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Evaluating the efficacy and safety of *Curcuma longa*, *Boswellia serrata*, and their mixed formulation in treating knee osteoarthritis: A systematic review and network meta-analysis

Chanya Inprasit [a,b], Siriwadee Bunyamahote [c], Kansak Boonpattharatthiti [d,e], Phiyanuch Thimkorn [d,f], Suwipa Intakhiao [c,*], Teerapon Dhippayom [d,g]

[a] *Faculty of Interdisciplinary Management and Technology, Kasetsart University, Bangkok, Thailand*
[b] *Faculty of Medicine, Kasetsart University, Bangkok, Thailand*
[c] *Faculty of Allied Health Sciences, Burapha University, Chonburi, Thailand*
[d] *The Research Unit of Evidence Synthesis (TRUES), Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand*
[e] *Faculty of Pharmaceutical Sciences, Burapha University, Chon buri, Thailand*
[f] *Abhaibhubejhr Collage of Thai Traditional Medicine, Prachinburi, Faculty of Public Health and Allied Health Sciences, Praboromarajchanok Institute, Ministry of Public Health, Thailand*
[g] *Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA*

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ABSTRACT

Background: Herbal interventions such as *Curcuma longa* (CL) and *Boswellia serrata* (BS) have demonstrated efficacy and safety in managing knee osteoarthritis (KOA); however, the effects of their combined formulation, including both direct and indirect outcomes, remain insufficiently explored. We performed systematic review and network meta-analysis for clinical effects of CL, BS, and their mixed formulation in alleviating KOA symptoms.

Methods: The CENTRAL, PubMed, EMBASE, and EBSCO Open Dissertations, databases and also from Snowballing and citation searching were searched through March 2025. The randomized controlled trials (RCTs) that studied effectiveness of CL or BS in KOA participants using Visual Analog Scale (VAS) and KOA severity by the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and adverse events as the main outcomes, were eligibly included. The Cochrane Risk of Bias a random-effects model, standardized mean differences (SMDs) along with 95 % confidence intervals (CIs) were employed.

Results: In total, 20 RCTs comprising 1633 participants were included. The modified formulations of CL showed a significant reduction in VAS compared to placebo (SMD: −2.82; 95 %CI: −5.30 to −0.33), while the modified formulations of BS demonstrated significant improvement in WOMAC pain, stiffness, and knee function compared to other intervention groups. No significant differences in adverse events were observed among all comparisons.

Conclusions: BS extract, particularly in modified formulations, improves joint function in patients with mild to moderate KOA, while only the modified formulation of CL demonstrates notable pain-reducing efficacy. The potential benefits of combined CL and BS preparations warrant further investigation.

1. Introduction

KOA imposes a substantial public health burden, with over 500 million individuals affected globally, leading to chronic pain, functional decline, and increased healthcare costs. Although conventional pharmacotherapy—such as NSAIDs, corticosteroids, and analgesics—can alleviate symptoms, their long-term use is frequently limited by gastrointestinal, cardiovascular, hepatic, and renal adverse effects, especially in older adults with comorbidities[1]. These safety concerns have prompted many patients to seek herbal and complementary

* Correspondence to: Faculty of Allied Health Sciences, Burapha University, 169 Long-Hard Bangsaen Road, Saensook Municipality, Muang District, Chon Buri Province 20131, Thailand.
E-mail address: Suwipa.in@go.buu.ac.th (S. Intakhiao).

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alternatives perceived as more natural and safer, often supported by traditional use and growing clinical evidence.

Nowadays, herbal plant extracts, traditional plant formulations, and natural products are widely used for reduce KOA symptoms, such as *Curcuma longa*, *Boswellia serrata*, *Zingiber officinale*, *Withania somnifera*, *Pistacia atlantica*, etc.[2,3]. Among these, CL and BS have demonstrated anti-inflammatory and analgesic effects, with meta-analyses indicating pain relief comparable to NSAIDs and fewer gastrointestinal side effects[4]. Despite promising individual efficacy, the comparative effectiveness and potential synergistic benefits of their combined use remain under-investigated[5]. CL and BS are available in various formulations—crude, extract, and enhanced bioavailability—each characterized by distinct compositional and pharmacokinetic profiles that influence their therapeutic potential. Crude preparations, which utilize unprocessed plant materials such as powdered rhizomes or resins, contain a diverse array of phytochemicals but typically yield low concentrations of bioactive constituents (e.g., curcumin, boswellic acids), resulting in poor solubility, limited gastrointestinal absorption, and suboptimal clinical efficacy. Extract formulations, developed through purification processes to concentrate key active components, offer greater potency; however, their therapeutic performance remains constrained by low systemic bioavailability due to rapid metabolism and poor absorption. In response to these limitations, advanced delivery systems—such as nanoparticle suspensions, liposomal encapsulations, phospholipid complexes, and formulations co-administered with bioenhancers like piperine—have been engineered to significantly enhance the bioavailability of these compounds. These technologies have demonstrated markedly improved pharmacokinetic profiles and may provide more consistent and effective anti-inflammatory outcomes in the management of KOA[6,7]. In 2018, the report of meta-analysis found that curcuminoid and boswellia formulations significantly improved pain and function in KOA compared to placebo and were associated with fewer gastrointestinal adverse events than NSAIDs[4].

Due to the absence of direct comparisons among CL, BS, and their combined formulation, this study aimed to evaluate clinical effects and safety of CL, BS, and their mixed formulation in alleviating KOA symptoms in RCTs using a network meta-analysis approach.

2. Method

This systematic review and network meta-analysis, was performed in accordance with the Cochrane Collaboration guidelines version 6.5, 2024[8] and reported in conformity with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) version 2020[9], as well as, an extension statement for network meta-analysis of intervention[10]. This study was registered in PROSPERO (CRD42024517194).

2.1. Selection criteria

RCTs that meet the following inclusion criteria were included in our study: 1) conducted in adults with KOA (aged over 18 years) who used oral CL and/or BS ingredients for at least 4 weeks; 2) studied the effect of pain symptom and knee function; 3) reported one of the following outcomes: VAS or WOMAC scores both with and without adverse events. Trials were excluded if they involved patients with the following conditions: rheumatoid arthritis, those who had undergone surgery, gonarthrosis, received non-oral administration herbal medicine, received modern medicine as a conventional treatment or comparison, formulas containing other herbal ingredients.

2.2. Search strategy

We used both free texts and thesaurus terms to search for relevant studies in the following three bibliographic databases: the Cochrane Central Register of Clinical Trials (CENTRAL), PubMed, and EMBASE, from the inception of each database up to March 9, 2025. EBSCO Open Dissertations was additionally searched as a source of grey literature. The key search domains were 1) knee osteoarthritis; 2) herbal medicine; turmeric; Curcuma; Boswellia; and 3) randomized controlled trial (detail of the comprehensive search strategies for each database was provided in Appendix 1). After screening process, we also used forward and backward citation tracking to identify reference of included studies and articles that cited the included trials in Scopus database.

2.3. Study selection

The search records were divided among three investigators (CI, SI, SB), with each article independently screened by two reviewers. Disagreements between reviewers were resolved by the third investigator. Full texts of the selected articles were then retrieved and reviewed to identify trials that meet the inclusion criteria.

2.4. Data extraction

Data of included RCTs were individually filled in a pre-specified data extraction form, which was modified from the Cochrane Handbook for Systematic Reviews of Interventions[8] (Data collection form Intervention review for RCT), by two independent investigators (CI and/or SI and/or SB). The data extracted included study design, purpose of the study, setting, duration of the intervention, number and characteristics of participants, inclusion and exclusion criteria, patient characteristics (gender, age, BMI, and disease severity), intervention details, comparator, clinical outcomes VAS, WOMAC, and adverse events, funding sources, and conflicts of interest. VAS, WOMAC, and adverse events were the main outcome of this study. VAS tool was used for pain score estimation, while WOMAC questionnaire was used for evaluation of osteoarthritis sign, symptoms, and function.

2.5. Risk of bias assessment

Two investigators (CI and SI) independently evaluated the risk of bias using the Cochrane Risk-of-Bias tool for randomized trials (RoB 2)[11]. The tool assesses five domains of bias: the randomization process, deviations from intended interventions, missing outcome data, measurements of outcomes, and selection of reported results. The overall risk of bias, based on these five domains, was classified as low risk, high risk, or some concerns. All disagreements were resolved and affirmed by another investigator (SB).

2.6. Analysis

We compared the effects of CL, its modified formulation (CLM), BS, its modified formulation (BSM), their mixed formulation (CCB) and their modified formulation (CCBM) in reducing symptoms of KOA using both direct and indirect evidence. A random-effects model in the frequentist framework was performed to compare the effects of different interventions, using placebo as a common comparator in each outcome. The standardized mean difference (SMD) was used as the effect estimate for VAS, while the mean difference (MD) was used for WOMAC scores; risk ratios (RR) was used for adverse outcome. All effect estimates are presented with their corresponding 95 % confidence intervals (CI). The surface under the cumulative ranking curves (SUCRA) were used to compare and rank the efficacy of interventions. SUCRA values range from 0 % to 100 %, with higher values indicating a greater likelihood of being better than other treatments[12].

Global network inconsistency tests were performed to verify the extent of disagreement between direct and indirect effects. In addition, transitivity assessments were conducted to explore the relative treatment variables (age, gender, BMI, VAS baseline, and WOMAC baseline) that might impact the outcomes of interest. Possible small-study effects as a proxy for publication bias were assessed using a funnel plot and Egger's test. A p-value was considered statistically significant when it

was less than 0.05. All analyses were conducted using Stata Statistical Software version 15 (StataCorp LLC, TX, United States).

3. Results

3.1. Search results

A total of 2315 records were obtained from bibliographic databases, and 310 records were eliminated due to duplication. After the title and abstract screening process, 19 articles met the inclusion criteria. Five articles were excluded after the full-text review. In addition, 2102 records were identified through forward and backward citation techniques. Only one RCT was included from this approach. A list of excluded articles and the reasons for exclusion from both screening procedures is described in Appendix 2. The result of study selection is shown in the PRISMA flow diagram (Fig. 1). In total, 20 trials were included in our study[13–32].

3.2. Study characteristics

Of the 20 selected RCTs, twelve were conducted in India[13–17,19,24,26,29–32]; three trials were conducted in Iran[20,21,28]; two trials were conducted in Australia[18,22]; and one trial each was conducted in Armenia[25], Belgium[23], and Japan[27] (Table 1). The duration of treatments ranged from 30 to 180 days. Of those included RCTs comprised of 1633 knee osteoarthritis participants. Their average age is between 47 and 72 years with the BMI of 21.90–30.60 kg/m^2. The information of KOA severity was presented in Table 1. Eighteen trials measured VAS[13–20,22–24,26–32], while 13 trials evaluated pain, stiffness, and function using WOMAC questionnaires[14–17,19,21,22,25,26,28,30–32]. All 20 trials reported severe adverse events that led to dropout[13–32].

3.3. Intervention characteristics

CL and/or BS preparations used in the included trials were single herbal or combined preparations in any form and concentration. For CL, the formulations included modified formulation derived from CL extract[13,19,23,26], curcuminoid extract[25,28], curcumin extract[20,21]. For conventional preparations were from CL extract[22,29], and curcuminoid extract[18]. There were two sources of BS preparations including modified formulation[14,16,30,31], and conventional formulation of BS gum resin extract[15,24,31,32]. CCB and CCBM was a blend containing extracts of CL and BS, composed of about 65–70 % CL and 30–35 % BS[17,25] (Appendix 3).

3.4. Quality of included trials

Quality of VAS, WOMAC, and adverse events tools were separately assessed by two independent researchers (CI and SI). Four trials were clarified as having a low risk of bias for VAS outcome[14,15,18,22], meanwhile, 14 trials showed being of some concerned[13,16,17,19,20,23,24,26–32]. There were seven trials reported being of low risk in WOMAC outcomes[14,15,22,25,30–32], and six trials were classified as being of some concern[16,17,19,21,26,28]. For adverse events outcome, three trials were classified as having low risk of bias[13,14,18], two trials were classified as high risk of bias[22,25], and the remaining 12 trials were considered of being some concern[15–17,19,21,24,26–31] (Appendix 4).

3.5. Pain as measure by VAS

Eighteen trials reported efficacy of herbal medicine for KOA pain reduction by VAS[13–20,22–24,26–32]. There were three trials investigating the efficacy of CL[18,22,29], seven for CLM[13,19,20,23,26–28], four for BS[15,24,

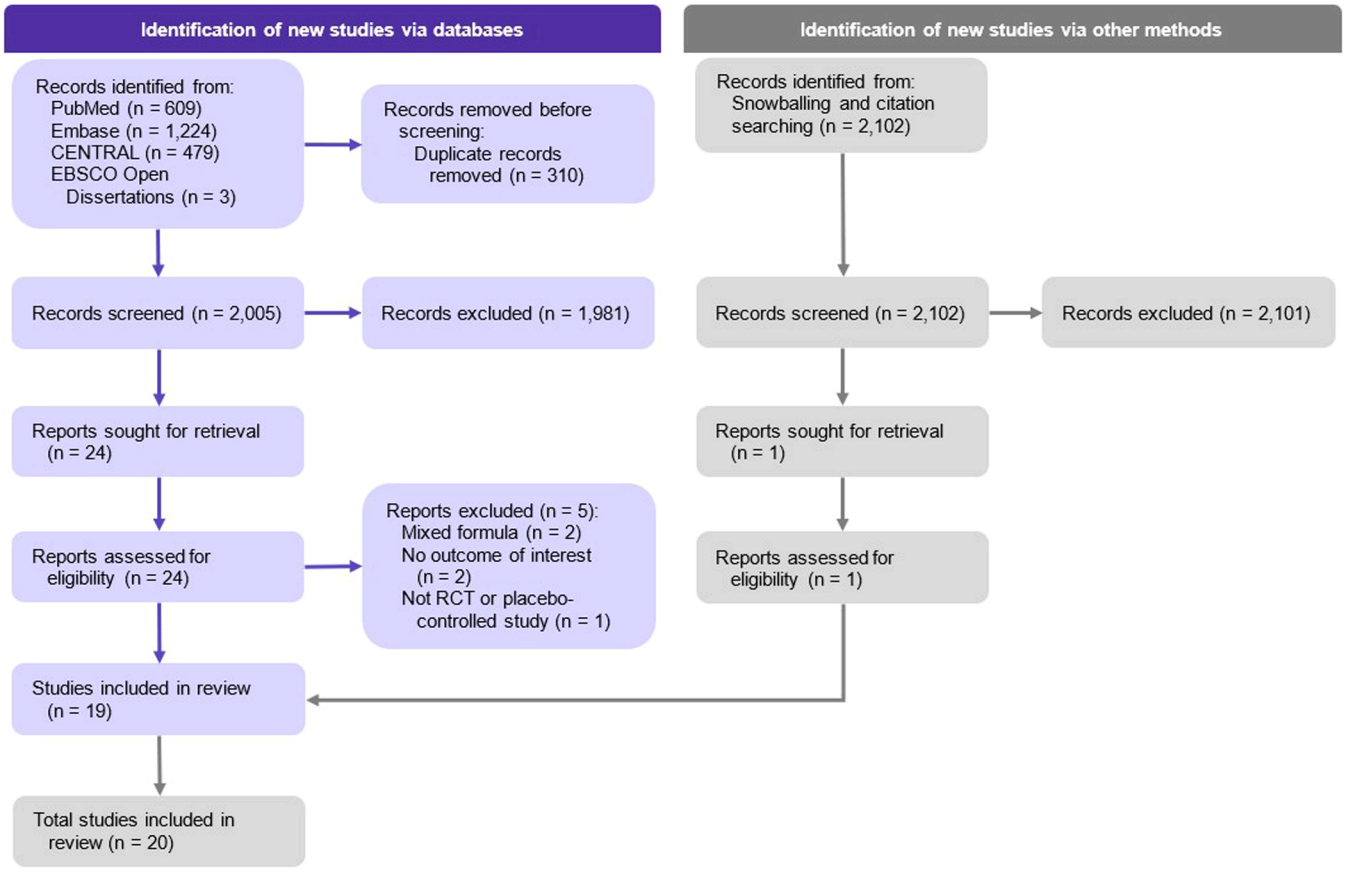

Fig. 1. PRISMA flow diagram.

Table 1
General characteristics of included studies.

First author	Country	Number of female subjects (%)		Age (year, mean ± SD)		BMI (kg/m^2, mean ± SD)		Severity of Knee OA	Duration of treatment (days)	Intervention group	Conflict of interest
		Intervention	Control	Intervention	Control	Intervention	Control				
Thanawala et al. (2025)[23]	India	70 (48.6)	70 (50.0)	57.0 ± 6.8	55.7 ± 6.9	23.8 ± 1.6	24.0 ± 1.7	K-L grade 2–3	90	CLM	No
Kumar et al. (2024)[24]	India	40 (45.0)	40 (47.5)	48.6 ± 7.4	47.9 ± 7.9	25.7 ± 1.2	25.9 ± 1.5	K-L grade 2–3	180	BSM	No
Majeed et al. (2024)[25]	India	35 (48.6)	35 (74.3)	54.7 ± 7.9	52.2 ± 7.2	26.3 ± 2.7	26.3 ± 2.6	KOA grade 2–3	90	BS	No
	India	35 (74.3)	-	51.8 ± 5.8	-	26.3 ± 2.1	-	KOA grade 2–3	90	BS	No
Karlapudi et al. (2023)[26]	India	35 (74.3)	35 (77.1)	51.6 ± 8.5	51.8 ± 7.2	25.3 ± 3.1	25.5 ± 3.2	NA	30	BSM	No
Prasad et al. (2023)[27]	India	50 (48.0)	50 (44.0)	51.0 ± 8.1	53.4 ± 9.3	25.3 ± 1.5	25.6 ± 1.3	K-L grade 2	30	CCB	No
Lopresti et al. (2022)[28]	Australia	51 (47.1)	50 (50.0)	59.6 ± 0.9	57.9 ± 0.9	28.9 ± 0.7	28.8 ± 0.6	NA	56	CL	No
Panda et al. (2021)[29]	India	25 (NA)	25 (NA)	55.4 ± 6.2	54.1 ± 6.4	23.6 ± 1.9	23.6 ± 1.7	NA	60	CLM	No
Atabaki et al. (2020)[30]	Iran	15 (100.0)	15 (100.0)	49.1 ± 1.5	48.3 ± 1.3	22.0 ± 0.4	21.9 ± 0.4	K-L grade 2–3	90	CLM	No
Hashemzadeh et al. (2020)[31]	Iran	40 (82.5)	40 (90.0)	54.1 ± 5.8	56.5 ± 5.8	NA	NA	K-L grade 2–3	42	CLM	No
Wang et al. (2020)[32]	Australia	36 (50.0)	34 (61.8)	61.3 ± 8.5	62.4 ± 8.8	29.9 ± 6.3	30.6 ± 7.2	OARSI grade 1–2 of joint space narrowing	84	CL	No
Henrotin et al. (2019)[33]	Belgium	49 (85.7)	47 (76.6)	61.4 ± 7.5	63.3 ± 7.7	30.4 ± 5.2	29.4 ± 5.2	NA	90	CLM	No
	Belgium	54 (81.5)	-	60.9 ± 9.8	-	29.4 ± 4.9	-	NA	90	CLM	No
Majeed et al. (2019)[34]	India	24 (NA)	24 (NA)	NA	NA	23.4 ± 4.0	23.3 ± 4.5	NA	120	BS	No
Haroyan et al. (2018)[35]	Armenia	66 (90.9)	68 (95.6)	54.7 ± 8.8	56.0 ± 8.6	28.3 ± 3.6	28.8 ± 3.4	K-L grade (2007) 1–3	84	CLM	No
	Armenia	67 (92.5)	-	57.9 ± 9.0		29.8 ± 4.0		K-L grade (2007) 1–3	84	CCBM	No
Panda et al. (2018)[36]	India	25 (NA)	25 (NA)	55.2 ± 8.6	53.1 ± 8.3	25.4 ± 2.8	24.9 ± 1.9	K-L grade 2–3	60	CLM	No
Nakagawa et al. (2014)[37]	Japan	25 (84.0)	25 (80.)	71.9 ± 5.30	66.1 ± 7.2	25.1 ± 2.7	24.8 ± 2.3	K-L grade 2–3	56	CLM	No
Panahi et al. (2014)[38]	Iran	27 (81.5)	26 (84.6)	57.3 ± 8.8	57.6 ± 9.1	28.8 ± 3.2	29.6 ± 4.5	Primary knee OA with mild - moderate severity	42	CLM	No
Madhu et al. (2013)[39]	India	30 (56.7)	30 (56.7)	56.6 ± 10.6	56.8 ± 10.0	27.0 ± 4.6	28.0 ± 4.2	K-L grade 2–3	42	CL	No
Vishal et al. (2011)[40]	India	30 (63.3)	30 (63.3)	53.2 ± 6.5	55.3 ± 8.8	25.7 ± 3.3	24.9 ± 2.6	symptoms of mild - moderate OA	30	BSM	No
Sengupta et al. (2010)[41]	India	20 (85.0)	20 (55.0)	51.6 ± 9.9	52.4 ± 7.5	25.1 ± 3.8	25.3 ± 4.4	K-L grade 2–3	90	BS	No
	India	20 (85.0)	-	53.2 ± 7.9	-	25.2 ± 3		K-L grade 2–3	90	BSM	No

Abbreviations: CL= *Curcuma longa*; CLM= *C. longa* modified formulation; BS= *Boswellia serrata*; BSM= *B. serrata* modified formulation; CCB= Combination of *C. longa* and *B. serrata;* CCBM= Combination of *C. longa* L and *B. serrata* modified formulation; PC= Placebo; K-L grade= Kellgren-Lawrence grade; KOA grade= Knee osteoarthritis grade; OARSI grade= Osteoarthritis Research Society International grading system; OA= Osteoarthritis; NA= Not Available; SD= standardize deviation

[31,32], four for BSM[14,16,30,31], and one for CCB[17]. There was no direct evidence among CL, CLM, and CCB with other interventions as shown in a network geometry of VAS (Fig. 2). VAS score decreased significantly more in the CLM treated groups than in the placebo group, with a SMD of −2.82 [95 %CI: −5.30, −0.33]. No significant differences were observed among other comparisons (Appendix 5.1). The probability of being better than other interventions in reducing pain level measured by VAS, as observed in SUCRA, were as follows: CLM (74.2 %), BSM (67.9 %), BS (61.0 %), CCB (38.7 %), CL (38.4 %), and placebo (19.7 %), respectively (Table 3).

3.6. Knee osteoarthritis symptoms as measure by WOMAC

There were only 13 trials that measured the severity of pain, stiffness, and functional limitation using WOMAC questionnaires[14–17,19,21,22,25,26,28,30–32]. Of those, one trial studied the efficacy of CL[22], five trials

Table 2
Effect estimates among treatment comparisons for studied outcomes.

Comparison	VAS (18 trials, 1352 participants), SMD (95 % CI)	WOMAC pain (13 trials, 1054 participants), MD (95 % CI)	WOMAC stiffness (13 trials, 1054 participants), MD (95 % CI)	WOMAC function (13 trials, 1054 participants), MD (95 % CI)	Adverse events (20 trials, 1624 participants), RR (95 % CI)
BS: BSM	0.42 (−3.69,4.52)	10.88 (5.56,16.19)*	11.36 (2.15,20.57)	8.12 (−0.22,16.47)	0.69 (0.06,8.67)
BS: CCB	−1.59 (−8.79,5.60)	−7.42 (−15.15,0.31)	−7.79 (−21.91,6.33)	−9.92 (−23.18,3.34)	0.66 (0.01,56.66)
BS: CCBM	NA	−6.94 (−13.85,−0.03)*	−7.24 (−20.16,5.67)	−4.83 (−17.18,7.52)	1.24 (0.07,21.35)
BS: CL	−1.36 (−6.92,4.20)	NA	NA	NA	NA
BS: CLM	0.71 (−3.31,4.72)	−5.90 (−10.86,−0.95)*	−5.71 (−14.66,3.25)	−1.42 (−10.23,7.38)	0.88 (0.08,9.67)
BS: PC	−2.11 (−5.26,1.04)	−9.46 (−13.51,−5.42)*	−9.16 (−16.37,−1.95)*	−12.26 (−19.01,−5.50)*	0.66 (0.08,5.68)
BSM: CCB	−2.01 (−9.21,5.18)	−18.30 (−25.91,−10.69)*	−19.15 (−32.98,−5.32)*	−18.04 (−30.94,−5.14)*	0.95 (0.01,66.93)
BSM: CCBM	NA	−17.82 (−24.60,−11.03)*	−18.60 (−31.22,−5.99)*	−12.96 (−24.91,−1.00)*	1.79 (0.14,22.25)
BSM: CL	−1.78 (−7.34,3.78)	NA	NA	NA	NA
BSM: CLM	0.29 (−3.73,4.31)	−16.78 (−21.56,−11.99)*	−17.07 (−25.62,−8.52)*	−9.55 (−17.79,−1.31)*	1.27 (0.17,9.39)
BSM: PC	−2.53 (−5.68,0.63)	−20.34 (−24.16,−16.52)*	−20.52 (−27.15,−13.89)*	−20.38 (−26.39,−14.37)*	0.95 (0.17,5.21)
CCB: CCBM	NA	0.48 (−8.16,9.13)	0.55 (−15.65,16.74)	5.08 (−10.30,20.47)	1.89 (0.03,142.01)
CCB: CL	0.23 (−7.69,8.16)	NA	NA	NA	NA
CCB: CLM	2.30 (−4.63,9.23)	1.52 (−5.66,8.70)	2.08 (−11.18,15.35)	8.49 (−4.20,21.18)	1.34 (0.02,75.98)
CCB: PC	−0.51 (−6.98,5.95)	−2.04 (−8.62,4.54)	−1.37 (−13.51,10.77)	−2.34 (−13.75,9.07)	1.00 (0.02,49.43)
CCBM: CL	NA	NA	NA	NA	NA
CCBM: CLM	NA	1.04 (−4.57,6.64)	1.54 (−9.18,12.26)	3.41 (−6.91,13.73)	0.71 (0.09,5.59)
CCBM: PC	NA	−2.52 (−8.13,3.08)	−1.92 (−12.64,8.80)	−7.42 (−17.74,2.89)	0.53 (0.08,3.37)
CL: CLM	2.07 (−3.14,7.28)	NA	NA	NA	NA
CL: PC	−0.75 (−5.32,3.83)	NA	NA	NA	NA
CLM: PC	−2.82 (−5.30,−0.33)*	−3.56 (−6.42,−0.70)*	−3.45 (−8.79,1.89)	−10.83 (−16.38,−5.28)*	0.75 (0.26,2.13)

*Statistically significant
Acronyms: BS= *Boswellia serrata*; BSM= *Boswellia serrata* modified formulation; CCB= Combination of *Curcuma longa* and *Boswellia serrata*; CCBM= Combination of *Curcuma longa* and *Boswellia serrata* modified formulation; CL= *Curcuma longa*; CLM= *Curcuma longa* modified formulation; PC= Placebo; NA= Not applicable; MD= mean difference; SMD= standardize mean difference; RR= risk ratio; VAS= Visual analog scale; WOMAC= The Western Ontario and McMaster Universities Arthritis Index

studied the efficacy of CLM[19,21,25,26,28], three trials studied the efficacy of BS[15,31,32], four trials studied the efficacy of BSM[15,16,30,31], and one each trials studied the efficacy of CCB[17] and CCBM[25]. In addition, there was two trails investigating the efficacy between interventions; BS and BSM[31]; CLM and CCBM[25], along with placebo. A network geometry for WOMAC presented a lack of direct evidence among CCB group and other interventions (Fig. 2).

3.7. Pain as measure by WOMAC

The results of pain as measured using WOMAC in BSM group significantly reduced when compared to other 5 groups including BS, CCB, CCBM, CLM, and placebo groups (SMD, −10.88 [95 %CI: −16.19, −5.56]; −18.30 [95 %CI: −25.91, −10.69]; −17.82 [95 %CI: −24.60, −11.03]; −16.78 [95 %CI: −21.56, −11.99]; −20.34 [95 %CI: −24.16, −16.52]), respectively. Besides, the analysis showed significant decreases in BS group when compared with CCBM, CLM, and placebo groups (SMD, −6.94 [95 %CI: −13.85, −0.03]; −5.90 [95 %CI: −10.86, −0.95]; −9.46 [95 %CI: −13.51, −5.42]). Additionally, there was significantly diminished between CLM and placebo groups (SMD, −3.56 [95 %CI: −6.42, −0.70]). On the other hand, there were insignificant decreases in WOMAC pain score as shown in Appendix 5.2. The SUCRA values for the WOMAC pain score showed that BSM (100 %) has the highest probability of being better than other interventions, followed by BS (78.7 %), CLM (46.2 %), CCBM (34.4 %), CCB (31.2 %), and placebo (9.5 %), respectively (Table 3).

3.8. Stiffness as measure by WOMAC

The outcome revealed significant decreases in BSM group when compared to other interventions including BS, CCB, CCBM, and CLM groups (SMD, 11.36 [95 %CI: −20.57, −2.15]; −19.15 [95 %CI: −32.98, −5.32]; −18.60 [95 %CI: −31.22, −5.99]; −17.07 [95 %CI: −25.62, −8.52]). Moreover, when compare with placebo, the magnitude of effects of BSM (-20.52 [95 %CI: −27.15, −13.89]) is higher than BS (-9.16 [95 %CI: −16.37, −1.95]). This was consistent with the findings of BSM vs BS showing BSM significantly lower WOMAC-stiffness than BS (-11.36 [95 %CI: −20.57, −2.15]). The findings among other comparisons were shown in Appendix 5.3. A similar tendencies of ranking (BSM, BS, CLM, CCBM, CCB, and placebo) and percentage (99.8 %, 72.4 %, 44.6 %, 33.7 %, 31.7 %, and 17.8 %) of SUCRA values were observed in WOMAC stiffness scores (Table 3).

3.9. Knee function as measure by WOMAC

The WOMAC outcomes revealed similar tendencies between stiffness and knee function scores across most comparisons (Appendix 5.4). However, for the comparison between CLM and placebo, only the knee function score showed a significant improvement in the CLM group (SMD, −10.83 [95 %CI: −16.38, −5.28]), while the difference in stiffness score was not statistically significant. The SUCRA values for functional WOMAC presented that BSM (98.9 %) has highest efficacy among other interventions, while lower values were showed in BS (67.1 %), CLM (60.4 %), CCBM (43.5 %), CCB (21.7 %), and placebo (8.4 %), respectively (Table 3).

3.10. Adverse Events

The mild adverse events were collected directly through self-report questionnaires in all trials. The signs and symptoms of the gastrointestinal system were most frequently reported after taking herbal medicine, such as nausea, vomiting, stomach pain, abdominal pain, bloating, acid-esophageal reflux, loose stools, or constipation[16,18,19,22,25,26,28,30]. However, there were insignificant differences in severe adverse events across comparison groups, as shown in Appendix 5.5.

3.11. Sensitivity analysis and subgroup analysis

Sensitivity analyses excluding trials with a high risk of bias and small studies confirmed the robustness of the main findings across outcomes.

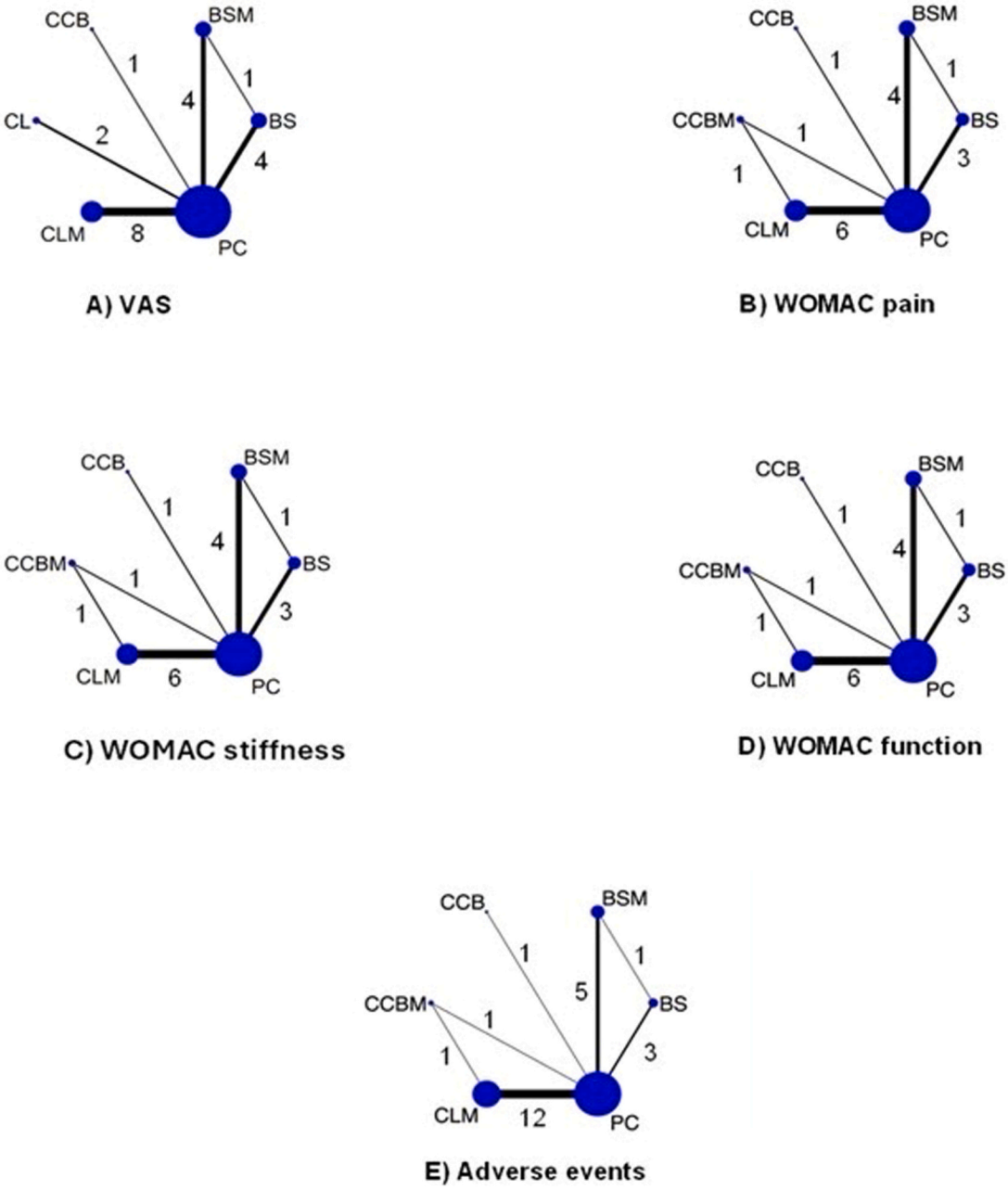

Fig. 2. Network geometry. Abbreviations: BS= *Boswellia serrata*; BSM= *Boswellia serrata* modified formulation; CCB= Combination of *Curcuma longa* and *Boswellia serrata*; CCBM= Combination of *Curcuma longa* and *Boswellia serrata* modified formulation; CL= *Curcuma longa*; CLM= *Curcuma longa* modified formulation; PC= Placebo; VAS= Visual analog scale; WOMAC= The Western Ontario and McMaster Universities Arthritis Index.

BSM consistently showed superior effects on pain and WOMAC stiffness compared to other interventions; however, its effect on WOMAC function was not consistently observed (Appendix 6). Subgroup analyses indicated that the effects of CLM and BSM were time-dependent: the benefits of CLM were limited to within 12 weeks, while the effects of BSM persisted beyond 12 weeks (Appendix 7). No significant differences in adverse events were observed between different subgroups.

3.12. Network consistency, transitivity, and publication bias

No inconsistency between direct and indirect evidence ($P > 0.05$) was observed in the network geometry of any outcome. Transitivity assessments among all comparisons within the network showed similarity in characteristics of participants in terms of age, gender, BMI, and disease severity as shown in Appendix 8. The estimation of publication bias indicated no risk of small-study effects in WOMAC pain, WOMAC stiffness, WOMAC function, and adverse events ($P > 0.05$) as shown in Appendix 9.2–9.5, although significant finding was observed in VAS ($P = 0.000$) (Appendix 9.1).

4. Discussion

This NMA, based on 20 double-blind RCTs, is the first study to compare the therapeutic efficacy of two herbal products, their combinations and their modified formulation in the treatment of KOA: CL, CLM, BS, BSM CCB and CCBM, against placebo. The findings provide comprehensive evidence to guide clinicians in selecting appropriate herbal therapies for KOA and further support decision-making regarding optimal formulation strategies. The NMA evaluated pain reduction efficacy using two instruments: the VAS and the WOMAC pain subscale.

Table 3
The surface under the cumulative ranking (SUCRA) of all treatments.

Treatments	VAS	WOMAC pain	WOMAC stiffness	WOMAC function	Adverse events
BS	61.00	78.70	72.40	67.10	56.50
BSM	67.90	100.00	99.80	98.90	42.90
CCB	38.70	31.20	31.70	21.70	45.10
CCBM	NA	34.40	33.70	43.50	64.80
CL	38.4	NA	NA	NA	NA
CLM	74.20	46.20	44.60	60.40	53.30
PC	19.70	9.50	17.80	8.40	37.40

Acronyms: BS= *Boswellia serrata*; BSM= *Boswellia serrata* modified formulation; CCB= Combination of *Curcuma longa* and *Boswellia serrata*; CCBM= Combination of *Curcuma longa* and *Boswellia serrata* modified formulation; CL= *Curcuma longa*; CLM= *Curcuma longa* modified formulation; NA= Not applicable; PC= Placebo

VAS, which is highly sensitive to acute pain perception, captures overall pain intensity at a specific time point. In contrast, the WOMAC pain subscale assesses pain during specific activities (e.g., walking, stair climbing), offering insight into functional, and context-specific pain. These tools reflect different dimensions of pain, and the variation in outcomes across interventions suggests that some treatments may primarily reduce pain intensity (as reflected by VAS), while others may improve functional performance despite residual pain (as reflected by WOMAC)[33–36].

Analysis showed that CLM, BS, and BSM were more effective than placebo in reducing knee pain. Notably, CLM significantly improved both pain VAS and WOMAC scores, while BS and BSM demonstrated improvements only in the WOMAC pain subscale, suggesting a broader analgesic effect of CLM. Given the significant result from Egger's test ($P = 0.000$) for the VAS outcome, there is a possibility of small-study effects, particularly in the case of CLM, which was the only intervention to show a statistically significant reduction in VAS compared to placebo. This may reflect a degree of publication bias, where smaller studies with null or negative findings are underrepresented, potentially leading to an overestimation of treatment effects. Therefore, while the findings for CLM are promising, they should be interpreted with appropriate caution. To mitigate this potential bias, we conducted a comprehensive literature search across multiple databases to ensure broad coverage and reduce the likelihood of selective reporting. Mechanistically, curcumin and boswellic acid, the active constituents of CL and BS, respectively, share similar anti-inflammatory actions. There are two pathways play important role in anti-inflammatory which alleviate inflammation-induced pain including arachidonic acid pathway and nuclear factor kappa B (NF-κB) signaling pathway. Both inhibit 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) are key enzymes in the arachidonic acid pathway, whilst, NF-κB signaling pathway suppresses the expression of pro-inflammatory mediators. Importantly, curcumin also enhances the expression of interleukin-10 (IL-10), a potent anti-inflammatory, and pro-resolving cytokine. IL-10 downregulates pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and promotes the release of endogenous opioid peptides from sensory neurons. These mechanisms contribute to curcumin's superior analgesic potential, particularly in osteoarthritis, where chronic low-grade inflammation is a key pathological driver[1,37–40].

For joint function, BS and BSM extracts showed greater efficacy than placebo in improving knee mobility, based on WOMAC stiffness and function scores. CLM was effective compared to placebo only in the WOMAC function domain. BSM demonstrated the most consistent results across WOMAC domains, suggesting therapeutic benefits of BS extract at both symptom and tissue levels. These findings are consistent with Christelle Sanchez et al.[39], which indicated that although CL and BS extracts share antioxidant, anti-inflammatory, and anti-cartilage degradation properties, only BS extract possesses a unique mechanism that may benefit knee joint pathophysiology. It can improve chondrocyte health through the upregulation of autophagy-related genes, which protect cartilage cells and may delay cellular aging.

Enhanced formulations (CLM, BSM) demonstrated superior efficacy compared to their conventional counterparts (CL, BS), with CLM outperforming CL in VAS pain reduction and BSM surpassing BS in both pain and stiffness. These findings suggest that formulation type significantly influences therapeutic outcomes, largely due to improved oral absorption of active compounds. For example, the bioavailability of acetyl-11-keto-β-boswellic acid (AKBA) is limited by its hydrophobicity and poor water solubility. Combining AKBA with non-volatile oils, as in proprietary formulations such as ApresFlex® and Aflapin®, has been shown to enhance absorption. In animal models, ApresFlex® exhibited significantly higher bioavailability than the conventional extract 5-Loxin® at equivalent doses[41,42].

Similarly, Curcumin, the principal active constituent of CL, exhibits significant pharmacokinetic limitations due to its very low aqueous solubility. Consequently, even at high oral doses, only a small fraction of curcumin is absorbed across the intestinal epithelium. Studies have shown that up to 75 % of orally administered curcumin is excreted unchanged in the feces. Once absorbed, curcumin undergoes rapid biotransformation via two metabolic phases. In Phase I, it is reduced by NADPH-dependent enzymes. In Phase II, the resulting metabolites are conjugated with glucuronides and sulfates, forming water-soluble but pharmacologically inactive compounds that are rapidly eliminated in the urine—often within 20 min. These factors; poor intestinal absorption, extensive metabolism, short half-life, and limited tissue distribution—collectively account for curcumin's low systemic bioavailability and constrain its therapeutic potential[43–45].

Combination products containing both CL and BS extracts did not show superior efficacy compared to the individual extracts. This outcome contrasts with multiple sources of evidence[1,39] suggesting a potential synergistic effect between the two extracts in osteoarthritis management. However, this discrepancy may be attributed to the limited clinical evidence currently available, with only one randomized controlled trial evaluating each combination type—conventional (CCB) and modified (CCBM). This small number of studies represents a significant limitation, potentially reducing the statistical power to detect true differences. Therefore, firm conclusions regarding the synergistic efficacy of combined CL and BS formulations cannot yet be drawn. Notably, the combined product employed a bioavailability-enhancing formulation containing only CL extract and administered at a lower dose than the standalone CLM regimen, while BS extract was used in its conventional form, containing a relatively low concentration of its key active compound, AKBA. Further investigations are warranted to clarify the therapeutic potential of this combination.

Regarding the incidence of severe adverse effects did not differ significantly between treatment groups and placebo. Extracts from CL and BS have been used in Ayurvedic medicine for over 4000 years and are recognized as "Generally Recognized as Safe" (GRAS) by the U.S. FDA[1]. According to Vidhu Sethi et al.[1], curcumin is generally well-tolerated, with mild gastrointestinal symptoms including abdominal pain, diarrhea, nausea, and flatulence. Occasional reports of headache and skin rash have also been noted. Similarly, BS extract shows a favorable safety profile, with common adverse effects such as epigastric pain, nausea, and heartburn. When used in combination, formulations containing both curcumin and boswellic acids remain well-tolerated, with side effects comparable to placebo. This overall safety profile likely contributes to the low participant dropout rates observed in clinical trials.

The findings indicate that CL extract significantly improves pain and functional outcomes compared to placebo, that are consistent with previous meta-analysis and network meta-analysis[4,46–49]. Similarly, the observed benefits of BS extract align with the results reported in previous meta-analyses[4,50]. However, it is important to note that these earlier investigations[4,42,46–49] did not distinguish between different product types namely, conventional formulations, enhanced-bioavailability

formulations, or combination products containing both CL and BS extracts which may limit the interpretability and clinical applicability of their conclusions.

These findings suggest that BSM may be a promising monotherapy for the treatment of KOA, as it effectively reduces pain and improves joint function in patients with mild to moderate disease severity. CLM also demonstrates notable analgesic efficacy. However, further investigation is warranted, particularly for combination formulations (CCBM and CCB), as the current clinical evidence remains limited. Additional research is needed to clarify the potential synergistic pharmacological effects of curcumin and boswellic acid in pain management and functional improvement among KOA patients. Importantly, both CL and BS extracts not only demonstrate clinical efficacy but also exhibit a favorable safety profile, making them attractive therapeutic options especially in the early stages of disease or as adjunctive treatments.

A key limitation of this study is the clinical and methodological heterogeneity across the included trials. Patient populations varied in terms of mean age and BMI, and the severity of knee osteoarthritis was assessed using different grading systems (e.g., Kellgren-Lawrence, OARSI). The treatment durations also ranged widely from 30 to 180 days. While our transitivity assessments showed similarity in participant characteristics to support the overall credibility of the analysis, these differences may still influence treatment effects. Furthermore, the subgroup analyses based on time confirmed that the effects of CLM and BSM were time-dependent, with the benefits of CLM limited to within 12 weeks and the effects of BSM persisting beyond 12 weeks. This highlights the importance of considering treatment duration when interpreting the results.

A potential limitation of this study lies in the transitivity assumption related to dosing, particularly in relation to formulations designed to enhance the bioavailability of the extracts. These products were administered at varying therapeutic doses based on the clinical trials of each formulation, making direct dose comparisons infeasible. At present, no established studies define equivalent dosing, which may distort indirect comparison results. Furthermore, some treatment arms included limited direct comparisons, potentially compromising the reliability of certain findings. When considered together, these factors, which include clinical heterogeneity, varying risks of bias across individual trials, and insufficient data available for combination formulations, highlight the need for cautious interpretation of the study findings. The conclusions drawn from this network meta-analysis should be regarded as preliminary until more high quality and reliable evidence becomes available. Nonetheless, we are confident that the quantity and quality of the included trials support the overall credibility of this network meta-analysis.

5. Conclusion

This NMA indicates that BS extract, particularly its modified formulation (BSM), offers substantial benefits for joint function in mild to moderate KOA. Meanwhile, only CLM demonstrates prominent efficacy in pain reduction. An important consideration when selecting either extract is the use of formulations designed to enhance bioavailability. Nonetheless, the therapeutic potential of combining CL and BS extracts warrants further investigation to establish clinical relevance.

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CRediT authorship contribution statement

Teerapon Dhippayom: Writing – review & editing, Validation, Supervision. **Suwipa Intakhiao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kansak Boonpattharatthiti:** Writing – review & editing, Validation, Formal analysis. **Phiyanuch Thimkorn:** Writing – review & editing, Validation, Formal analysis. **Chanya Inprasit:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Siriwadee Bunyamahote:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2025.103256.

Data availability statement

The data used and presented in this study are available from the corresponding author on reasonable request.

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