on prolapse of lumbar intervertebral disc: a systematic review of randomized control trails. *J Tradit Chin Med*. 2013;33(2):145–155.
25. Wu G, Chen W, Fan H, Zheng C, Chu J, Lin R, et al. Duhuo Jisheng decoction promotes chondrocyte proliferation through accelerated G1/S transition in osteoarthritis. *Int J Mol Med*. 2013;32(5):1001–1010.
26. Wu G, Fan H, Huang Y, Zheng C, Ye J, Liu X. Duhuo Jisheng decoction-containing serum promotes proliferation of interleukin-1β-induced chondrocytes through the p16-cyclin D1/CDK4-Rb pathway. *Mol Med Rep*. 2014;10(5):2525–2534.
27. Liu F, Liu G, Liang W, Ye H, Weng X, Lin P, et al. Duhuo Jisheng decoction treatment inhibits the sodium nitroprussiate-induced apoptosis of chondrocytes through the mitochondrial-dependent signaling pathway. *Int J Mol Med*. 2014;34(6):1573–1580.
28. Chen CW, Sun J, Li YM, Shen PA, Chen YQ. Action mechanisms of du-huo-ji-sheng–tang on cartilage degradation in a rabbit model of osteoarthritis. *Evid Based Complement Alternat Med*. 2011;2011:571479.
29. Wang X, He Y, Guo B, Tsang MC, Tu F, Dai Y, et al. In vivo screening for anti-osteoporotic fraction from extract of herbal formula Xianlinggubao in ovariectomized mice. *PLoS One*. 2015;10(2):e0118184.
30. Chen B, Zhan H, Marszalek J, Chung M, Lin X, Zhang M, et al. Traditional Chinese medications for knee osteoarthritis pain: a meta-analysis of randomized controlled trials. *Am J Chin Med*. 2016;44(4):677–703.
31. Lin Z, Zheng J, Chen M, Chen J, Lin J. The efficacy and safety of Chinese herbal medicine in the treatment of knee osteoarthritis: an updated systematic review and meta-analysis of 56 randomized controlled trials. *Oxid Med Cell Longev*. 2022;2022:6887988.
32. Lao L, Hochberg M, Lee DYW, Gilpin AMK, Fong HHS, Langenberg P, et al. Huo-Luo-Xiao-Ling (HLXL)-Dan, a Traditional Chinese medicine, for patients with osteoarthritis of the knee: a multi-site, randomized, double-blind, placebo-controlled phase II clinical trial. *Osteoarthritis Cartilage*. 2015;23(12):2102–2108.
33. Chen R, Chen M, Su T, Zhou M, Sun J, Xiong J, et al. Heat-sensitive moxibustion in patients with osteoarthritis of the knee: a three-armed multicentre randomised active control trial. *Acupunct Med*. 2015;33(4):262–269.