ORIGINAL ARTICLE

Comparative Efficacy and Safety of Benjakul vs. Naproxen in Primary Knee Osteoarthritis: A Multicenter RCT

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Objective: To compare the efficacy and safety of Benjakul (BJK) and Naproxen (NPX) for treating primary knee osteoarthritis (KOA) in a multicenter randomized trial.

Materials and Methods: Three hundred fifty participants were randomly assigned to receive either BJK or NPX for four weeks. The primary endpoint was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Similarly, secondary endpoints including the 40-meter fast-paced walk test (40mFPWT), Timed Up and Go test (TUG), WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS), and the 12-item Short Form Survey (SF-12V2). Statistical analysis revealed comparable improvements across all measures ($p \leq 0.05$), confirming treatment equivalence. Safety evaluations were performed through laboratory tests.

Results: BJK showed notable improvements in pain reduction and functional outcomes compared to NPX, with significant improvements in VAS, TUG, total WOMAC score, and individual categories of the KOOS score at 14 and 28 days. The adverse event rate was dry lips and throat in 8.2% in the BJK group and 6.5% in the NPX group with abdominal discomfort, and constipation being the most common side effect.

Conclusion: BJK demonstrates comparable efficacy and safety to NPX in treating KOA, with no significant safety concerns identified in the clinical trial. This suggests that BJK can be recommended as a natural anti-inflammatory drug for patients suffering from knee osteoarthritis.

Keywords: Thai Traditional Remedy; Knee Osteoarthritis; Clinical Efficacy and Safety; Randomized Controlled trial; Adverse events

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Primary knee osteoarthritis (KOA) is a prevalent and debilitating condition affecting Thai elderly population[1,2]. It is traditionally managed with non-steroidal anti-inflammatory drugs (NSAIDs) such as Naproxen (NPX)[3-5]. While NSAIDs effectively alleviate pain and inflammation, their long-term use poses risks of gastrointestinal and cardiovascular complications, necessitating the exploration of safer alternatives[6]. Benjakul (BJK), a traditional Thai herbal formulation comprising five medicinal plants, *Piper retrofractum* Vahl, *Piper sarmentosum* Roxb., *Piper interruptum* Opiz., *Plumbago indica* Linn., and *Zingiber officinale* Roscoe, has demonstrated promising anti-inflammatory properties through laboratory and clinical investigations[5-10]. Grounded in traditional Thai medicine principles of balancing the five elemental components [Patawi (earth), Apo (water), Wayo (air), Thejo (fire), and Ethereal (space)][11,12], BJK has shown preliminary evidence of safety and efficacy in KOA treatment[13-15]. However, its clinical efficacy and safety in comparison to standard treatments like NPX remain unclear.

This multicenter, randomized clinical trial aimed to address this gap by evaluating the efficacy and safety of BJK at 300 mg/day, as listed in the National List of Essential Medicines of Thailand[12] against NPX. The present study focused on alleviating pain, improving functional impairment, and enhancing the quality of life for KOA patients, potentially providing a safer alternative to conventional therapies.

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Table 1. Medicinal plants in BJK remedy formulation

Thai name	Scientific name	Specimen voucher	Part used
Dee-plee	*Piper retrofractum* Vahl	SKP146160301	Fruits
Chaa-ploo	*Piper sarmentosum* Roxb.	SKP146161901	Root
Sa-kan	*Piper interruptum* Opiz.	SKP146160901	Vine
Jet-ta-moon-plerng-daeng	*Plumbago indica* Linn.	SKP148160901	Root
Khing	*Zingiber officinale* Roscoe.	SKP206261501	Rhizome

BJK=Benjakul; NPX=Naproxen

Materials and Methods

Study design and randomization

The present study was a multicenter, double-blind, randomized controlled trial (Thai Clinical Trials Registry, TCTR20200827001) that evaluated the efficacy and safety of BJK versus NPX in treating KOA. The study was approved by Thammasat University's Medical Ethics Committee (MTU-EC-TM-4-057/62) and adhered to the latest Declaration of Helsinki principles. The study, conducted between May 2020 and June 2022, employed block randomization, in size of six, to ensure balanced one to one allocation between treatment arms. The randomization schedule was generated by an independent statistician and overseen by an impartial expert without conflicts of interest. Treatment efficacy, safety, and adherence were monitored through follow-up assessments on days 14 and 28 post-treatment initiation, with medication provided continuously until the study's completion.

Sample size and power analysis

The study's sample size was determined through a power analysis, which indicated a requirement of 350 participants to detect a minimum 15% difference in the primary outcome measure [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score] between the intervention groups, with 80% power at a significance level of 0.05. The pooled standard deviation was derived from the previous research[16,17], and to compensate for an anticipated 15% attrition rate, 175 participants were allocated to each treatment arm, thereby maintaining adequate statistical power for the analysis.

Recruitment of patients

Participant recruitment was conducted across four Thai hospitals, Thammasat University Hospital in Pathum Thani, Dansai Crown Prince Hospital in Loei, Thapkhlo Hospital in Phichit, and Phonthong Hospital in Roi Et, which were chosen based on patient volume, geographic distribution, and resource availability. The study population comprised individuals aged 50 to 80 years who met the American College of Rheumatology clinical criteria for primary KOA, presenting with knee pain scoring of 3 or higher on the pain scale, radiological evidence graded 1 to 3 on the Kellgren-Lawrence scale, and a minimum two-week washout period from previous treatments. Participants were excluded if they were pregnant, had hypertension, body mass index (BMI) of more than 32 kg/m^2, or reported a history of peptic ulcers, gastroesophageal reflux disease, heart disease, kidney disease, liver disease, or allergies to herbs or NPX, with all conditions verified through laboratory testing. Prior to study initiation, participating hospitals engaged in a joint training session to standardize research protocols and data collection methodologies, and informed consent was obtained using a study-approved declaration explained in Thai, with fingerprints accepted as an alternative to signatures when necessary.

Drug preparation and blinding

All components of the BJK remedy as shown in Table 1 were cleaned of foreign matter, dried at 50°C, and weighed in equal proportions. The ingredients were mixed, ground into a coarse powder, and macerated with 95% ethanol at room temperature for three days. The mixture was filtered, and the residue was re-macerated twice. The extracts were concentrated with a rotary evaporator (Rotavapor R-205, Buchi, Switzerland) and dried through lyophilization. The final extract was processed into powder and encapsulated at a concentration of 100 mg per capsule. All herbal ingredients and the BJK preparation underwent quality control in accordance with the Thai Herbal Pharmacopeia. Stability was evaluated using accelerating shelf-life testing (ASLT) while chemical stability was assessed by high-performance liquid chromatography (HPLC) with piperine as the chemical marker. The piperine content in BJK extract was determined to be 144.29 mg/g. For comparison, NPX, 250 mg capsules, twice a day,

(Naprosyn LE®) were supplied by Roche Thailand Ltd. and Omeprazole, 20 mg, (Miracid, Berlin) was included as an over-the-counter medication. Blinding was rigorously maintained throughout the study. Both participants and investigators were blinded to treatment allocation. Capsules containing BJK or NPX were identical in appearance, size, and color to prevent any unintentional bias. In addition, randomization codes were kept confidential and were only revealed after data analysis was completed. To further ensure blinding, the study coordinators conducted periodic checks to verify that participants and investigators remained unaware of the treatment assignments.

Study duration and rationale

The present study duration was set at 28 days to assess the short-term efficacy and safety of both treatments. This period was chosen based on the typical treatment course for KOA and the expected timeline for measurable improvements in pain and function. The authors acknowledged that while 28 days may not fully capture long-term effects, it allowed for the evaluation of initial therapeutic responses and safety outcomes. Longer-term follow-up studies may be necessary to assess sustained efficacy and any delayed adverse events (AEs).

Quality control for laboratory tests

To ensure accuracy and reliability of laboratory tests, quality control measures were implemented at all participating sites. Blood samples were processed in certified central laboratories with standardized protocols for each assay. Calibration and validation of equipment were conducted regularly, and duplicate testing was performed on 10% of samples to check for consistency. Additionally, laboratory staff were trained on standardized procedures and blinded to participant treatment allocation.

Efficacy and safety assessments

The 28-days study evaluated pain outcomes using the visual analog scale (VAS), 40-meter fast-paced walk test (40mFPWT), Timed Up and Go (TUG), WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS), and 12-item Short Form Health Survey (SF-12V2). AEs were recorded if participants experienced new symptoms. Drug toxicity was considered following U.S. Food and Drug Administration (FDA) guidelines for toxicity classification, such as creatinine greater than 1.7 mg/dL, blood urea nitrogen (BUN) greater than 26 mg/dL, aspartate transaminase (AST) and alanine transaminase (ALT) greater than 2.5 times the upper limit (ULN), or alkaline phosphatase (ALP) greater than 2.0 times the ULN, at which patient discontinuation occurred. Overall outcomes and patient satisfaction were evaluated at the end of the study.

Statistical analysis

All randomized patients who were treated double-blind with BJK or NPX were included in the intention-to-treat (ITT) population for the efficacy analysis. One-way repeated measurement analysis of variance (ANOVA) was used to examine the variations in means between baseline and days 14 and 28 for each group, and two-way repeated measurement ANOVA was used to analyze the interaction effect between the treatment duration factor and the two different drug exposure groups. The t-test for independent samples (Student's t-test) was used to compare the means between the two groups. The chi-square test, with p-value less than 0.05 indicating a significant difference, was used to compare the global assessments of the two groups. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

Three hundred fifty participants were randomized into the NPX and BJK groups. The ITT analysis was conducted for all participants assigned to a treatment group and received at least one treatment session. Missing data were addressed using the last observation carried forward (LOCF) method[18]. Participant flow through the study is shown in Figure 1. Of these, 340 participants, or 170 per group, completed the study. Baseline characteristics, including age, gender, BMI, and baseline pain severity (measured by the VAS), were similar between groups ($p>0.05$ for all comparisons), ensuring comparability of treatment groups (Table 2).

Efficacy

At the 28-day follow-up, both the BJK and NPX groups showed significant improvements in WOMAC pain scores compared to baseline. The mean reduction in pain scores was 5.9 points (95% CI 5.0 to 6.7) for the BJK group and 6.9 points (95% CI 6.1 to 7.8) for the NPX group, with no statistically significant difference between groups (mean difference –1.1, 95% CI –2.2 to 0.1, $p=0.08$).

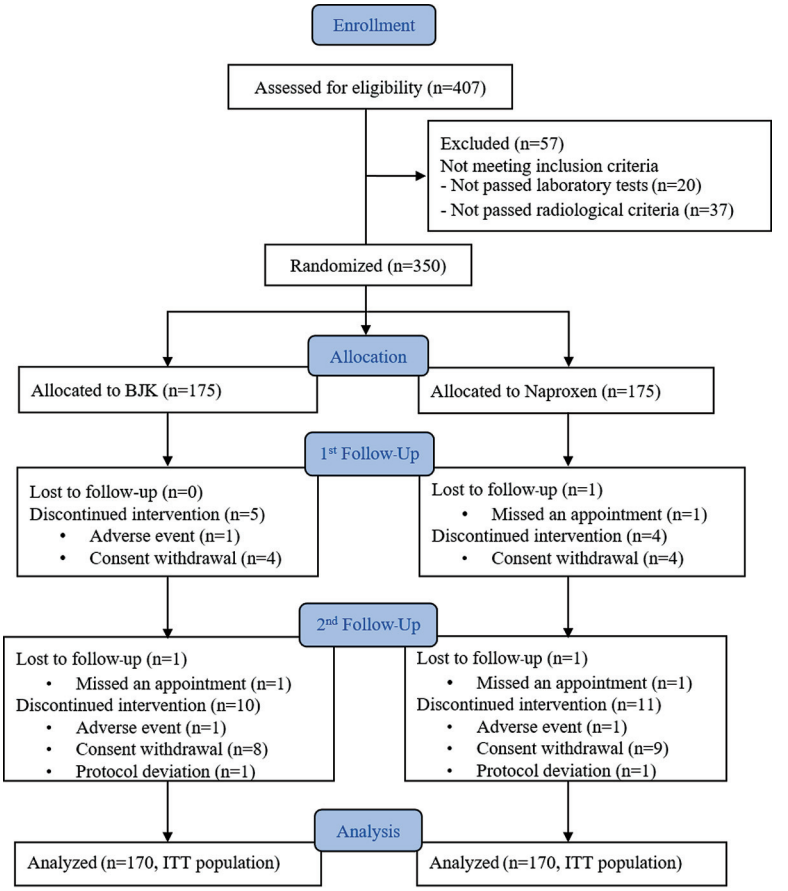

Figure 1. Flow of chart of the study design.

Table 2. Baseline characteristics of patients

Characteristics	BJK (n=170)	NPX (n=170)	p-value*
Female; n (%)	143 (84.1)	144 (84.7)	0.881[c]
Age (years); mean [SD]	61.94 [6.63]	61.15 [7.17]	0.293[t]
BMI; mean [SD]	25.30 [3.71]	25.70 [3.63]	0.311[t]
Kellgren-Lawrence grade; n (%)			0.536[c]
Grade 1	30 (17.6)	37 (21.8)	
Grade 2	67 (39.4)	59 (34.7)	
Grade 3	73 (42.9)	74 (43.5)	
VAS (mm); mean [SD]	59.94 [17.05]	62.00 [18.55]	0.287[t]
40mFPWT (m/second); mean [SD]	1.01 [0.40]	1.01 [0.38]	0.976[t]
TUG (second); mean [SD]	12.92 [3.82]	13.28 [5.12]	0.469[t]

BJK=Benjakul; NPX=Naproxen; BMI=body mass index; VAS=visual analog scale; 40mFPWT=40 m fast-paced walk test; TUG=time up and go test; SD=standard deviation

* Statistical analysis: (c) Chi-square test ($p \leq 0.05$), (t) Independent t-test ($p \leq 0.05$)

This indicates comparable efficacy of BJK and NPX, with a mild effect size observed in both groups (Cohen's d=0.19).

In secondary outcomes, both groups showed significant improvements in the TUG test and VAS pain scores. The BJK group had a mean reduction in TUG time of 2.5 seconds (95% CI 2.0 to 3.1), and the NPX group showed a reduction of 3.0 seconds (95% CI 2.4 to 3.7), with both improvements achieving statistical significance ($p<0.001$). However, the between-group difference was not significant (mean difference –0.5 seconds, 95% CI –1.4 to 0.4, p=0.25). For VAS, the BJK group experienced a mean reduction of 26.8 points (95% CI 22.59 to 31.1), while the NPX group showed a reduction of 28.12 points (95% CI 24.2 to 32.0), with no significant difference between groups (p=0.66).

Both groups demonstrated significant decreases in the WOMAC index, including pain, stiffness, physical function, and total scores. Additionally, KOOS scores across all components showed significant improvements on day 14. SF-12 results revealed significant increases in physical component summary (PCS) scores for both groups on day 28, while mental component summary (MCS) scores

Table 3. Experimental results of BJK and NPX

Data	Follow-up	Treatment[a]; mean (SD)		p-value[t]	p-value[w]
		BJK (n=170)	NPX (n=170)		
Physical function tests					
VAS (mm)	Day 0	59.94 (17.05)	62.00 (18.55)	0.287	0.850
	Day 14	40.59 (21.67)†††	42.06 (20.47)†††	0.520	
	Day 28	33.12 (23.44)†††	33.88 (23.61)†††	0.765	
40mFPWT (m/second)	Day 0	1.01 (0.40)	1.01 (0.38)	0.976	0.809
	Day 14	1.04 (0.22)	1.06 (0.19)	0.533	
	Day 28	1.06 (0.22)	1.07 (0.20)†	0.536	
TUG (second)	Day 0	12.92 (3.82)	13.28 (5.12)	0.469	0.277
	Day 14	10.86 (2.72)†††	10.73 (2.87)†††	0.670	
	Day 28	10.39 (2.63)†††	10.24 (2.50)†††	0.597	
WOMAC index scores					
Pain index	Day 0	9.20 (4.58)	10.09 (4.40)	0.068	0.056
	Day 14	6.24 (3.83)†††	6.01 (3.56)†††	0.557	
	Day 28	3.35 (3.42)†††	3.17 (3.24)†††	0.631	
Stiffness index	Day 0	2.73 (2.23)	3.11 (2.24)	0.121	0.052
	Day 14	2.51 (1.90)	2.35 (1.73)†††	0.438	
	Day 28	2.20 (1.76)††	2.04 (1.65)†††	0.368	
Physical function index	Day 0	27.63 (12.74)	28.27 (13.51)	0.655	0.657
	Day 14	22.89 (13.05)†††	22.47 (12.46)†††	0.761	
	Day 28	18.66 (12.67)†††	18.23 (12.68)†††	0.759	
Total score	Day 0	38.00 (17.39)	40.10 (18.08)	0.275	0.189
	Day 14	31.69 (17.40)†††	30.84 (16.35)†††	0.644	
	Day 28	25.88 (17.17)†††	24.97 (16.95)†††	0.624	
KOOS scores					
Symptoms index (%)	Day 0	33.63 (17.67)	35.88 (19.35)	0.264	0.116
	Day 14	28.36 (17.45)†††	27.92 (17.29)†††	0.815	
	Day 28	26.05 (17.00)†††	24.26 (17.09)†††	0.335	
Pain index (%)	Day 0	38.66 (18.41)	39.40 (18.72)	0.714	0.327
	Day 14	32.88 (18.23)†††	32.44 (16.94)†††	0.817	
	Day 28	27.24 (18.05)†††	25.05 (17.04)†††	0.253	
Activities of daily living index (%)	Day 0	35.06 (19.96)	36.88 (20.46)	0.408	0.442
	Day 14	30.27 (18.47)†††	29.80 (18.37)†††	0.813	
	Day 28	25.22 (17.81)†††	24.92 (18.79)†††	0.882	
Sport and recreation function index (%)	Day 0	68.31 (23.39)	67.97 (26.83)	0.902	0.941
	Day 14	58.18 (25.76)†††	57.32 (26.58)†††	0.763	
	Day 28	51.74 (27.41)†††	51.76 (28.09)†††	0.993	
Knee-related quality of life index (%)	Day 0	59.93 (18.15)	60.92 (20.38)	0.636	0.326
	Day 14	52.90 (18.72)†††	52.34 (18.41)†††	0.779	
	Day 28	49.05 (20.23)†††	46.76 (19.61)†††	0.289	
SF-12V2					
Physical component summary (%)	Day 0	63.07 (13.70)	61.68 (15.35)	0.378	0.025
	Day 14	63.12 (13.06)	62.87 (14.58)	0.868	
	Day 28	65.41 (12.63)†	68.39 (14.04)†††	0.040	
Mental component summary (%)	Day 0	71.41 (15.80)	71.08 (14.91)	0.842	0.114
	Day 14	73.08 (14.29)	72.37 (14.61)	0.653	
	Day 28	74.01 (15.68)	76.65 (15.72)†††	0.122	

BJK=Benjakul, NPX=Naproxen, VAS=visual analog scale; 40mFPWT=40 m fast-paced walk test; TUG=time up and go test; SD=standard deviation

(a) One-way repeated measured ANOVA (Bonferroni), (t) Independent t-test, (w) Two-way repeated measured ANOVA (Follow-up*Treatment), † Significant different from day 0 within group ($p \leq 0.05$), †† Significant different from day 0 within group ($p \leq 0.01$), ††† Significant different from day 0 within group ($p \leq 0.001$)

Table 4. Effect of BJK and NPX on renal functions, and liver functions

Data	Follow-up	Treatment[a]; mean (SD)		p-value[t]
		BJK (n=32)	NPX (n=31)	
Renal functions				
BUN (mg/dL) (normal range 7.0 to 18.0)	Day 0	14.18 (3.85)	14.19 (6.41)	0.992
	Day 28	13.20 (4.55)††	15.16 (4.17)	<0.001
Creatinine (mg/dL) (normal range 0.66 to 1.44)	Day 0	0.79 (0.17)	0.77 (0.18)	0.486
	Day 28	0.81 (0.16)†	0.81 (0.24)††	0.788
eGFR (mL/minute/1.73 m^2) (reference >60)	Day 0	84.78 (13.57)	86.25 (14.81)	0.343
	Day 28	82.03 (13.67)†††	83.66 (17.99)††	0.349
Liver function tests				
AST (U/L) (normal range 5 to 35)	Day 0	26.06 (10.28)	26.59 (11.20)	0.652
	Day 28	26.11 (9.63)	28.13 (16.21)	0.164
ALT (U/L) (normal range 0 to 40)	Day 0	26.59 (14.85)	27.92 (14.66)	0.409
	Day 28	29.63 (32.29)	29.04 (16.58)	0.830
ALP (U/L) (normal range 40 to 120)	Day 0	79.27 (20.08)	82.38 (22.98)	0.186
	Day 28	81.42 (20.44)†	86.39 (26.08)†††	0.051

BJK=Benjakul, NPX=Naproxen; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; AST=aspartate transaminase; ALT=alanine transaminase; ALP=alkaline phosphatase

(a) Repeated measured ANOVA (Bonferroni), (t) Independent t-test, † Significant different from day 0 within group (p≤0.05), †† Significant different from day 0 within group (p≤0.01), ††† Significant different from day 0 within group (p≤0.001)

improved only in the NPX group during the same period. No significant differences were observed between groups in follow-up measures except for PCS on day 28 (Table 3).

Although the present study-controlled duration limited the ability to observe substantial differences, the improvements noted suggest modest benefits in participants' quality of life. Both groups achieved SF-12V2 scores exceeding 50 points, indicating better-than-normative outcomes and overall positive effects[19].

Safety

In the BJK-treated group, BUN and estimated glomerular filtration rate (eGFR) values significantly decreased, while creatinine levels significantly increased. Similarly, the NPX-treated group showed an increase in creatinine and a significant decrease in eGFR. Despite these changes, all renal function parameters remained within normal ranges. Notably, BUN values differed significantly between groups, with a decrease observed in the BJK group and an increase in the NPX group, resulting in divergent trends. Liver function tests revealed no significant changes in AST and ALT levels after 28 days of treatment. However, ALP levels showed a statistically significant increase in both groups (p=0.05 for BJK and p=0.001 for NPX) (Table 4). AE rates were comparable between groups. In the BJK group, the most common AEs were dry lips and throat for 8.2% and mild gastrointestinal discomfort for 7.1%. For the NPX group, gastrointestinal discomfort and constipation were most frequently reported by 6.5%. There were no serious AEs related to the treatment in either group (Table 5).

Global assessment

The global assessment was an overall efficacy evaluation. There was no statistically significant difference between the two groups. The results demonstrate that both groups exhibit greater than 80% of the overall assessment as moderate, better to excellent. The results also showed no significant difference between the two groups.

Discussion

The present study investigated the clinical efficacy and safety of BJK extract compared to NPX in primary KOA. The findings demonstrate that BJK offers a promising natural alternative with anti-inflammatory properties, providing a safe and effective option for managing KOA. While NSAIDs like NPX are effective, their use is often limited by gastrointestinal side effects, including dyspepsia, nausea, ulcers, and bleeding[4], which can lead to therapy discontinuation. In contrast, gastrointestinal symptoms associated with BJK, such as dry mouth and mild abdominal discomfort, were less frequent and less severe, likely to improve patient adherence and quality of life, particularly in individuals with or

Table 5. Adverse events (AEs) comparison between BJK and NPX

Adverse events	BJK (n=170); n (%)	NPX (n=170); n (%)	Overall AEs (n=340); n (%)	Risk ratio (95% CI)	Effect size (Cohen's h)	p-value
Any AE	37 (21.76)	41 (24.12)	78 (22.94)	0.90 (0.61 to 1.33)	–0.068	0.388
Dry lips and throat	14 (8.2)	9 (5.3)	23 (6.76)	1.56 (0.69 to 3.50)	0.116	0.388
Abdominal discomfort	12 (7.1)	11 (6.5)	23 (6.76)	1.09 (0.50 to 2.40)	0.022	1.000
Constipation	7 (4.1)	11 (6.5)	18 (5.29)	0.64 (0.25 to 1.60)	–0.116	0.469
Insomnia	4 (2.4)	10 (5.9)	14 (4.12)	0.40 (0.13 to 1.25)	–0.180	0.170
Palpitation	5 (2.9)	7 (4.1)	12 (3.53)	0.71 (0.23 to 2.21)	–0.064	0.770
Tinnitus	4 (2.4)	7 (4.1)	11 (3.24)	0.57 (0.17 to 1.92)	–0.098	0.542
Heartburn	6 (3.5)	4 (2.4)	10 (2.94)	1.50 (0.43 to 5.22)	0.064	0.750
Dizziness	3 (1.8)	6 (3.5)	9 (2.65)	0.50 (0.13 to 1.97)	–0.110	0.502
Nausea	4 (2.4)	4 (2.4)	8 (2.35)	1.00 (0.25 to 3.93)	0.000	1.000
Fatigue	2 (1.2)	6 (3.5)	8 (2.35)	0.33 (0.07 to 1.63)	–0.158	0.283
Appetite	1 (0.6)	1 (0.6)	2 (0.59)	1.00 (0.06 to 15.86)	0.000	1.000
Headache	0 (0.0)	1 (0.6)	1 (0.29)	-	–0.155	1.000

BJK=Benjakul; NPX=Naproxen; CI=confidence interval
Statistical analysis: chi-square test ($p \leq 0.05$)

at risk for gastrointestinal comorbidities. These AEs, potentially attributable to the warming properties of the herbal formula, are mild and unlikely to pose long-term clinical harm[20]. In addition, this research contributes to the evolving body of knowledge on alternative herbal osteoarthritis treatments and potentially paves the way for improved therapies for this common and debilitating condition.

The results confirm the efficacy of BJK in relieving pain, reducing inflammation, and improving daily functioning. Both BJK and NPX exhibited clinically meaningful improvements in pain index from day 28 compared to baseline, surpassing the minimal clinically important difference (MCID) threshold and indicating substantial therapeutic potential[21]. The multiple properties associated with BJK constituents such as 6-gingerol and 6-shogaol found in ginger emphasize its potential in the treatment of pain and inflammation. The BJK extract inhibits the secretion of nitric oxide and the production of the COX-2-enzyme, which underlines its anti-inflammatory properties. The extract effectively reduces the inflammation-induced ear swelling in rats and prevents the formation of granulomas, which results in its anti-inflammatory effect[5,7]. An improvement in 40mFPWT and TUG was observed in both groups, indicating a reduction in time from day 14 and suggesting enhanced balance with a reduced risk of falling. Although the assessment of quality of life, especially the physical component, increased significantly in both groups on day 28, this indicates a positive influence on physical well-being.

BJK is a combination of five herbs whose biological effects on the ability to support or treat KOA have been reported. The anti-inflammatory effects of *Piper retrofractum* suggest that the plant may relieve pain and inflammation associated with KOA, accompanied by analgesic properties that may provide relief from knee pain. Similarly, *Piper sarmentosum* shows anti-inflammatory and antipyretic activities, reduces the activities of inflammatory cytokines, and possesses antioxidant, anti-inflammatory, as well as anti-angiogenesis properties[5-10,13-15]. *Piper interruptum* has demonstrated potent analgesic and anti-inflammatory properties, with active compounds such as piperine and piperlongumine inhibiting critical inflammatory pathways and safeguarding cartilage. Its potential to treat KOA was positively studied in vivo[22-24]. *Plumbago indica*, traditionally used for rheumatism, has analgesic, antioxidant, and anti-inflammatory properties. *Zingiber officinale*, or ginger, which is used as a remedy for KOA, has anti-inflammatory and circulation-promoting effects. The collective bioactivity and medicinal properties of these herbal constituents, including BJK, suggest their potential treatment of KOA[5-10,13-15].

The results of the present study are consistent with the phase 2 study of BJK, which investigated the efficacy of BJK extract in the treatment of primary KOA. In this study, BJK extract was compared with diclofenac, with both groups showing a reduction in pain, using VAS scores, and an improvement in walking times[14]. The WOMAC scores decreased significantly in both groups. Safety testing revealed no serious AEs in either group and BJK extract

showed no apparent toxicity to renal or liver function, underlining its potential as a safe and effective treatment for KOA.

BJK, a traditional Thai medicine containing piperine as its key active component, demonstrates potential as a natural anti-inflammatory treatment for KOA through both laboratory and clinical evidence[25]. However, current research is constrained by limited follow-up duration and subjective pain assessments, lacking objective measures like imaging or biomarkers to track disease progression. Future investigations should prioritize comprehensive evaluations, including extended follow-up periods, objective outcome measures, and cost-effective analyses, with particular emphasis on Thai rural populations where herbal remedies are integral to healthcare practices. Comparative studies with other NSAIDs would further elucidate BJK's clinical value and therapeutic efficacy.

Conclusion

In the presented study, the authors conducted a rigorous multi-center data collection in Thailand to improve the robustness and generalizability of the study findings. The present study findings and analysis demonstrate that BJK at a daily dose of 300 mg and NPX at a daily dose of 500 mg are equally effective in the primary KOA treatment while providing the important reassurance of minimal safety concerns. These findings substantiate the potential of BJK as a natural anti-inflammatory option for individuals afflicted with KOA. Furthermore, the present investigation brought to light an intriguing aspect, as it established the non-inferiority of BJK when compared to NPX in terms of pain relief and the enhancement of physical function in patients with primary KOA. Most importantly, the authors observed a significantly lower incidence of AEs associated with BJK extract than NPX, highlighting its potential as a safe and effective Thai Herbal Remedy treatment alternative for those afflicted with primary KOA. These findings underscore the importance of BJK extract as a therapeutic option for patients requiring treatment for the challenges associated with this condition.

What is already known about this topic?

BJK, a traditional Thai remedy, is known for its anti-inflammatory properties and potential in managing KOA. Studies suggest BJK as a promising, safe natural treatment option.

What does this study add?

This large Phase 3 multicenter trial in four provinces of Thailand confirms that BJK is as effective as NPX in treating KOA. This study provides comprehensive data on efficacy, safety, and quality of life, supporting BJK as a safe, natural treatment alternative for KOA.

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Conflicts of interest

The authors declare no conflict of interest.

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