CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2026; 32: e951501
DOI: 10.12659/MSM.951501

Received: 2025.09.11
Accepted: 2026.04.20
Available online: 2026.05.22
Published: 2026.XX.XX

Efficacy and Safety of Celecoxib Combined With Jintiange Capsules for the Treatment of Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Jiaxin Zhao
ACD 1 Yongwei Li
BE 1 Yulin Wang
BF 2 Shuo Wang
BD 1 Jidong Song
CEG 1 Wei Wang

1 The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, PR China
2 Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, PR China

Corresponding Author: Wei Wang, Department of Comprehensive Orthopaedics, Second Affiliated Hospital, Xi'an Jiaotong University, No. 157, Xiwu Road, Xi'an, Shaanxi, China, Phone: +86 15129222929, e-mail: dr.wangwei@xjtu.edu.cn

Financial support: This work was supported by the National Natural Science Foundation of China (grant number: 82072522) and the Integrated Traditional Chinese and Western Medicine Clinical Collaboration Innovation Project of the Shaanxi Administration of Traditional Chinese Medicine (2020-ZXY-003)

Conflict of interest: None declared

Background: Knee osteoarthritis (KOA) poses a substantial global health burden, and conventional nonsteroidal anti-inflammatory drug (NSAID) therapy with celecoxib is hindered by adverse effects. This study evaluated the efficacy and safety of combining celecoxib with Jintiange capsules, a synthetic tiger bone formulation used in traditional Chinese medicine (TCM), to manage symptomatic KOA.

Material/Methods: This 12-week, randomized, double-blind, placebo-controlled trial enrolled 120 patients with KOA (age ≥40 years; visual analog scale [VAS] score 4-7). Participants received celecoxib (200 mg/day tapered to 100 mg/day) combined with either Jintiange capsules (3.6 g/day) or placebo. The primary outcome was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score. Secondary outcomes included WOMAC subscale scores (pain, function, and stiffness), VAS scores, and adverse drug reaction reports.

Results: The experimental group demonstrated a 23.5-point (37.8%) reduction in WOMAC total score from baseline ($P<0.001$); the control group showed a 13.2-point (21.6%) reduction ($P<0.001$). The experimental group achieved 51.6% improvement in the WOMAC pain subscale ($P<0.001$), whereas the control group showed 33.3% improvement ($P<0.001$). Relative to the control group, the experimental group demonstrated a greater reduction in VAS score ($P<0.001$). Combined TCM-NSAID therapy produced significantly greater pain relief and functional improvement than NSAID monotherapy.

Conclusions: Celecoxib combined with Jintiange capsules provided clinically meaningful improvements in pain relief and functional outcomes relative to celecoxib monotherapy in patients with KOA. These findings support integration of TCM with conventional pharmacotherapy for osteoarthritis management.

Keywords: Celecoxib • Medicine, Chinese Traditional • Osteoarthritis, Knee • Osteoarthritis • Dyskinesias • Southwestern United States • Pain • Randomized Controlled Trial

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/951501

5273 3 7 36

APPROVED GALLEY PROOF

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

APPROVED GALLEY PROOF

Introduction

Knee osteoarthritis (KOA) is a prevalent musculoskeletal disorder characterized by pain, deformity, and impaired mobility [1,2]. This condition substantially contributes to the global disease burden, with studies projecting a 74.9% increase in prevalence by 2025 [3]. The American College of Rheumatology Guidelines for the Management of Osteoarthritis of the Knee strongly recommend oral nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with KOA [4], among which celecoxib is widely used in clinical practice [5]. However, Wang and colleagues demonstrated that the incidence of cardiovascular, gastrointestinal, renal, and other adverse effects associated with celecoxib progressively increased according to treatment duration [6].

Traditional Chinese medicine has emerged as a complementary therapeutic approach for chronic musculoskeletal disorders, with demonstrated efficacy in conditions such as osteoporosis, rheumatoid arthritis, and KOA [7]. Clinical evidence suggests that traditional Chinese medicine can provide efficacy comparable to or greater than that of conventional pharmacotherapy while causing fewer adverse effects [8,9]. Studies have shown that the physicochemical and biochemical properties of Jintiange—including nitrogen content, dynamic viscosity, and optical rotation—closely resemble those of natural tiger bone, without substantial differences in pharmacological activity. Jintiange reportedly exerts anti-inflammatory, analgesic, bone-healing, and bone metabolism-enhancing effects [10,11]. Jintiange is produced using bones obtained from legally sourced and sustainably raised domestic edible animals, including *Sus scrofa domestica* L., *Capra hircus* Linnaeus, and *Cervus nippon* Temminck. Its mineral composition contains approximately 18% calcium and 8% phosphorus, as well as peptides and proteins [12,13]. Consequently, Jintiange was approved as a Class I new drug by the China Food and Drug Administration (China, Z20030080) and has been widely used in the treatment of osteoporosis and osteoarthritis [14]. Previous studies have demonstrated that Jintiange is a cost-effective and efficacious therapeutic option [15,16]. The principal component of Jintiange is synthetic tiger bone, a traditional Chinese medicinal formulation with demonstrated therapeutic efficacy in the treatment of bone-related disorders, including osteoporosis, osteoarthritis, and rheumatoid arthritis [17,18]. In a 48-week randomized, double-blind, controlled clinical trial involving 248 patients, Chen et al found that Jintiange showed efficacy superior to placebo in the treatment of KOA while maintaining a comparable safety profile [19].

Celecoxib is widely used for the management of KOA; however, its systemic adverse effects are well documented and may vary according to treatment duration. Building on previous findings, we investigated whether combined therapy with celecoxib and Jintiange capsules could provide greater clinical improvement in patients with symptomatic KOA. Additionally, we aimed to determine whether this combination therapy, administered alongside a scientifically guided reduction in celecoxib dosage, could reduce drug-related adverse effects more effectively than celecoxib monotherapy.

Material and Methods

Ethics Approval

The study protocol was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Xi'an Jiaotong University (Approval No. 2022040) on December 15, 2023, prior to participant enrollment. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The trial was prospectively registered in the Chinese Clinical Trial Registry on January 5, 2024 (registration number: ChiCTR2400079541), and all study procedures were initiated after ethics approval.

Study Design and Population

Sample size calculations were performed using PASS software with the superiority test module for comparing means between 2 groups. The Type I error rate (α) was set at 0.05, and the statistical power ($1-\beta$) was set at 80%. The calculated minimum sample size was 46 participants per group. To adjust for potential attrition, the sample size was increased by 15%, resulting in a final target enrollment of 60 participants per group.

This study was designed as a randomized, double-blind, placebo-controlled clinical trial. A total of 120 participants, including 72 women and 48 men aged 40 years and older, were randomly recruited from local community groups in Xi'an, Shaanxi Province, China, between January 2024 and June 2024. The study flowchart is presented in **Figure 1**.

Enrollment and Treatments

Among the 120 participants screened and enrolled, 68 were randomly assigned to the experimental group and 52 to the control group. In the experimental group, all 68 participants completed the 2-week assessment. At week 4, 1 participant was lost to follow-up, leaving 67 participants. At week 8, 4 additional participants withdrew (2 lost to follow-up, 1 with a protocol violation, and 1 without a reported reason), resulting in 63 remaining participants. By week 12, 5 more participants withdrew (2 lost to follow-up, 1 with a protocol violation, and 2 without a reported reason), leaving 58 participants who completed the study. Overall, 10 participants (14.7%) withdrew from the experimental group (5 lost to follow-up, 2 with protocol violations, and 3 without a reported reason).

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

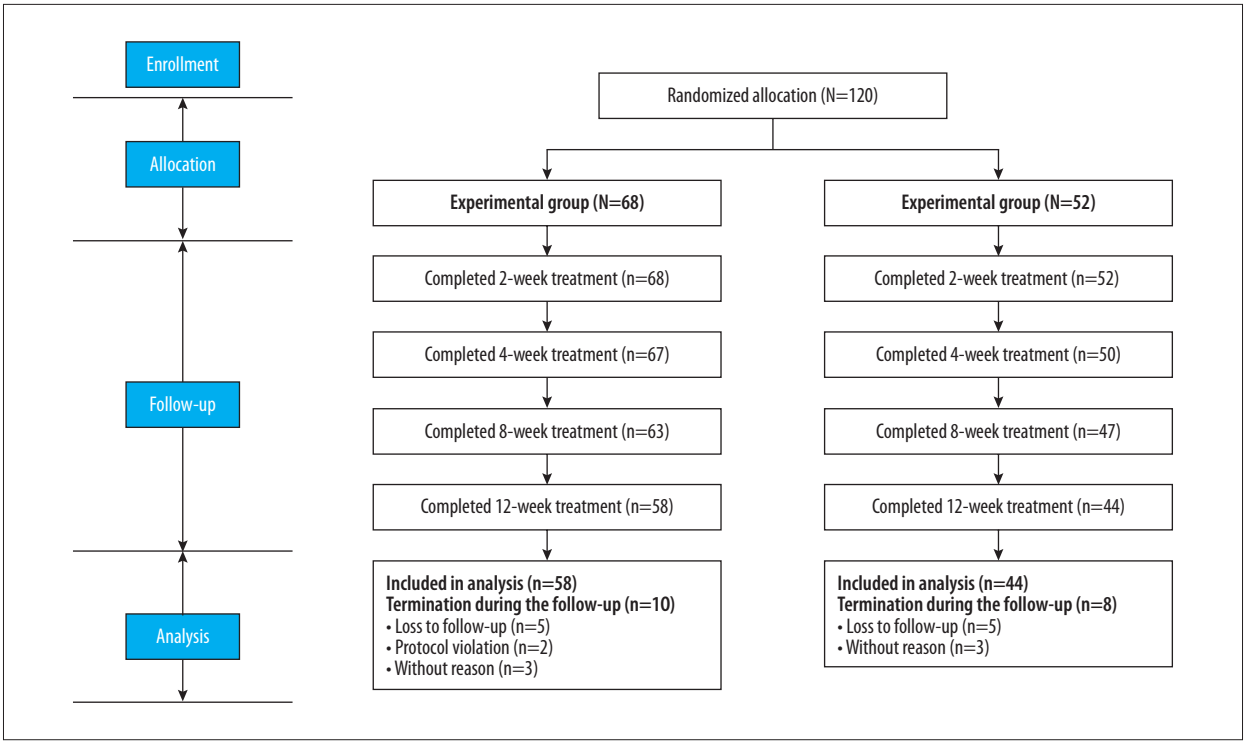

Figure 1. Participant intervention flowchart.

In the control group, all 52 participants completed the 2-week assessment. At week 4, 2 participants were lost to follow-up, leaving 50 participants. At week 8, 3 additional participants withdrew (1 lost to follow-up and 2 without a reported reason), resulting in 47 remaining participants. By week 12, 3 more participants withdrew (1 lost to follow-up and 2 without a reported reason), leaving 44 participants who completed the study. Overall, 8 participants (15.4%) withdrew from the control group (5 lost to follow-up and 3 without a reported reason).

Analysis Cohorts

The intention-to-treat (ITT) cohort included all 120 randomized participants. Missing data from 18 participants (experimental group: n=10; control group: n=8) were addressed using multiple imputation with predictive mean matching across 10 imputed datasets. The per-protocol cohort included participants who completed all treatment phases: 58 in the experimental group and 44 in the control group. Participants with major protocol deviations, including non-adherence and loss to follow-up, were excluded from the per-protocol analysis.

Inclusion and Exclusion Criteria

Participants were enrolled if they met the following eligibility criteria: (1) fulfillment of the clinical diagnostic criteria for KOA; (2) age between 40 and 70 years, with no sex restrictions; (3) body mass index (BMI) up to 35 kg/m^2; (4) classification in either the remission or recovery phase of KOA; (5) baseline visual analog scale (VAS) pain score between 4 and 7; (6) no pharmacological treatment, intra-articular injection, or surgical intervention for KOA within the preceding 3 months; (7) willingness to comply with the study protocol, including scheduled visits and clinical assessments; and (8) provision of written informed consent after a full explanation of the study objectives, procedures, and potential risks.

Participants were excluded if they met any of the following criteria: (1) traumatic knee arthritis, acute joint trauma within 6 weeks before enrollment, knee osteoarticular tuberculosis, or musculoskeletal malignancy; (2) rheumatoid arthritis, other seropositive arthropathies, active systemic lupus erythematosus, or vasculitis; (3) major organ dysfunction, including clinically significant cardiovascular disease (New York Heart Association class III/IV), cerebrovascular accident within the previous 6 months, hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase >2× the upper limit of normal), renal impairment (estimated glomerular filtration rate <45 mL/min/1.73 m^2), or hematologic disorders (platelet count <100×10^9/L or hemoglobin <10 g/dL); (4) documented psychotic disorders, neuropathic arthralgia refractory to standard therapy, or active peptic ulcer disease confirmed by endoscopy; (5) prior unilateral or bilateral knee arthroplasty or arthroscopic surgery within the previous 12 months; (6) use of organ-toxic medications within 4 weeks before enrollment, including chemotherapeutic or immunosuppressive agents, use of

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

APPROVED GALLEY PROOF

Figure 2. Randomization and blinding process. Randomization codes were generated with a computer-based random number allocation method. Participants were assigned to the experimental or control group according to the generated randomization sequence. To maintain allocation concealment and blinding, study medications were packaged identically and labeled using non-identifying color-coded section labels without disclosure of treatment assignment.

herbal preparations or proprietary Chinese medicines for KOA within 2 weeks before enrollment, or chronic opioid therapy for more than 30 consecutive days; (7) pregnancy, lactation, positive serum β-human chorionic gonadotropin test result, or known hypersensitivity to celecoxib or Jintiange components; or (8) inability to comply with study procedures due to language barriers or cognitive impairment, or concurrent participation in another interventional clinical trial.

Randomization and Blinding

Randomization was performed using computer-generated random numbers to ensure unbiased group allocation. Participants, healthcare providers, and outcome assessors were blinded to treatment assignments throughout the study. The randomization sequence was generated using SPSS Statistics 26.0 software, which produced a stratified allocation scheme according to the study protocol. Eligible participants were randomly assigned to either the experimental group (celecoxib combined with Jintiange capsules) or the control group (celecoxib combined with placebo capsules) using computer-generated randomization codes (**Figure 2**). To adjust for potential medication loss or wastage, the total quantity of study medication exceeded the number required for the enrolled participants. Consequently, although the target enrollment was 60 participants per group, the final group sizes were not perfectly equal.

To maintain blinding, all medication boxes were identically packaged and labeled with non-identifying color-coded section labels (yellow or blue) that did not indicate treatment allocation. The appearance of the active medication and placebo packaging was identical across groups. Allocation concealment was ensured via sealed envelopes containing the randomization codes, which were opened sequentially after participant enrollment. This procedure minimized selection bias and maintained methodological rigor in accordance with CONSORT guidelines for randomized controlled trials.

Experimental Group

Participants in the experimental group received 2 medications for the treatment of KOA with baseline VAS pain scores ranging from 4 to 7. Celecoxib was administered orally at an initial dose of 200 mg once daily. After 4 weeks of treatment, the dosage was reduced to 100 mg once daily. Celecoxib treatment was discontinued completely after 8 weeks. Jintiange capsules were administered at a dose of 400 mg per capsule, with a total daily dose of 3.6 g (3 capsules taken orally 3 times daily). The Jintiange regimen was maintained continuously for 12 weeks (3 months).

Study medications were dispensed in 4 sequential distributions corresponding to scheduled clinical visits. At the baseline visit (week 0), participants received an initial 2-week medication supply. At the 2-week follow-up visit, an additional 2-week supply was provided. At the 4-week visit, participants received a 4-week supply covering weeks 4 through 8. At the 8-week visit, the final supply of Jintiange capsules was dispensed for weeks 8 through 12. This staggered distribution strategy was designed to support medication adherence while permitting dose adjustment according to clinical response. The celecoxib tapering regimen was implemented to reduce the risk of treatment-related adverse effects; the fixed-dose Jintiange regimen was maintained to provide sustained symptomatic relief throughout the 12-week intervention period.

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Control Group

Eligible participants with KOA and baseline VAS pain scores ranging from 4 to 7 received celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor. Celecoxib was administered orally at a dose of 200 mg once daily during weeks 0 through 4. During weeks 5 through 8, the dose was reduced by 50% to 100 mg once daily. Treatment with celecoxib was completely discontinued after week 8. Participants in the control group also received visually identical placebo capsules matching the physical characteristics of Jintiange capsules. The placebo capsules were administered orally at 3 capsules per dose (1.2 g total), 3 times daily for 12 consecutive weeks.

To ensure treatment adherence and facilitate dose adjustments, study medications were dispensed in 4 sequential distributions corresponding to scheduled clinical assessment visits. At the baseline visit (week 0), participants received a 2-week medication supply covering days 1 through 14. At week 2, an additional 2-week supply was dispensed for days 15 through 28. At week 4, participants received a 4-week supply covering days 29 through 56. At week 8, participants in the placebo group received the final 4-week placebo supply covering days 57 through 84. The celecoxib tapering regimen was designed to balance therapeutic efficacy with long-term safety considerations; the fixed placebo regimen maintained blinding throughout the 12-week intervention period. The staggered medication distribution strategy also enabled ongoing monitoring of treatment response and promoted protocol adherence.

Data Collection

Participant characteristics collected were age, sex, alcohol and tobacco use, clinical parameters (systolic blood pressure, diastolic blood pressure, and BMI), medical history (hypertension, diabetes mellitus, and coronary artery disease), and medication use, including proprietary Chinese medicines, NSAIDs, and slow-acting anti-inflammatory drugs.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used as the primary outcome measure, and the VAS served as a secondary outcome measure. Both instruments are validated patient-reported outcome measures commonly used in musculoskeletal research. The WOMAC, specifically developed for osteoarthritis assessment, evaluates pain, stiffness, and physical function, whereas the VAS provides a unidimensional assessment of subjective pain intensity. Data were collected at baseline and during follow-up visits at weeks 2, 4, 8, and 12 (**Figure 1**).

Face-to-face interviews were conducted with participants at baseline and during the 2-, 4-, and 8-week follow-up visits. At the initial visit, physicians measured height and weight. Blood pressure was measured twice using an electronic sphygmomanometer after participants had rested for 10 minutes in a seated position with back support. The average of the 2 measurements was recorded as the final blood pressure value.

Outcome Measures

The WOMAC LK 3.1 validated version was used to assess pain, stiffness, and physical function. This self-administered questionnaire consists of 24 items: 5 pain items, 2 stiffness items, and 17 physical function items. Each item was scored on a 5-point Likert scale ranging from 0 (none) to 4 (extreme). Subscale scores for pain (0-20), stiffness (0-8), and physical function (0-68), as well as the total WOMAC score (0-96), were calculated by summing the corresponding item scores. Higher scores indicated more severe symptoms and greater functional impairment. The questionnaire was administered at baseline before treatment initiation and at weeks 2, 4, 8, and 12 after randomization. Participants completed the questionnaire independently during clinic visits, with assistance from a research coordinator when necessary. The WOMAC LK 3.1 has been extensively validated for KOA assessment; it demonstrates high internal consistency (Cronbach's α >0.85) and responsiveness to clinical change.

Pain intensity was assessed using a 100-mm horizontal VAS anchored at 0 mm ("no pain") and 100 mm ("worst imaginable pain"). Participants recorded pain intensity at rest and during activity, such as walking, on paper forms. VAS scores were determined by measuring the distance in millimeters from the 0-mm anchor point to the participant's mark; measurements to the nearest millimeter were performed by blinded assessors. VAS assessments were conducted at the same timepoints as WOMAC assessments: baseline and weeks 2, 4, 8, and 12. The VAS is a widely accepted standard tool for pain assessment with high test-retest reliability (intraclass correlation coefficient >0.90) and sensitivity to treatment effects.

All outcome measures were collected within 24 hours before treatment initiation at baseline and during scheduled follow-up visits throughout the 12-week intervention period. Outcome assessors underwent standardized professional training and remained blinded to treatment allocation throughout the study. Participants were instructed not to disclose their group assignments during assessments. Missing data were addressed using multiple imputation with predictive mean matching across 10 imputed datasets as the primary approach; last observation carried forward served as a sensitivity analysis to assess the robustness of the findings. Functional assessments were repeated when initial measurements were considered invalid.

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

APPROVED GALLEY PROOF

KOA Definition

This study used the latest diagnostic criteria for KOA established by the Chinese Orthopaedic Association [20]. The diagnostic criteria included: (1) knee pain within the previous month; (2) radiographic evidence of joint space narrowing, subchondral bone sclerosis, cystic degeneration, and osteophyte formation at the joint margins; (3) age 50 years and older; (4) morning stiffness lasting 30 minutes or less; and (5) crepitus during joint movement. KOA was diagnosed when criterion 1 and at least 2 of criteria 2 through 5 were met.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation with 95% confidence intervals; categorical variables are presented as frequencies and percentages.

Baseline demographic and clinical characteristics were compared between groups using independent-samples t-tests for normally distributed continuous variables, as assessed by the Shapiro-Wilk test; Levene's test was used to evaluate homogeneity of variance. Non-normally distributed variables were analyzed via the Mann-Whitney U test. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate.

The primary analysis followed the ITT principle, in which all randomized participants (n=120) were included regardless of protocol adherence or withdrawal status. Missing data (n=18) were addressed using multiple imputation with predictive mean matching across 10 imputed datasets to preserve randomization integrity. Sensitivity analysis using the last observation carried forward method demonstrated consistent effect estimates, confirming the robustness of the results.

Outcome measures (ie, WOMAC and VAS scores) were analyzed using repeated-measures analysis of variance, with group (experimental vs control) as the between-participants factor and time (baseline, 4 weeks, and 8 weeks) as the within-participants factor. Post hoc pairwise comparisons were performed using Bonferroni correction for multiple comparisons. Although the primary repeated-measures analysis of variance included baseline, 4-week, and 8-week assessments to evaluate treatment efficacy, supplementary analyses also incorporated 2-week data to assess early treatment response and 12-week data to evaluate the durability of treatment effects.

Effect sizes were calculated using Cohen's d for t-tests and partial eta squared (η^2p) for analysis of variance. All statistical tests were 2-tailed, and the statistical significance threshold was regarded as $P<0.05$. The Benjamini-Hochberg procedure was utilized to control the false discovery rate associated with multiple hypothesis testing. This analytical approach was designed to ensure robust interpretation of treatment effects while controlling for potential confounding factors and maintaining Type I error control. Assumptions underlying repeated-measures analysis of variance were also evaluated. Mauchly's test indicated no violation of sphericity ($P=0.08$); however, the Greenhouse-Geisser correction was applied conservatively. Quantile-quantile plots demonstrated acceptable residual normality for the primary outcomes, and Shapiro-Wilk test results were non-significant ($P>0.05$). Homogeneity of variance was confirmed using Levene's test ($P=0.12$). Bonferroni correction was additionally applied for secondary endpoint analyses involving multiple comparisons.

Results

Baseline Characteristics of the Overall Population

Baseline demographic, clinical, and laboratory characteristics of the overall cohort (N=120) and the intervention groups (experimental group, n=68; control group, n=52) are summarized in **Table 1**. Continuous variables are presented as mean±standard deviation; categorical variables are expressed as frequencies and percentages. The mean participant age was 56.4±7.4 years, with no significant difference between the experimental group (56.6±7.5 years) and control group (55.9±7.6 years; $P=0.963$). The cohort was predominantly female (66.67%); there was a slightly higher percentage of women in the experimental group (70.59%) than in the control group (61.54%).

The mean baseline WOMAC total score was 61.6±6.7, with comparable scores between the experimental group (62.1±6.6) and control group (61.1±6.8). Subscale analyses also demonstrated similar baseline scores for pain (12.0±1.8), physical function (43.9±5.4), and stiffness (5.4±0.6) across both groups. The mean baseline VAS score was 6.1±0.7 in both groups. Anthropometric measurements showed no clinically meaningful differences in height (165.5±8.5 cm overall) or body weight (67.0±12.0 kg overall), although BMI was slightly higher in the control group than in the experimental group (25.5±2.5 vs 24.3±3.5 kg/m^2).

Hematologic indices demonstrated only minor variations between groups. Hemoglobin level was slightly higher in the control group than in the experimental group (141.3±14.0 g/L vs 137.0±15.2 g/L), whereas platelet count (231.5±67.7×10^9/L) and leukocyte count (5.6±1.6×10^9/L) were comparable between groups. Liver function parameters, including alanine aminotransferase (20.8±10.0 IU/L) and aspartate aminotransferase (23.2±5.9 IU/L), as well as renal function indices, including

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Baseline characteristics of the overall study population.

Clinical variables	Overall	Experimental group	Control group
Numbers	120	68	52
Age	56.4±7.4	56.6±7.5	55.9±7.6
Sex			
Male	40 (33.33%)	20 (29.41%)	20 (38.46%)
Female	80 (66.67%)	48 (70.59%)	32 (61.54%)
WOMAC score	61.6±6.7	62.1±6.6	61.1±6.8
Pain subscale	12.0±1.8	12.0±1.9	12.0±1.7
Function subscale	43.9±5.4	42.8±5.2	43.3±5.6
Stiffness subscale	5.4±0.6	5.3±0.6	5.3±0.6
VAS score	6.1±0.7	6.1±0.7	6.1±0.7
Height (cm)	165.5±8.5	165.3±8.7	167.1±10.1
Weight (kg)	67.0±12.0	66.5±12.2	71.7±11.8
BMI (kg/m^2)	24.4±3.4	24.3±3.5	25.5±2.5
Hypertension	13 (10.8%)	7 (10.3%)	6 (11.5%)
RBC (10^{12}/L)	4.5±0.5	4.5±0.5	4.4±0.4
WBC (10^9/L)	5.6±1.6	5.7±1.6	5.6±1.5
Hb (g/L)	137.90±15.3	137.0±15.2	141.3±14.0
Plt (10^9/L)	231.5±67.7	232.3±70.1	233.86±64.1
DBIL (μmol/L)	3.1±1.5	3.0±1.5	3.8±1.6
BU (μmol/L)	10.0±4.3	10.0±4.5	10.1±4.7
ALT (IU/L)	20.8±10.0	20.7±10.4	19.8±9.3
AST (IU/L)	23.2±5.9	23.3±6.1	22.7±6.6
TP (g/L)	73.0±4.0	73.0±4.1	72.6±2.7
ALB (g/L)	45.1±2.8	45.0±4.1	45.4±2.6
Glb	27.9±3.9	28.1±3.9	27.2±3.2
Urea (mmol/L)	4.8±1.3	4.8±1.4	5.0±1.3
CREA (μmol/L)	59.8±13.1	59.5±13.5	64.1±11.5
eGFR-EPI	117.8±29.6	116.6±30.1	121.4±27.00

Values are presented as mean±standard deviation or No. (%). Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BU, indirect bilirubin; CREA, creatinine; DBIL, direct bilirubin; eGFR-EPI, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; Glb, globular proteins; Hb, hemoglobin; Plt, platelets; RBC, red blood cells; TP, total protein; VAS, visual analog scale; WBC, white blood cells; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

creatinine (59.8±13.1 μmol/L) and estimated glomerular filtration rate (calculated via the Chronic Kidney Disease Epidemiology Collaboration equation; 117.8±29.6 mL/min/1.73 m^2), did not significantly differ between groups.

Between-group comparisons performed using independent-samples t-tests for continuous variables and chi-square tests for categorical variables revealed no statistically significant differences for any baseline parameter (all P>0.05), indicating good baseline comparability between intervention groups.

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

APPROVED GALLEY PROOF

Table 2. Estimated changes from baseline and mean differences in outcomes between experimental and control groups.

Variable	Change from baseline (95% CI), Δ%		Mean difference (95% CI), Δ%	*P*
	Experimental group	Control group	β (95% CI)	
WOMAC score				
Baseline	62.1	61.1	61.6	
Total subscale				
2-week change	-8.1 (-8.6, -7.6), 13.0%	-6.0 (-6.8, -5.2), 9.8%	-6.9 (-7.6, -6.3), 11.2%	0.000
4-week change	-14.5 (-15.0, -14.0), 23.3%	-9.3 (-10.4, -8.1), 15.2%	-12.0 (-13.2, -10.8), 19.5%	0.000
8-week change	-19.0 (-19.9, -18.1), 30.6%	-11.5 (-13.0, -9.9), 18.8%	-15.3 (-17.0, -13.6), 24.8%	0.000
12-week change	-23.5 (-24.7, -22.3), 37.8%	-13.2 (-14.9, -11.4), 21.6%	-18.6 (-20.8, -16.3), 30.2%	0.000
Pain subscale				
Baseline	12	12	12	
2-week change	-2.3 (-2.6, -2.0), 19.2%	-1.6 (-2.0, -1.2), 13.3%	-1.9 (-2.1, -1.7), 15.8%	0.001
4-week change	-4.0 (-4.4, -3.5), 33.3%	-2.6 (-3.0, -2.2), 21.7%	-3.3 (-3.7, -2.9), 27.5%	0.000
8-week change	-5.0 (-5.6, -4.4), 41.7%	-3.4 (-4.0, -2.8), 28.3%	-4.2 (-4.7, -3.7), 35.0%	0.000
12-week change	-6.2 (-7.0, -5.5), 51.6%	-4.0 (-4.8, -3.3), 33.3%	-5.2 (-5.8, -4.5), 43.3%	0.000
Function subscale				
Baseline	43.9	42.8	43.3	
2-week change	-4.5 (-4.9, -4.1), 10.3%	-3.2 (-3.8, -2.7), 7.5%	-3.9 (-4.3, -3.5), 9.0%	0.000
4-week change	-8.3 (-8.8, -7.8), 18.9%	-5.2 (-5.8, -4.7), 12.1%	-6.8 (-7.5, -6.1), 15.7%	0.000
8-week change	-11.4 (-12.2, -10.7), 30.0%	-6.5 (-7.3, -5.8), 15.2%	-9.1 (-10.2, -8.0), 21.0%	0.000
12-week change	-14.6 (-15.6, -13.7), 33.3%	-7.8 (-8.6, -7.0), 18.2%	-11.3 (-12.8, -9.8), 26,1%	0.000
Stiffness subscale				
Baseline	5.4	5.3	5.3	
2-week change	-1.3 (-1.6, -1.0), 24.1%	-1.0 (0, 0), 18.9%	-1.2 (-1.3, -1.0), 22.6%	0.038
4-week change	-2.2 (-2.6, -1.9), 40.7%	-1.5 (-1.9, -1.1), 28.3%	-1.9 (-2.1, -1.6), 35.8%	0.004
8-week change	-2.4 (-2.6, -2.0), 44.4%	-1.5 (-2.0, -1.1), 28.3%	-2.0 (-2.3, -1.7), 37.7%	0.002
12-week change	-2.6 (-2.9, -2.3), 48.1%	-1.5 (-1.9, -1.1), 28.3%	-2.0 (-2.4, -1.7), 37.7%	0.000
VAS score				
Baseline	6.1	6.1	6.1	
2-week change	-1.8 (-2.4, -1.2), 29.5%	-0.5 (-1.2, -0.1), 8.2%	-1.1 (-1.8, -0.3), 18.0%	0.002
4-week change	-2.6 (-3.0, -2.2), 42.6%	-0.9 (-1.2, -0.4), 14.8%	-1.2 (-1.9, -0.8), 19.7%	0.006
8-week change	-3.1 (-3.4, -2.8), 50.8%	-1.1 (-1.5, -0.7), 18.0%	-2.0 (-2.5, -1.4), 32.8%	0.000
12-week change	-3.4 (-3.8, -3.0), 55.7%	-1.2 (-1.5, -0.9), 19.7%	-2.5 (-2.8, -2.0), 41.0%	0.000

Percentage change (Δ%)=Absolute value of change/baseline. Abbreviations: CI, confidence interval; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, visual analog scale.

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

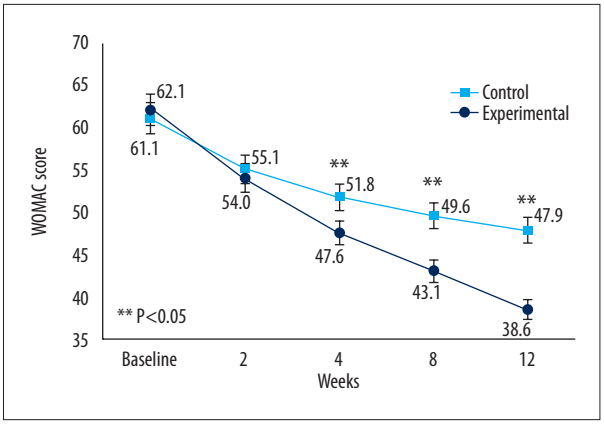

Figure 3. Changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in the experimental and control groups over 12 weeks.

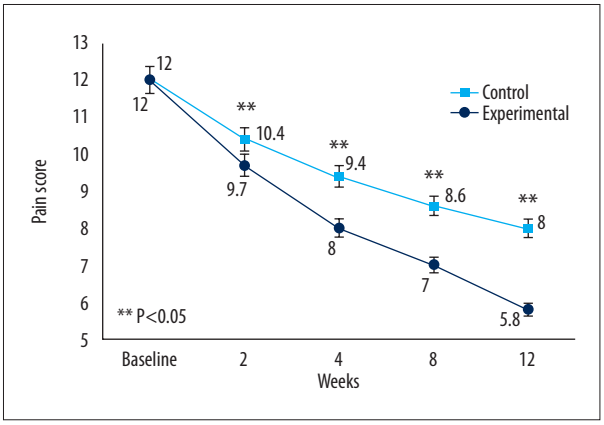

Figure 4. Changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores in the experimental and control groups over 12 weeks.

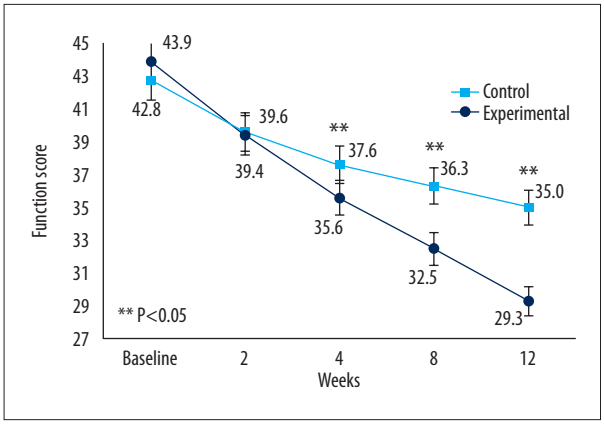

Figure 5. Changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscores in the experimental and control groups over 12 weeks.

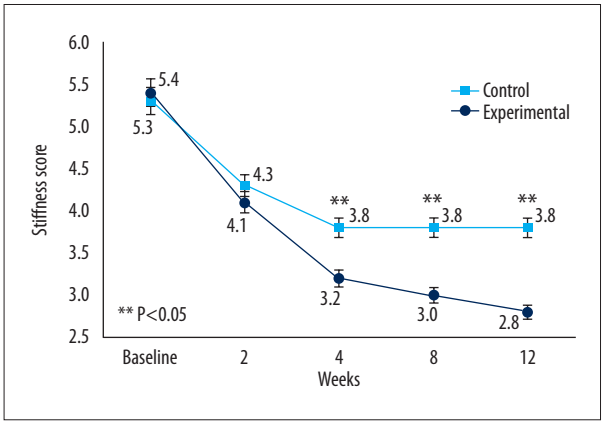

Figure 6. Changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness subscores in the experimental and control groups over 12 weeks.

Changes in WOMAC Scores During the Trial Period

As shown in **Figure 3**, both groups demonstrated progressive reductions in WOMAC scores throughout the study period, indicating symptomatic improvement. However, the experimental group exhibited a steeper decline beginning at week 4 and achieved significantly greater reductions than the control group at weeks 4, 8, and 12 (all $P<0.05$). During the 12-week follow-up period, the experimental group demonstrated a 23.5-point reduction in WOMAC total score, whereas the control group showed a 13.2-point reduction over the same interval (**Table 2, Figure 3**).

Figure 4 demonstrates that the experimental group achieved greater pain reduction than the control group. The magnitude of improvement in WOMAC pain scores was significantly greater in the experimental group (6.2±1.2 points) than in the control group (4.0±1.5 points), corresponding to 51.6% and 33.3% improvements from baseline, respectively. Significant between-group differences were observed at all assessment timepoints (weeks 2, 4, 8, and 12; all $P<0.05$). The superiority of the experimental intervention remained evident at week 12, when the experimental group achieved near-normal pain scores (5.8±0.9), but the control group continued to exhibit moderate pain levels (8.0±1.1).

The randomized controlled trial also demonstrated superior efficacy of the experimental intervention in improving physical function compared with the control treatment. The clinical relevance of these findings was supported by the persistence of statistically significant differences throughout the 12-week follow-up period. At study completion, participants in the experimental group retained 26% greater functional improvement than those in the control group (29.3 vs 35.0; **Figure 5**).

Significant between-group differences in WOMAC stiffness subscores emerged at weeks 4, 8, and 12 (all $P<0.05$). Although

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

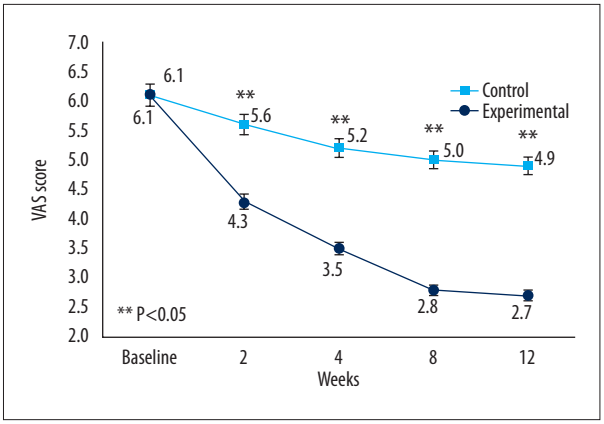

Figure 7. Changes in visual analog scale (VAS) scores in the experimental and control groups over 12 weeks.

stiffness scores in the control group plateaued after week 4 (3.8±0.6), the experimental group demonstrated continued improvement through week 12, with scores decreasing from 3.8±0.7 at baseline to 2.8±0.5 at week 12. This divergent trajectory resulted in a 26% greater improvement in stiffness in the experimental group by the end of the study (**Figure 6**).

Changes in VAS Scores During Follow-Up

As illustrated in **Figure 7**, statistically significant differences in VAS scores were observed between the experimental and control groups at weeks 2, 4, 8, and 12 (all $P<0.05$). The temporal pattern of pain reduction was consistent with the findings of the WOMAC pain subscale, supporting concordance between subjective pain assessment and functional outcome measures in this study.

Adverse Drug Reactions

No significant gastrointestinal adverse reactions, including abdominal pain, nausea, or vomiting, were observed during the follow-up period. Additionally, no abnormalities were detected in routine fecal or urinary examinations at baseline or during the intervention period (**Table 3**). No serious adverse drug reactions occurred during the 12-week study period. In the experimental group, 2 participants reported pruritus, which spontaneously resolved within 1 week. In the control group, 1 participant reported abnormal knee joint sensation, which also resolved within 1 week. However, the relatively small sample size and short study duration may limit comprehensive evaluation of the long-term cardiovascular and gastrointestinal safety of NSAID therapy, particularly involving celecoxib. Furthermore, the 12-week intervention period and the selected study population may limit the generalizability of the safety findings.

ITT vs Per-Protocol Results

The primary analysis was conducted according to the ITT principle and included all 120 randomized participants, with missing data addressed through multiple imputation. In the ITT analysis, the experimental group demonstrated a reduction of 23.5 points in WOMAC total score (62.1 to 38.6, $P<0.001$) and a mean VAS pain reduction of 3.4±0.5 points (7.2 to 3.8). A secondary per-protocol analysis included the 102 participants who completed the study (experimental group: 58; control group: 44) and excluded participants with major protocol deviations. The per-protocol analysis reflected outcomes under optimal treatment adherence conditions and demonstrated treatment effects consistent with—but generally greater than—those observed in the ITT analysis.

Discussion

This 12-week clinical trial demonstrated that celecoxib combined with Jintiange capsules was more effective than celecoxib combined with placebo capsules. At weeks 2, 4, 8, and 12 after treatment initiation, the experimental group exhibited significantly lower WOMAC total scores and lower pain, physical function, and stiffness subscores compared with the control group (all $P<0.05$). These findings indicate that the combination of Jintiange capsules and celecoxib provides clinically

Table 3. Adverse drug reactions.

	Overall	Experimental group	Control group
Variable adverse reactions	0	0	0
Redness and swelling of the knee	2	2	0
Pruritus	0	0	0
Skin rash	0	0	0
Abdominal pain	0	0	0
Nausea	0	0	0
Abnormal laboratory findings	0	0	0
Abnormal sensation in the knee	1	0	1

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

meaningful improvements in pain relief, physical function, and joint stiffness in patients with KOA. The sustained reductions in WOMAC scores across all domains further support the therapeutic potential of this integrated pharmacological approach for improving patient-reported outcomes. No serious adverse events were observed during the study period; the safety profile of combined celecoxib and Jintiange therapy appeared comparable to that of celecoxib monotherapy during the 12-week treatment period. Nevertheless, longer-term studies with larger sample sizes are required to comprehensively evaluate the safety and tolerability of this combination therapy, particularly regarding potential cardiovascular and gastrointestinal risks associated with NSAID use. Given the favorable efficacy and safety findings observed in this study, multicenter phase IV clinical trials are warranted to validate the generalizability of these results to broader and more diverse patient populations.

A review of the literature revealed no previous studies investigating combined use of celecoxib and Jintiange capsules for the treatment of KOA. To our knowledge, this is the first study to evaluate the efficacy and safety of this pharmacological combination for the management of osteoarthritic knee pain. A meta-analysis by Nurmohamed et al indicated that celecoxib demonstrated a favorable safety profile relative to other NSAIDs in patients with rheumatoid arthritis and osteoarthritis, without a statistically significant increase in cardiovascular adverse events [21]. Zeng et al reported that sodium hyaluronate combined with celecoxib was superior to sodium hyaluronate or celecoxib monotherapy for improving knee symptoms, enhancing clinical efficacy, reducing VAS scores, and decreasing adverse effects in patients with KOA [22]. However, intra-articular injection is an invasive procedure, and some patients may be unwilling to tolerate the associated pain and discomfort [23]. Shen et al investigated the metabolic alterations associated with Jintiange treatment through serum metabolomics in mice with complete-Freund's-adjuvant-induced inflammatory pain. Their findings suggested that Jintiange attenuates inflammatory pain via modulation of the glycerophospholipid/protein kinase C/transient receptor potential vanilloid 1 (TRPV1) signaling pathway [24]. Compared with the present clinical trial, their study provided mechanistic insights into the potential analgesic effects of Jintiange. Another meta-analysis demonstrated that Jintiange capsules significantly improved bone mineral density in patients with KOA, thereby alleviating clinical symptoms [25]. A systematic review concluded that Jintiange capsules, administered either alone or in combination with other therapies, effectively reduced bone loss, relieved pain severity, and decreased adverse event incidence [18].

Park et al conducted a prospective, randomized, double-blind, multicenter study comparing the efficacy and safety of celecoxib and GCSB-5, a novel formulation derived from 6 herbal extracts, for the treatment of KOA. WOMAC scores improved by 20.5 points in the celecoxib group and 21.3 points in the GCSB-5 group (P=0.79). Corresponding percentage reductions in WOMAC scores were 42.0% and 38.9%, respectively (P=0.54); VAS pain scores decreased by 29.9 points and 27.9 points, respectively (P=0.58). No significant differences were observed between treatment groups regarding pain reduction, functional improvement, or safety outcomes [26]. Xu et al recruited 40 patients with muscle atrophy after orthopedic surgery and randomly assigned them to 2 groups. The control group received routine rehabilitation training once daily, whereas the observation group received routine rehabilitation training combined with Jintiange capsule treatment. Significantly greater improvement in muscle strength was observed in the observation group compared with the control group, suggesting that Jintiange capsules may mitigate skeletal muscle atrophy after orthopedic surgery [27]. Previous studies have also demonstrated that Jintiange provides favorable therapeutic effects in both women and men, with comparable efficacy across sexes [11,16]. Relative to other proprietary Chinese medicines, Jintiange appears to be a more cost-effective therapeutic option [15]. Liang et al evaluated the efficacy of Jintiange capsules combined with alfacalcidol for improving musculoskeletal outcomes in patients with primary osteoporosis or osteopenia [28]. Their study enrolled 400 participants who completed a 52-week intervention period. The results showed statistically significant improvements in muscle strength and lower extremity balance function in the treatment group compared with the positive control group. In the present study, combination therapy with Jintiange and celecoxib led to significant improvements in WOMAC subscores compared with placebo-treated controls, including a 6.2-point reduction in pain (P<0.05), a 14.6-point improvement in physical function (P<0.01), and a 2.6-point reduction in stiffness (P<0.05) after the 12-week intervention period. VAS pain scores also demonstrated a corresponding 3.4-point reduction relative to baseline in the active treatment group. These findings suggest that Jintiange can provide therapeutic benefits in both osteoporotic and osteoarthritic populations. In our intervention group, skeletal muscle strength significantly improved relative to measurements in placebo controls (P<0.01). Among patients with KOA, Jintiange treatment was associated with clinically meaningful reductions in WOMAC pain and stiffness subscores, accompanied by improvements in physical function. Nevertheless, we acknowledge limitations related to study population selection. Shared environmental exposures, similar lifestyle factors, and potential genetic clustering within localized communities may limit the representativeness of the study population relative to broader populations. Consequently, the findings may not fully address regional differences in healthcare access, dietary habits, or genetic polymorphisms affecting drug metabolism. Additionally, internal validity may have been influenced by unmeasured confounding factors associated with community-based recruitment, including social influences on treatment adherence and reporting bias.

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

APPROVED GALLEY PROOF

Principal symptoms of KOA include joint pain, stiffness, and impaired mobility. The disease typically progresses slowly and may ultimately lead to loss of joint function and disability [29]. Given that pain is the most common symptom of KOA [30], pain relief is a critical indicator for evaluating treatment efficacy. Pelletier et al conducted a randomized, double-blind, multicenter clinical trial involving 288 participants over a 6-month period. They reported WOMAC pain score reductions of 11.1 points in the bisacodyl group and 11.8 points in the celecoxib group, relative to baseline [31]. In the present study, 12-week reductions in WOMAC pain scores were 5.2 points in the overall cohort, 6.2 points in the experimental group, and 4.0 points in the control group. The smaller magnitude of improvement observed in our study was likely related to the shorter intervention duration. At the 12-week follow-up, the control group demonstrated a WOMAC pain score of 8.0 points, whereas the experimental group maintained a lower score of 5.8 points. Compared with earlier assessments, both groups showed progressive improvement in pain scores, suggesting that Jintiange continued to exert therapeutic effects during the later phase of the trial, even after discontinuation of celecoxib. A meta-analysis by Gabriel et al (studies published between 1975 and 1990) demonstrated that NSAID users had an approximately 3-fold greater risk of serious gastrointestinal adverse events compared with non-users [32]. Thus, treatment efficacy evaluation must be balanced against the risk of treatment-related adverse events. In the present study, celecoxib dosage was gradually tapered during the intervention period and completely discontinued by week 8. Previous studies have shown that prolonged celecoxib use can lead to adverse effects such as peptic ulcer disease and myocardial infarction [33]. Furthermore, celecoxib-associated adverse reactions have been reported to emerge as early as 4 weeks after treatment initiation [34,35]. In the present study, the celecoxib dose was reduced by 50% after 4 weeks whereas the Jintiange dosage remained constant throughout the intervention period. Under this regimen, the experimental group demonstrated significantly greater therapeutic efficacy than the control group.

Several limitations should be acknowledged concerning the present study. First, the participants primarily comprised patients with KOA from northwestern China. Given the known regional differences in disease presentation and progression [36], this geographic concentration may limit the generalizability of the findings. Second, although 120 participants were enrolled, the relatively modest sample size warrants cautious interpretation of the results. Future studies with larger sample sizes and multicenter designs are needed to further validate the efficacy of this combined pharmacological approach. Third, the potential effects of placebo response and selection bias on study outcomes could not be fully determined because these factors were not systematically evaluated or controlled in the study design.

Conclusions

Combination therapy with celecoxib and Jintiange capsules demonstrated superior therapeutic efficacy relative to celecoxib combined with placebo capsules. The incidence of treatment-emergent adverse events was low and did not significantly differ between groups, suggesting no clinically meaningful short-term safety differences between treatment regimens.

Institution Where the Work Was Performed

Department of Comprehensive Orthopaedics, Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, PR China.

Data Availability Statement

The datasets generated and analyzed during the current study are maintained by the investigators and are available from the corresponding author upon reasonable request.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Glyn-Jones S, Palmer AJR, Agricola R, et al. Osteoarthritis. Lancet. 2015;386(9991):376-87
2. Sharma L. Osteoarthritis of the knee. N Engl J Med. 2021;384(1):51-59
3. Zhu S, Qu W, He C. Evaluation and management of knee osteoarthritis. J Evid Based Med. 2024;17(3):675-87
4. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2020;72(2):149-62
5. Puljak L, Marin A, Vrdoljak D, et al. Celecoxib for osteoarthritis. Cochrane Database Syst Rev. 2017;5(5):CD009865
6. Wang YC, Chiang JH, Hsu HC, Tsai CH. Decreased fracture incidence with traditional Chinese medicine therapy in patients with osteoporosis: A nationwide population-based cohort study. BMC Complement Altern Med. 2019;19(1):42
7. Zhang P, Li J, Han Y, et al. Traditional Chinese medicine in the treatment of rheumatoid arthritis: A general review. Rheumatol Int. 2010;30(6):713-18
8. Lin J, Zhu J, Wang Y, et al. Chinese single herbs and active ingredients for postmenopausal osteoporosis: From preclinical evidence to action mechanism. Biosci Trends. 2017;11(5):496-506
9. Wang M, Liu L, Zhang CS, et al. Mechanism of traditional Chinese medicine in treating knee osteoarthritis. J Pain Res. 2020;13:1421-29

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

10. Guo X, Ye J, Li J. Research progress on the skeleton of tiger and its substitute. J Shaanxi Normal Univ Nat Sci Ed. 2006;(S1):218-21
11. Li W, Ye B, Meng S, et al. The effect of Jintiange capsules on pain in patients with primary osteoporosis: A systematic review and meta-analysis. BMC Musculoskelet Disord. 2025;26(1):465
12. Liu Y, Zhao L, He X, et al. Jintiange proteins promote osteogenesis and inhibit apoptosis of osteoblasts by enhancing autophagy via PI3K/AKT and ER stress pathways. J Ethnopharmacol. 2023;311:116399
13. Luo Y, Liu X, Xu Z. Letter to the editor regarding "Effects of Jintiange on the healing of osteoporotic fractures in aged rats." J Orthop Surg Res. 2025;20(1):527
14. Man Y, Na J, Wang H, Lan F, Yu L. Efficacy and safety of Jintiange in the treatment of osteoporosis: A systematic review and meta-analysis. Front Pharmacol. 2025;16:1592184
15. Wang C, Lin X, Liu J, et al. Cost-effectiveness analysis of Chinese patent medicines for the treatment of postmenopausal osteoporosis in China. Front Public Health. 2025;13:1596676
16. Wang Y, Chen G, Zhou Z, et al. Male osteoporosis: A comprehensive review of treatment approaches in modern pharmacotherapy and traditional Chinese medicine interventions. Endocr Metab Immune Disord Drug Targets. 2025 [Online ahead of print]
17. Ren S, Jiao G, Zhang L, et al. Bionic tiger-bone powder improves bone microstructure and bone biomechanical strength of ovariectomized rats. Orthop Surg. 2021;13(3):1111-18
18. Zhao YR, Wei X, Jiang JJ, et al. Systemic review of Jintiange capsules in treatment of postmenopausal osteoporosis. Zhongguo Zhong Yao Za Zhi. 2019;44(1):186-92
19. Chen ZG, Xu H, Wang KZ, et al. The efficacy and safety of bionic tiger bone powder for the treatment of knee osteoarthritis in early stage: A randomized, double-blind, placebo-controlled, multicenter clinical trial. Altern Ther Health Med. 2023;29(6):370-76
20. Wang K. Osteoarthritis diagnosis and treatment guidelines. Chin J Orthop. 2018;38(12):705-15
21. Nurmohamed M, Cheng BR, Chen JQ, et al. Cardiovascular safety of celecoxib in rheumatoid arthritis and osteoarthritis patients: A systematic review and meta-analysis. PLoS One. 2021;16(12):e0261239
22. Zeng M, Wu Z, Liang J, Gong A. Efficacy and safety of sodium hyaluronate combined with celecoxib for knee osteoarthritis: A systematic review and meta-analysis. Asian J Surg. 2024;47(3):1331-38
23. Perruccio AV, Young JJ, Wilfong JM, et al. Osteoarthritis year in review 2023: Epidemiology and therapy. Osteoarthritis Cartilage. 2024;32(2):159-65
24. Shen Y, Ren QR, Liu YL, et al. Metabolomics reveals glycerophospholipid metabolism as the action mechanism of Jin-Tian-Ge capsules in ameliorating inflammatory pain. J Ethnopharmacol. 2026;355(Pt A):120589
25. Zhao J, Zeng L, Wu M, et al. Efficacy of Chinese patent medicine for primary osteoporosis: A network meta-analysis. Complement Ther Clin Pract. 2021;44:101419
26. Park YG, Ha CW, Han CD, et al. A prospective, randomized, double-blind, multicenter comparative study on the safety and efficacy of celecoxib and GCSB-5, dried extracts of six herbs, for the treatment of osteoarthritis of knee joint. J Ethnopharmacol. 2013;149(3):816-24
27. Xu J, Wang SG, Xu JC, Zhu JW. Jin-Tiange capsule combined with rehabilitation training for the treatment of skeletal muscle atrophy after surgery. Asian J Surg. 2024;47(8):3620-21
28. Liang H, Wang O, Cheng Z, et al. Jintiange combined with alfacalcidol improves muscle strength and balance in primary osteoporosis: A randomized, double-blind, double-dummy, positive-controlled, multicenter clinical trial. J Orthop Translat. 2022;35:53-61
29. Dulay GS, Cooper C, Dennison EM. Knee pain, knee injury, knee osteoarthritis and work. Best Pract Res Clin Rheumatol. 2015;29(3):454-61
30. Haq SA, Davatchi F. Osteoarthritis of the knees in the COPCORD world. Int J Rheum Dis. 2011;14(2):122-29
31. Pelletier JP, Raynauld JP, Dorais M, et al. An international, multicentre, double-blind, randomized study (DISSCO): Effect of diacerein vs celecoxib on symptoms in knee osteoarthritis. Rheumatology (Oxford). 2020;59(12):3858-68
32. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med. 1991;115(10):787-96
33. Solomon DH, Husni ME, Wolski KE, et al. Differences in safety of nonsteroidal antiinflammatory drugs in patients with osteoarthritis and patients with rheumatoid arthritis: A randomized clinical trial. Arthritis Rheumatol. 2018;70(4):537-46
34. Xiao J, Jia SJ, Wu CF. Celecoxib-induced drug fever: A rare case report and literature review. J Clin Pharm Ther. 2022;47(3):402-6
35. Navarro SL, Herrero M, Martinez H, et al. Differences in serum biomarkers between combined glucosamine and chondroitin versus celecoxib in a randomized, double-blind trial in osteoarthritis patients. Antiinflamm Antiallergy Agents Med Chem. 2020;19(2):190-201
36. Long H, Liu Q, Yin H, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: Findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172-83

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]