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Original Article

Retrospective analysis of traditional Chinese medicine external therapies for knee osteoarthritis: clinical outcomes for blood stasis syndrome

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Abstract: Objective: Knee osteoarthritis (KOA) is a common degenerative joint disease with limited treatment options. For patients with KOA characterized by blood stasis syndrome, traditional Chinese medicine (TCM) therapies, including herbal application and meridian massage, may provide effective help. Methods: This study retrospectively analyzed the data from 240 KOA patients with blood stasis syndrome (120 TCM patients and 120 control patients). The TCM group received a 2-week regimen of herbal application combined with meridian massage, in addition to conventional physical therapy. The control group received only conventional physical therapy, specifically therapeutic deep-heat irradiation (TDP lamp). The differences in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Visual Analog Scale (VAS) for pain, SF-36 Quality of Life scale, objective knee range of motion (AROM), Work Limitations Questionnaire (WLQ-26), TCM Blood Stasis Syndrome Score, and inflammation biomarkers (IL-1β, TNF-α, hs-CRP) were compared between the two groups of patients, and the safety of the drug was evaluated. Results: Compared to the conventional physical therapy group, the TCM group, which received herbal application combined with meridian massage, demonstrated greater improvements in WOMAC score and VAS pain (both $P<0.05$). Significant enhancements in quality of life of were observed in the TCM group ($P<0.05$), along with a marked reduction in serum inflammatory markers. In addition, the TCM group showed superior treatment compliance ($P<0.05$) and an excellent safety profile with no adverse events reported, compared to a 5% incidence in the control group. Conclusion: When added to conventional physical therapy, the combined external TCM treatment of herbal application and meridian massage can more effectively relieve pain, improve quality of life, and reduce inflammation in patients with KOA, demonstrating an excellent safety profile. However, the study design did not allow for the isolation of the independent effects of each TCM modality.

Keywords: Knee Osteoarthritis (KOA), Traditional Chinese Medicine (TCM), blood stasis syndrome, herbal application, meridian massage, clinical outcomes

Introduction

Knee osteoarthritis (KOA) is a chronic degenerative joint disease that is highly prevalent among the elderly. As the global population aging process accelerates, the incidence is increasing year by year. Globally, osteoarthritis affects over 500 million people, equivalent to approximately 7% of the world's population [1]. KOA is characterized by joint cartilage degeneration, subchondral bone lesions, and synovial inflammation [2]. The symptoms are pain, soreness and numbness in joints, muscles, and unfavorable joint flexion and extension, rigidity, swelling, and deformation [3, 4]. Western medicine treatment of the disease includes non-drug treatment, oral antipyretic analgesic and anti-inflammatory drugs, oral opioids, joint injection of long-acting glucocorticoids, joint injection of hyaluronic acid, local medication, and arthroscopic surgery, while complementary and alternative medicine, including traditional Chinese medicine and acupuncture, has garnered increasing attention [5].

TCM classifies KOA into the category of "bone arthralgia" and is closely related to syndrome differentiation [6]. Pathogenic factors obstruct-

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ing the collaterals, leading to pain from blockage, is a key pathogenesis of KOA in TCM. Consequently, TCM practitioners place great importance on treating osteoarthritis based on syndrome patterns [7]. Herbal application and meridian massage in TCM aim to resolve blood stasis and promote circulation, thereby restoring joint function through both local and systemic action [8]. Some studies have found that these therapies may reduce inflammation and enhance cartilage metabolism in patients with KOA, but their efficacy in patients with blood stasis syndrome is unknown [9-11]. This retrospective study aimed to evaluate the effect of external TCM treatment on pain relief, functional improvement, and quality of life in patients with KOA characterized by blood stasis syndrome.

Patients and methods

Study design and participants

This retrospective cohort study analyzed 240 patients diagnosed with KOA and blood stasis syndrome who received treatment between January 2022 and December 2024 at our institution. Patients were divided into two groups: 120 were assigned to a TCM group, receiving external therapies (herbal compresses and meridian massage), while the remaining 120 were assigned to the control group, receiving conventional physical therapy. The study was approved by the Institutional Review Board, with waiver of informed consent granted for retrospective analysis of anonymized clinical data.

Intervention method

The control group received conventional physical therapy, consisting of therapeutic deep-heat irradiation (TDP lamp) on the affected knee for 30 minutes, once daily, for 14 days. The TCM group received the same conventional physical therapy, with two additional interventions: herbal application and meridian massage. It is important to note that this study design lacked single-modality control groups (herbal application alone or meridian massage alone), which limited the ability to distinguish the independent efficacy of each intervention from their potential synergistic effects. For the herbal application, a standardized warm medicinal oil matrix was administered once every other day. This matrix, designed to enhance transdermal delivery, was comprised of a base of sesame oil (50% v/v) and beeswax (10% w/v). Carthamus tinctorius (safflower) extract (15% w/v), Commiphora myrrha (myrrh) essential oil (5% v/v), Boswellia serrata (frankincense) extract (10% w/v), and Angelica sinensis (dong quai) extract (10% w/v) were added into this base. The preparation process involved heating the sesame oil to 80°C, dissolving the beeswax, and then slowly incorporating the herbal extracts under continuous stirring until a homogeneous ointment was formed. Before application, the product should be cooled to 40°C with strict quality control. The herbal extracts were standardized to their marker compounds: safflower extract to a minimum of 1.5% safflower yellow (SY), and myrrh essential oil to a minimum of 30% total volatile oils. The final ointment was examined for microbial content and heavy metal limits (lead <10 ppm, arsenic <2 ppm, cadmium <1 ppm) according to the Chinese Pharmacopoeia standards. For meridian massage, performed once daily following the physical therapy session, targeted acupoints included Xiyan (EX-LE5), Yanglingquan (GB34), Yinlingquan (SP9), Zusanli (ST36), Xuehai (SP10), Weizhong (BL40), Chengshan (BL57), and Liangqiu (ST34), once daily, with each point massaged for 1-2 minutes. Before this study, a validation (n=20) confirmed no cases of significant skin irritation or allergic reaction, ensuring the matrix's safety.

Outcome measures

Primary outcomes included: 1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores; 2) Visual Analog Scale (VAS). Secondary outcomes contained: 1) SF-36 quality of life; 2) Serum inflammatory markers (IL-1β, TNF-α, hs-CRP) detected by ELISA; 3) Pittsburgh Sleep Quality Index (PSQI). Safety outcomes involved adverse event details and treatment completion rates. All outcomes were assessed at baseline and 15-day post-treatment. Knee Osteoarthritis Blood Stasis Syndrome Scale was used to evaluate the severity of blood stasis syndrome and its response to treatment. The scale includes purplish tongue color (0-2 points), wiry pulse (0-2 points), and the nature of pain (e.g., fixed, sharp, stabbing pain; 0-4 points), with a higher total score indicating more severe blood stasis. Furthermore, to assess the quality of life and physical function, eight domains of the SF-36 questionnaire

Table 1. Baseline characteristics of knee osteoarthritis patients with blood stasis syndrome (N=240)

Variable	TCM Group (n=120)	Control Group (n=120)	*p*-value
Age (years), mean ± SD	62.7±5.5	63.1±5.8	0.58
Gender, n (%)			0.52
Female	84 (70.0)	80 (66.7)	
Male	36 (30.0)	40 (33.3)	
BMI (kg/m^2), mean ± SD	26.5±3.0	26.2±2.8	0.41
Disease Duration (years), mean ± SD	5.4±2.3	5.1±2.2	0.28
K-L Grade, n (%)			0.89
Grade II	42 (35.0)	45 (37.5)	
Grade III	56 (46.7)	52 (43.3)	
Grade IV	22 (18.3)	23 (19.2)	
VAS Pain Score (0-10), mean ± SD	6.6±1.1	6.4±1.0	0.15
WOMAC Total Score, mean ± SD	58.5±5.8	58.0±5.6	0.51
Blood Stasis Signs, n (%)			
Purplish Tongue	91 (75.8)	89 (74.2)	0.76
Wiry Pulse	97 (80.8)	95 (79.2)	0.73
Fixed Pain	101 (84.2)	98 (81.7)	0.59
Comorbidities, n (%)			
Hypertension	56 (46.7)	53 (44.2)	0.69
Diabetes	30 (25.0)	26 (21.7)	0.52
Prior Treatments, n (%)			
NSAIDs Use	82 (68.3)	78 (65.0)	0.57
Physical Therapy	52 (43.3)	48 (40.0)	0.60

were analyzed: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Additionally, objective knee joint mobility was measured using a standard goniometer to record the maximum active range of motion (AROM) in degrees for both flexion and extension. Patient work ability was assessed using the Work Limitations Questionnaire (WLQ-26).

Statistical analysis

Data were analyzed using SPSS 27.0. Continuous variables were compared using independent t-tests or Mann-Whitney U tests as appropriate. Categorical variables were analyzed with χ^2 or Fisher's exact tests. Changes from baseline were assessed with paired t-tests. Multivariable linear regression adjusted for potential confounding factors including age, BMI, disease duration, Kellgren-Lawrence (K-L) grade, concomitant medication use, and baseline scores. Additionally, a univariate comparative analysis was performed as a sensitivity analysis to further validate the robustness of the primary outcomes. P<0.05 was considered significant, with two-tailed tests used throughout. Missing data (<5%) were handled using multiple imputation.

Results

Baseline characteristics of study participants

A total of 240 KOA patients (120 TCM group vs. 120 control group) with blood stasis syndrome were included in this retrospective analysis. The baseline characteristics were well-balanced between groups (all P>0.05, **Table 1**).

WOMAC score improvement

The TCM group demonstrated significantly greater improvement in total WOMAC scores compared to the control group (P<0.05), a superior trend that was consistently observed across all subscales (P<0.05) (**Table 2**).

VAS pain reduction

As illustrated in **Figure 1**, the TCM combination therapy resulted in a significantly greater reduction in VAS pain scores compared to the control group (P<0.05). Patients' pain was significantly

Table 2. WOMAC score changes before and after treatment

Indicator	TCM Group		Control Group		*p*-value
	Baseline	Post-Treatment	Baseline	Post-Treatment	
Total WOMAC	58.2±6.1	32.5±5.4	57.8±5.9	47.3±6.2	<0.001
Pain Subscale	12.4±2.1	6.8±1.5	12.1±2.0	9.5±1.8	0.002
Stiffness Subscale	5.3±1.2	2.9±0.8	5.2±1.1	4.1±1.0	0.003
Function Subscale	40.5±4.8	22.8±4.1	40.5±4.6	33.7±4.9	<0.001

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

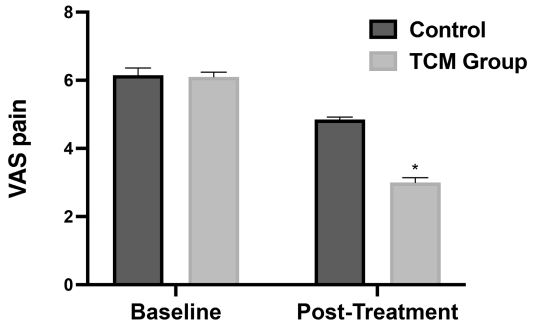

Figure 1. Changes in VAS pain scores from baseline to post-treatment in TCM and control groups. *P<0.05 TCM vs. control group. VAS: Visual Analog Scale; TCM: Traditional Chinese Medicine. Y-axis: VAS Pain Score (0-10); X-axis: Time Point.

relieved after TCM intervention, highlighting its use as a front-line treatment for KOA-related pain.

SF-36 quality of life improvement

As illustrated in **Figure 2**, the SF-36 results showed that TCM treatment significantly improved patients' joint function and mobility and reduced their pain (both P<0.001) (**Figure 2**). These findings suggest that the TCM intervention not only alleviated KOA symptoms but also contributed to the restoration of overall health, daily activities, and social skills.

Multivariate regression analysis

To further verify the treatment effect and control for possible confounding factors, we performed a multivariate linear regression analysis. In a univariate analysis without adjusting for confounding factors, the improvement in the primary outcome measure was significantly better in the TCM group than in the control group (**Table 2**; **Figure 1**). As shown in **Table 3**, after adjusting for age, BMI, baseline score, disease duration, K-L classification, and concomitant medication, combination treatment with TCM remained an independent predictor of significant improvement in WOMAC total score and VAS pain score (both P<0.001). This suggests that the clinical benefits of TCM combination therapy remained robust even after considering these key disease-related variables.

Treatment adherence & safety

Compared to conventional treatment, patients in the TCM group had better treatment compliance and safety. Although both groups showed high treatment completion rates, no adverse events occurred in the TCM group, while mild skin irritation caused by TDP lights occurred in the control group. Consequently, patient satisfaction scores were significantly higher in the TCM group (P<0.001) (**Table 4**). These findings suggest that external TCM therapy was not only highly safe but also well-accepted by patients, which supports its excellent rate of compliance.

Inflammatory biomarker changes

The TCM external therapy demonstrated a significant anti-inflammatory effect. Post-treatment serum levels of IL-1β, TNF-α, and hs-CRP were all significantly lower in the TCM group compared to the control group (all P<0.05) (**Figure 3**). The reduction in key inflammatory factors suggested that TCM can not only relieve KOA symptoms, but also inhibit potential inflammatory responses in the progression of KOA.

Patient-reported sleep quality

TCM therapy led to a significant improvement in sleep quality. As detailed in **Table 5**, the TCM group experienced a greater decrease in PSQI global scores and sleep latency compared to the control group. These improvements sug-

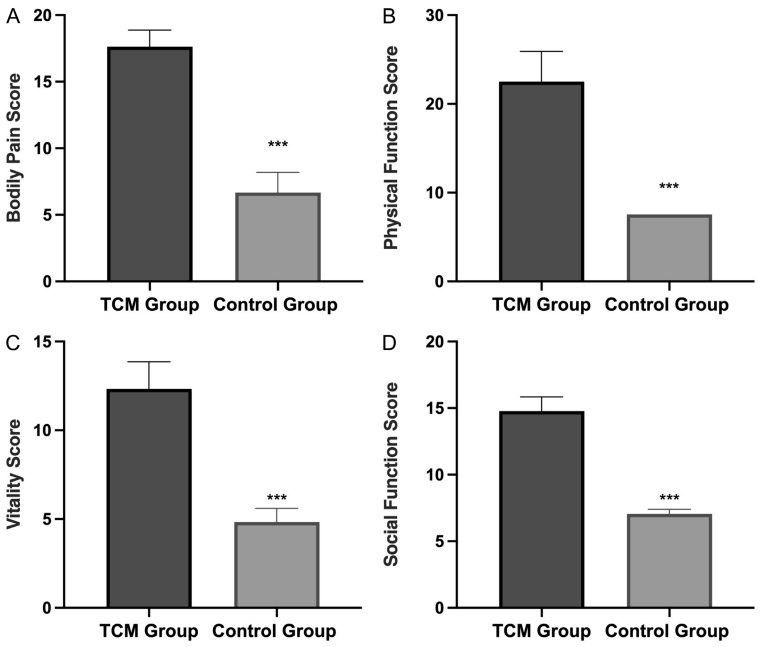

Figure 2. Comparison of SF-36 domain score improvements between TCM and control groups. ***P<0.001 TCM vs. control group. Y-axis: Change from Baseline (Score); X-axis: SF-36 Domains (PF, RP, BP, GH, VT, SF, RE, MH); TCM: Traditional Chinese Medicine.

gest TCM's secondary benefits in addressing sleep disturbances associated with KOA pain.

TCM syndrome score and objective functional outcomes

The targeted effect of the therapy was confirmed by a significant reduction in the Blood Stasis Syndrome Score in the TCM group (**Table 6**). Objective functional gains were also superior, with the TCM group showing greater improvement in knee active range of motion (AROM) for both flexion and extension and reporting significantly better work ability recovery (WLQ-26 scores) compared to controls (all P<0.001).

Subgroup analysis

To further explore the therapy's efficacy, subgroup analyses were conducted. Stratification by Kellgren-Lawrence (K-L) grade showed that TCM therapy was effective across all stages of KOA, even in advanced Grade IV cases (**Figure 4**). Further analysis by demographics and clinical characteristics indicated that the most profound benefits were seen in younger patients (<60 years) and those with a shorter disease duration (<3 years), though efficacy was maintained in older patients and those with comorbidities (**Table 7**).

Analysis of synergistic effects of exploratory treatment

To explore indirect possible synergistic effects of treatment options, we conducted a post-hoc exploratory analysis within the TCM group. Patients were divided into a "fully compliant group" (completing all 7 treatments, n=102) and a "partially compliant group" (missing at least 1 treatment, n=18) based on their compliance with herbal topical treatment. There were no significant differences between the two groups in baseline age, WOMAC total score, or VAS pain score (all P>0.05), indicating comparability between the groups. As shown in **Table 8**, no significant differences were observed between the two subgroups in terms of changes in primary outcome measures. This preliminary finding suggested that the overall cumulative effect of combination therapy may be the main factor driving clinical benefit rather than perfect compliance with monotherapy. However, this was an exploratory analysis, its interpretation was speculative, and the sample size was small (especially for some compliance groups), and the conclusions still need to be verified in future factorial design trials.

Discussion

Traditional Chinese medicine believes that "the liver governs the muscles, and the kidneys govern the bones". After middle age, people gradually gradual decline in liver and kidney function, and their muscles and bones lose nourishment; wind, cold and dampness take advantage of the deficiency to invade and stay in the joints, and traumatic injuries occur, resulting in stagnation of bones and veins. Therefore, liver and kidney deficiency is considered the root cause of the disease, while invasion by pathogenic factors (wind, cold, dampness) and traumatic injury are the precipitating factors [12-14]. Therefore, treatment should replenish liver and kidney, expel wind and cold, relax muscles and tendons, promote blood circulation, regulate qi, and relieve pain. The basic functions of mas-

Table 3. Results of multivariate linear regression analysis of primary outcome measures

Outcome	Predictive Variable	β (95% Confidence Interval)	*p*-value
WOMAC Total Score Change	Treatment Group (TCM vs. Control)	-10.21 (-12.88, -7.54)	<0.001
	Age (years)	-0.08 (-0.21, 0.05)	0.23
	BMI (kg/m^2)	-0.15 (-0.42, 0.12)	0.27
	Baseline WOMAC Score	0.91 (0.78, 1.04)	<0.001
	Disease Duration (years)	-0.23 (-0.49, 0.03)	0.08
	K-L Grade (per grade increase)	-1.12 (-2.35, 0.11)	0.07
	Concomitant NSAID Use (Yes/No)	-0.65 (-1.89, 0.59)	0.30
VAS Pain Score Change	Treatment Group (TCM vs. Control)	-2.15 (-2.98, -1.32)	<0.001
	Age (years)	-0.01 (-0.04, 0.02)	0.51
	BMI (kg/m^2)	-0.02 (-0.09, 0.05)	0.56
	Baseline VAS Score	0.82 (0.71, 0.93)	<0.001
	Disease Duration (years)	-0.05 (-0.12, 0.02)	0.16
	K-L Grade (per grade increase)	-0.18 (-0.51, 0.15)	0.28
	Concomitant NSAID Use (Yes/No)	-0.21 (-0.58, 0.16)	0.26

Table 4. Treatment adherence and safety outcomes

Variable	TCM Group	Control Group	*p*-value
Treatment Completion			0.16
Completed full course, n (%)	114 (95.0%)	106 (88.3%)	
Discontinued early, n (%)	6 (5.0%)	14 (11.7%)	
Reasons for Discontinuation			
Adverse events, n (%)	0 (0.0%)	6 (5.0%)*	0.03
Personal reasons, n (%)	4 (3.3%)	6 (5.0%)	0.47
Lost to follow-up, n (%)	2 (1.7%)	2 (1.7%)	0.51
Adverse Events			
Skin irritation, n (%)	0 (0)	6 (5.0)	0.01
Joint swelling, n (%)	0 (0)	0 (0)	-
Systemic reactions, n (%)	0 (0)	0 (0)	-
Treatment Satisfaction (VAS 0-10)			
Mean score ± SD	8.9±1.1	7.2±1.5	<0.001
Score ≥8, n (%)	102 (85.0%)	76 (63.3%)	0.006

Notes: Note: All skin irritation cases in the control group were mild and alleviated within 72 hours after the TDP lamp was discontinued. **p*-value for adverse events was recalculated using Fisher's exact test.

sage treatment are adjusting the viscera, dredging the meridians and collaterals, promoting qi and blood circulation, and regulating muscles and tendons and reducing injuries. When treating knee osteoarthritis, massage techniques can promote blood circulation in local tissues, promote the absorption of local inflammation, and eliminate pain. Combined with corresponding acupoint application, this can stimulate the qi of meridians and channels and effectively regulate the function of the knee joint [15-18]. Our results demonstrate that compared with conventional physical therapy, herbal application combined with meridian massage treatment can relieve pain, improve knee joint function, reduce inflammation, and significantly improve patients' quality of life. These outcomes align with the TCM principle that resolving blood stasis and qi stagnation is essential for treating musculoskeletal diseases. In addition, our findings suggest that this combination therapy does not merely provide symptomatic relief but may also address the underlying pathologic process, thus providing a comprehensive and superior therapeutic strategy for KOA.

The results of this study found that the WOMAC score of patients in the TCM group decreased significantly, indicating that combined TCM therapy can improve the recovery of joint function. The WOMAC subscale also reflects this improvement, including reduction in joint stiffness and restoration of physical function, indicating that the therapy has a broad spectrum of efficacy [19, 20]. This sustained improvement across multiple functional domains highlights the potential of TCM as a disease-modifying therapy [21].

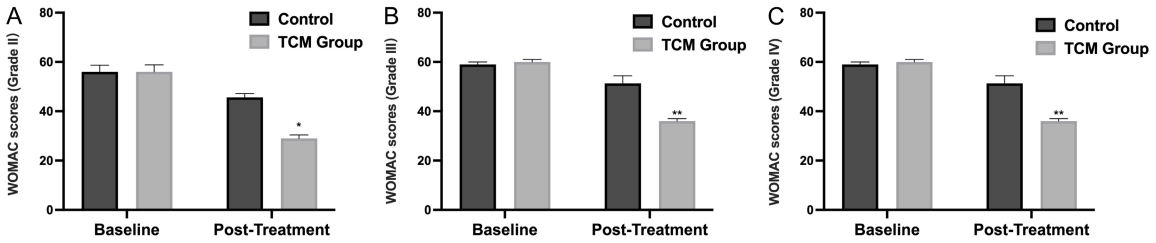

Figure 3. Improvement in WOMAC total score stratified by Kellgren-Lawrence grade. Y-axis: Mean Change in WOMAC Score; X-axis: K-L Grade; *P<0.05, **P<0.01 TCM vs. control group.

Table 5. Changes in sleep quality indicators after treatment

Indicator	TCM Group		Control Group		*p*-value
	Baseline	Post-Treatment	Baseline	Post-Treatment	
PSQI Global Score	5.2±1.8	2.1±0.9	5.4±1.7	4.3±1.2	<0.001
Sleep Latency (min)	25.1±8.2	12.3±4.5	26.8±9.1	20.5±6.3	0.005

Table 6. Changes in TCM syndrome score and objective functional outcomes

Outcome Measure	Group	Baseline	Post-Treatment	Change from Baseline	*p*-value (for Change)
Blood Stasis Syndrome Score (0-8)	TCM	6.5±1.5	1.7±0.9	-4.8±1.2	<0.001
	Control	6.4±1.4	4.3±1.1	-2.1±1.0	
Knee Flexion AROM (degrees)	TCM	105.2±10.1	127.7±9.8	+22.5±5.1	<0.001
	Control	106.1±9.9	118.4±9.5	+12.3±4.8	
Knee Extension Lag (degrees)	TCM	4.1±1.8	0.9±0.7	-3.2±1.5	<0.001
	Control	4.0±1.7	2.9±1.3	-1.1±1.2	
Work Limitations Questionnaire (WLQ-26) Score†	TCM	38.6±6.1	15.3±4.2	-23.3±5.5	<0.001
	Control	39.1±5.9	22.1±5.6	-17.0±4.9	

Notes: ROM: Active Range of Motion. †For WLQ-26, a lower score indicates fewer work limitations and better work ability.

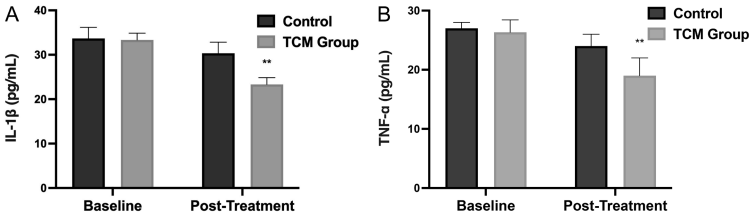

Figure 4. Serum levels of inflammatory biomarkers (IL-1β, TNF-α, hs-CRP) before and after treatment. **P<0.01 TCM vs. control group. Y-axis: Serum Concentration (pg/mL) for IL-1β and TNF-α; (mg/L) for hs-CRP; X-axis: Biomarker.

IL-1β, TNF-α, and hs-CRP are important inflammatory regulatory factors that participate in synovial inflammatory lesions, degradation of articular cartilage matrix, and interfere with the function of chondrocytes. They are closely related to the occurrence and progression of knee osteoarthritis. TNF-α is the initiator of the inflammatory response, which can stimulate the release of other pro-inflammatory factors and aggravate inflammatory damage to tissues. It is an important mediator in the degradation of cartilage matrix and synovial damage. Therefore, serum IL-1 and TNF-α levels can reflect the severity of knee osteoarthritis to a certain extent and can be used to evaluate the condition and treatment effect. This study found that TCM treatment significantly reduced the levels of IL-1β, TNF-α and hs-CRP in patients, indicating that the combined therapy can inhibit the pro-inflammatory cascade, thereby mitigating cartilage degeneration and the synovial inflammatory response characteristic of KOA. Studies have found that in patients with KOA, there is gene overexpression of inflammatory cytokines IL-1β and IL- 8 [22-24]. The anti-inflammatory effect of Chinese herbal

Table 7. Subgroup analysis of WOMAC score improvement by age and VAS score improvement by disease duration

Subgroup Stratification	Subgroup Category	Outcome Measure	TCM Group	Control Group	*p*-value (Between Groups)
Age (years)	<60	WOMAC Score Change	-28.5±4.2	-15.1±4.5	<0.001
	60-70	WOMAC Score Change	-25.1±4.8	-10.5±4.9	<0.001
	>70	WOMAC Score Change	-21.3±5.1	-8.2±5.3	<0.001
	p for trend†		<0.01	<0.01	N/A
Disease Duration (years)	<3	VAS Score Change	-5.2±0.9	-2.5±1.0	<0.001
	3-5	VAS Score Change	-4.5±1.0	-2.1±1.1	<0.001
	>5	VAS Score Change	-3.8±1.1	-1.8±1.2	0.004
Presence of Comorbidities‡ (TCM Group)	With Comorbidities (n=56)	WOMAC Score Change	-24.8±5.3	-11.2±5.5	<0.05
		VAS Score Change	-4.3±1.2	-2.0±1.3	<0.05

Notes: WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. VAS: Visual Analog Scale. †p *for trend* was calculated across the age subgroups within each treatment arm to assess if the treatment effect systematically varied with age. ‡Comorbidities include hypertension and/or diabetes.

Table 8. An exploratory analysis of compliance and efficacy within TCM groups

Outcome Measure	Strict Adherence Subgroup† (n=102)	Minor Deviation Subgroup‡ (n=18)	*p*-value§
Baseline Characteristics			
Age (years), mean ± SD	62.5±5.4	63.9±5.9	0.28
Baseline WOMAC Total Score, mean ± SD	58.3±5.7	59.1±6.2	0.61
Baseline VAS Pain Score, mean ± SD	6.5±1.0	6.8±1.2	0.22
Primary Outcomes (Change from Baseline)			
WOMAC Total Score Change, mean ± SD	-26.1±5.3	-24.8±6.1	0.42
VAS Pain Score Change, mean ± SD	-4.8±1.1	-4.5±1.4	0.38

Notes: † Strict adherence subgroup: Patients who completed all 7 scheduled herbal application sessions. ‡ Minor Deviation Subgroup: Patients who missed at least one herbal application session (≤6 sessions completed). § *p*-value: Comparisons between the two subgroups were made using the independent t-test for continuous variables.

medicine ingredients has been confirmed in many previous clinical studies, and some ingredients inhibit inflammatory responses through NF-κB signaling and downstream cytokines [25]. The data from this study are consistent with previous studies and provide clinical translational evidence of the potential of TCM. However, the underlying molecular mechanisms warrant deeper investigation. Based on the existing literature, we hypothesize that the observed effects are multifactorial. Active components from safflower may inhibit cartilage degradation by downregulating matrix metalloproteinases (MMPs) and upregulating their tissue inhibitors (TIMPs) [26]. Future studies should analyze these cartilage metabolic markers in synovial fluid or serum. Furthermore, the potent anti-inflammatory effects likely involve the modulation of key signaling pathways. Volatile oils from Commiphora myrrha and boswellic acids from Boswellia serrata have been shown to inhibit the NF-κB and MAPK pathways in chondrocytes and synoviocytes, thereby suppressing the transcription of pro-inflammatory cytokines like IL-1β and TNF-α [27]. In the future, animal research or western blot or immunohistochemical analysis of synovial tissue sample sections can be carried out. Effective transdermal delivery determines the efficacy of external use. Although the formulation for this study was designed to enhance penetration, direct evidence is still needed. In the future, *ex vivo* skin penetration experiments using Franz diffusion cells can be carried out, combined with high performance liquid chromatography (HPLC) or mass spectrometry, to quantify the transdermal flux and joint tissue concentration of key herbal ingredients, and establish a direct connection between local application and pharmacologic effects at the target site.

Acupoint application is one of the commonly used and characteristic nursing techniques in TCM. It was first seen in the “Fifty-Two Disease Prescription” and has been widely used in the intervention of various diseases after continu-

ous improvement by doctors. Acupoint application intervention is based on the idea that acupoints are the surface treatment points of diseases, and acupoints relate to each other and form a meridian system. By adjusting the meridian system, local symptoms can be eliminated [28]. This study found that compared with the control group, the VAS score in the TCM group decreased significantly, indicating that the combination treatment can reduce pain in patients. Analgesia takes effect quickly, indicating that TCM combination therapy can work through both peripheral and central mechanisms [29]. Local herbal application may bring local relief by regulating local heat receptors and improving microcirculation, while meridian massage may affect endogenous opioid treatment and descending pain suppression pathways to play a pain-relieving effect [30]. For chronic pain, this multimodal mechanism of combined TCM treatment is often superior to single-target intervention and contrasts with conventional intra-articular analgesic strategies. A systematic review on intra-articular morphine for post-arthroscopic pain found no high-quality evidence supporting its superiority over placebo, with uncertainty regarding its comparative efficacy against local anesthetics and other analgesics [31]. In addition, the multimodal analgesic effect observed is consistent with the holistic approach of TCM. Meridian massage may stimulate endogenous opioid release, like the mechanism proposed for acupuncture, while the herbal application likely contributes through improved microcirculation and topical counter-irritant effects-mechanisms partially shared by some topical NSAIDs but achieved here through phytochemical pathways. This synergistic combination likely explains the superior pain relief observed in our study.

The benefits of combination therapy with TCM are also reflected in further improvements in quality of life measured by SF-36. This study found that the improvements in physical function, pain index, vitality, and social function of patients in the TCM group were better than those of the control group, highlighting the multi-faceted improvement of TCM combination treatment on KOA and patients' quality of life [32]. Importantly, the correlation between patient pain reduction and improved sleep quality suggests the benefits to patient health of effective reduction in core symptoms [33]. Given that patients with KOA frequently present with multiple co-occurring issues such as chronic pain, sleep disorders and depression, the benefits of combined treatment with TCM are extensive and in-depth. By simultaneously addressing pain, joint mobility, and systemic inflammation, TCM therapy can improve patients' quality of life while treating pain.

The results of this study found that the safety of TCM therapy was higher than that of traditional KOA physical therapy. Nonsteroidal anti-inflammatory drug treatment can cause gastrointestinal bleeding and cardiovascular events in patients, while intra-articular drug injection treatment can further accelerate the degeneration of closed joints. In contrast, TCM treatment has no obvious systemic side effects, so it is particularly suitable for elderly patients and patients with KOA combined with other diseases. The high score in patient satisfaction in the results of this study reflects the therapeutic effect of combined TCM treatment and the positive experience brought to patients by personalized care. This dual result of drug safety and high patient acceptance supports the feasibility of incorporating TCM into the main treatment strategy of KOA.

Subgroup analysis further revealed the consistent benefits of patients with different K-L grades from TCM treatment, indicating that TCM treatment can bring treatment benefits to patients at different disease stages. Although the improvement was optimal in grade II patients, even patients with grade IV KOA showed statistically and clinically significant improvements. This finding contradicts the idea that traditional therapies are effective only for early knee osteoarthritis and suggests that TCM can provide effective alternative treatment options for patients who cannot operate or who want to postpone joint replacement. These detailed subgroup analyses suggest that while the TCM external therapy is broadly applicable, it produces the most profound benefits in younger patients and those with a shorter disease history. Importantly, its efficacy and safety profile are maintained in older patients and those with common comorbidities like hypertension and diabetes, making it a particularly valuable option for this complex patient demographic who may have limited choices with conventional therapies. However, this study also has sev-

eral limitations: However, this study has several limitations that warrant careful consideration. First, the control group only received TDP lamp physical therapy, lacking a single-factor control group for either simple herbal application or simple meridian massage. This design precluded the ability to distinguish the independent efficacy of each TCM intervention from their synergistic effect. Second, while the multivariate regression was adjusted for key confounders such as disease duration, K-L grading, and concomitant medication, the retrospective nature of the study still carried a risk of unmeasured confounding and potential attribution bias of efficacy differences. The inclusion of a univariate comparative analysis partially mitigated this but did not eliminate it. Third, this study was retrospective and had potential biases in patient selection. Future studies will carry out prospective studies with longer follow-up periods, which can provide better insight into patients' optimal treatment options and the durability of treatment response.

In summary, this retrospective analysis demonstrated that external treatment of TCM provides a safe and efficient method for the treatment of patients with KOA blood stasis syndrome. External treatment of TCM can reduce patient pain, improve joint activity, reduce inflammation, and improve quality of life. As the medical community increasingly recognizes the limitations of current KOA treatments, an integrative approach that combines TCM with conventional care holds promise as an optimal strategy for managing this challenging condition.

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Disclosure of conflict of interest

None.

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