

Unani Medicine Interventions for Knee Osteoarthritis: A Systematic Review and Narrative Synthesis of Clinical Studies

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Abstract

Background. Knee osteoarthritis (KOA) is a common cause of chronic pain and functional loss in older adults, and prolonged use of NSAIDs and corticosteroids is limited by gastrointestinal, cardiovascular, and renal toxicity. Unani medicine offers oral, topical, and regimenal treatments that are widely used in South Asia, but their clinical value in KOA has not been appraised systematically.

Objective. To evaluate the efficacy and safety of Unani interventions for KOA using the available clinical evidence.

Methods. This systematic review was conducted and reported according to PRISMA 2020 and prospectively registered in PROSPERO (CRD420261306714). PubMed/MEDLINE, Google Scholar, IndMED, and DHARA were searched from inception to 15 March 2025. Clinical studies of Unani pharmacological or regimenal interventions in adults with primary KOA were eligible. Risk of bias was assessed with RoB 2 and ROBINS-I, and certainty of evidence with GRADE. Owing to clinical and methodological heterogeneity, findings were synthesised narratively using the Synthesis Without Meta-analysis (SWiM) framework.

Results. Eight studies met the eligibility criteria: five randomised or comparative trials and three single-arm or pre-post studies, with individual studies enrolling between 20 and 60 participants (338 in total). Interventions comprised oral compound formulations, topical herbal oils, cupping (Hijamah), and therapeutic massage (Dalk). Seven of eight studies reported short-term reductions in pain (VAS), all eight reported gains in physical function (WOMAC, KOOS, or Lequesne Index), and none reported a serious treatment-related adverse event. Certainty of evidence was low to very low across outcomes, reflecting small samples, short follow-up, and limited blinding.

Conclusion. Unani interventions may provide short-term symptomatic relief in KOA with acceptable short-term safety, but the current evidence is too weak to support firm clinical recommendations. Adequately powered, multicentre randomised trials using standardised formulations, validated outcomes, and longer follow-up are needed.

Keywords: knee osteoarthritis; Unani medicine; Hijamah; cupping; herbal medicine; integrative medicine; systematic review

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1. Introduction

Knee osteoarthritis (KOA) is one of the most prevalent chronic musculoskeletal disorders and a major cause of pain, functional limitation, and disability among older adults. It is characterised by progressive deterioration of articular cartilage accompanied by subchondral bone remodelling, osteophyte formation, and variable degrees of synovial inflammation (1–3). The global burden of KOA has increased steadily, driven in part by population ageing, rising obesity rates, and increasingly sedentary lifestyles (2). Clinically, patients commonly experience activity-related knee pain, stiffness, and restricted joint movement, which can progressively compromise physical function, independence, and quality of life (3). Beyond its clinical consequences, KOA imposes a substantial economic burden on individuals and healthcare systems. Direct costs include outpatient consultations, diagnostic imaging, pharmacological management, and, in advanced disease, joint replacement, whereas indirect costs arise from work absenteeism, reduced productivity, and informal caregiving. These indirect consequences may be particularly pronounced in ageing populations and lower-resource healthcare settings, where access to arthroplasty remains limited (2). As the prevalence of KOA is expected to increase with demographic ageing, interventions that are affordable, accessible, and potentially capable of delaying or reducing dependence on long-term pharmacological or surgical management are of considerable clinical and health-economic interest. This provides an important practical rationale for the rigorous evaluation of widely used traditional therapies, including those derived from Unani medicine.

Management of KOA is predominantly symptomatic and focuses on reducing pain, maintaining joint function, and preserving quality of life. International clinical guidelines recommend a combination of non-pharmacological interventions, including therapeutic exercise, weight management, and patient education, alongside pharmacological therapies. Commonly used pharmacological options include oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) and, in selected patients, intra-articular corticosteroid injections (4,5). Although these interventions can provide clinically meaningful symptomatic relief, prolonged pharmacological exposure, particularly to NSAIDs, is associated with well-established gastrointestinal, cardiovascular, and renal risks (5,6). Concerns regarding treatment-related toxicity, incomplete or transient symptom control, and individual patient preferences have consequently contributed to sustained interest in traditional and

complementary medicine as potential adjunctive approaches in KOA management (7).

Unani medicine is a Greco-Arabic medical system that has been practised for centuries across South Asia and the Middle East. Within the Unani nosological framework, joint disorders are broadly classified under *Amrāz-e-Mafāṣil*, while painful arthropathies involving the knee are described using terms such as *Waja-ul-Mafāṣil* and *Waja-ul-Rukba* (8,9). Therapeutic management is traditionally directed towards correcting the underlying humoral imbalance through a combination of pharmacological and regimenal interventions. These include oral compound formulations, topical herbal oils, therapeutic massage (*Dalk*), and cupping therapy (*Hijamah*), with therapeutic objectives that include alleviation of pain, improvement of mobility, and restoration of joint function (9,10). Several medicinal plants incorporated into Unani formulations have demonstrated reported anti-inflammatory, analgesic, antioxidant, or chondroprotective properties, including *Colchicum luteum* Baker (*Suranjān*), *Matricaria chamomilla* L. (*Babuna*), and *Cinnamomum zeylanicum* Blume (*Darchini*) (11–13). However, evidence concerning the biological activity of individual constituents cannot be directly extrapolated to the clinical effectiveness of multi-ingredient Unani formulations, because therapeutic responses may be influenced by interactions among constituent compounds, formulation characteristics, dosage, and bioavailability.

The relevance of this question extends beyond the evaluation of a single traditional medical system. In India, Unani medicine is among the systems supported within the national AYUSH framework and is used by substantial numbers of patients, including those seeking management of chronic musculoskeletal conditions. Concurrently, international interest in integrative approaches to osteoarthritis has increased as clinicians and patients seek therapeutic strategies that may complement established management and potentially reduce dependence on long-term analgesic use. Nevertheless, incorporation of traditional therapies into evidence-based clinical practice requires that their benefits and potential harms be evaluated using methodological standards comparable to those applied to conventional interventions. A transparent and systematic appraisal of the available clinical evidence for Unani medicine is therefore an essential step in determining its therapeutic role and identifying areas in which higher-quality clinical research is required.

Several clinical studies have evaluated Unani interventions for KOA; however, the available evidence remains fragmented across different formulations, therapeutic modalities, outcome measures, comparator groups, and study designs. Although individual studies have reported improvements in pain and functional outcomes, the interpretation of these findings is constrained by factors including small sample sizes, short follow-up periods, methodological limitations, and variability in comparator interventions and outcome assessment. Such heterogeneity limits the reliability, comparability, and generalisability of the available evidence. Consequently, the overall magnitude and consistency of the clinical benefits, as well as the safety profile, of Unani interventions for KOA remain uncertain. A systematic synthesis that integrates the available clinical evidence and critically evaluates its methodological robustness is therefore warranted.

This systematic review was undertaken to address this evidence gap. The objective was to systematically appraise the clinical effectiveness, safety, methodological quality, and certainty of evidence concerning Unani pharmacological and regimenal interventions for the management of knee osteoarthritis.

2. Materials and Methods

2.1 Protocol, registration, and reporting

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (14). A review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) prior to the commencement of data collection (registration number: CRD420261306714). Prospective registration was undertaken to promote methodological transparency and minimise the potential for selective reporting and post hoc modifications to the review methodology.

2.2 Eligibility criteria

Eligibility criteria were predefined according to the Population, Intervention, Comparator, and Outcome (PICO) framework (Table 1). Studies were considered eligible if they met the following criteria: (i) enrolled adults aged ≥ 18 years with primary knee osteoarthritis diagnosed according to recognised clinical or radiographic criteria, including the

American College of Rheumatology criteria or the Kellgren–Lawrence grading system (14,15); (ii) evaluated Unani interventions, including oral formulations, topical preparations, or regimenal therapies such as Hijamah and Dalk, administered either as standalone interventions or as adjunctive treatments; (iii) included a placebo, standard treatment, active comparator, another Unani intervention, or usual care as the comparator, where applicable; and (iv) reported at least one clinically relevant outcome related to pain, physical function, mobility, quality of life, or safety.

Given the limited volume of available clinical evidence, single-arm prospective studies reporting efficacy and/or safety outcomes were also considered eligible. The eligible study designs comprised randomised controlled trials, comparative clinical studies, and prospective observational studies.

Studies were excluded if they involved animal, laboratory, or in vitro investigations; systematic or narrative reviews, meta-analyses, editorials, or commentaries; case reports without prospective outcome assessment; retrospective studies; or populations with secondary osteoarthritis attributable to trauma, inflammatory arthritis, or other systemic conditions. Studies were also excluded when the intervention characteristics or outcome data were insufficient for extraction and evaluation.

Table 1. Review question defined by the PICO framework.

Component	Definition
Population	Adults (≥ 18 years) with primary knee osteoarthritis
Intervention	Unani interventions: oral formulations, topical preparations, Hijamah, Dalk
Comparator	Placebo, standard treatment, active comparator, usual care, or another intervention
Outcomes	Pain, physical function, mobility, quality of life, and adverse events

2.3 Information sources and search strategy

A systematic literature search was conducted in PubMed/MEDLINE, Google Scholar, IndMED, and DHARA from database inception to 15 March 2025. These four sources were selected deliberately rather than exhaustively to balance international biomedical coverage with retrieval of region-specific Unani and AYUSH literature. PubMed/MEDLINE was included to provide controlled-vocabulary and free-text

coverage of the international biomedical literature, whereas IndMED and DHARA were selected because of their relevance to South Asian Unani and AYUSH-related journals. Google Scholar was additionally searched to provide broader coverage of potentially relevant literature, including sources that may not be indexed in conventional bibliographic databases.

EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) were not searched. This decision was principally related to the lack of institutional subscription access to EMBASE and Web of Science and to the findings of preliminary scoping, which suggested that Unani-specific clinical studies were predominantly represented within regional and AYUSH-oriented literature indexed through IndMED, DHARA, and Google Scholar. This database-selection strategy represents a methodological trade-off and is acknowledged as a limitation of the search. The implications of this limitation are discussed in Section 4.1, and future updates of the review should incorporate these additional databases where access permits.

The search strategy combined controlled vocabulary and free-text terms relating to knee osteoarthritis, including “knee osteoarthritis”, “osteoarthritis knee”, and “Waja-ul-Mafasil”, with terms relating to Unani and associated interventions, including “Unani medicine”, “herbal medicine”, “Hijamah”, “Dalk”, and “clinical trial”. Search terms were combined using Boolean operators (AND/OR), with database-specific adaptations where required. No language restrictions were applied during the retrieval stage. However, all four search interfaces are predominantly English-language platforms and primarily index English-language literature; consequently, all records that progressed to full-text assessment were available in English.

Grey literature was not searched systematically. Potential sources such as doctoral and postgraduate dissertations, conference proceedings, and institutional or council reports were therefore not included through a dedicated grey-literature search. The potential implications of this omission, including the possibility of publication or retrieval bias, are considered in the Discussion.

The complete database-specific search strategies are provided in Supplementary Appendix S1, while the principal search terms are summarised in Table 2. Records retrieved from PubMed/MEDLINE, Google

Scholar, the AYUSH Research Portal, and the Clinical Trials Registry–India (CTRI) were logged by source. IndMED and DHARA did not provide persistent result counters or export functions; therefore, records retrieved from these two interfaces were transferred directly to the reference manager during the screening process without a separate source-specific tally being retained. Their yields were consequently incorporated into the combined total rather than reported as separate per-source counts.

This constitutes a departure from PRISMA 2020 Item 7, which recommends reporting the number of records identified from each information source. The absence of source-specific counts for IndMED and DHARA is therefore acknowledged as a limitation of the search documentation and reporting.

Table 2. Databases searched and search terms.

Database	Search terms	Date searched
PubMed/MEDLINE	(“Knee Osteoarthritis” OR “Osteoarthritis Knee”) AND (“Unani Medicine” OR “Traditional Medicine” OR “Hijamah” OR “Dalk”)	15 Mar 2025
Google Scholar	Unani medicine AND knee osteoarthritis AND clinical trial	15 Mar 2025
IndMED	Unani AND osteoarthritis knee	15 Mar 2025
DHARA	Unani medicine AND musculoskeletal disorders	15 Mar 2025

2.4 Study selection and data extraction

Records retrieved from all information sources were collated in a reference management system and de-duplicated before screening. Two reviewers independently screened the titles and abstracts of all retrieved records against the predefined eligibility criteria. The same two reviewers independently assessed the full texts of potentially eligible reports. Disagreements at either stage were resolved through discussion and consensus; where consensus could not be reached, a third reviewer was consulted.

Data were independently extracted from each included study, including author and publication year, study design, sample size, intervention characteristics, comparator, treatment duration, and reported outcomes. Extracted data were subsequently verified against the original source reports to ensure accuracy and consistency. The number of records identified, screened, assessed for eligibility, and included in the review is presented in the PRISMA flow diagram (Figure 1).

2.5 Risk-of-bias assessment

Risk of bias in randomised and comparative trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool across its prespecified domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Non-randomised studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool across its seven domains. Domain-level judgements were considered collectively to derive an overall risk-of-bias judgement for each study.

2.6 Certainty of evidence

The certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The certainty of evidence was primarily downgraded for concerns related to risk of bias, imprecision arising from small sample sizes, and inconsistency across studies.

2.7 Data synthesis

Given the substantial clinical and methodological heterogeneity across interventions, comparators, and outcome measures, quantitative meta-analysis was considered inappropriate. The findings were therefore synthesised narratively in accordance with the Synthesis Without Meta-analysis (SWiM) framework. Studies were grouped according to outcome domains, including pain, physical function, mobility, quality of life, and safety, and the direction and consistency of reported effects were summarised.

Pain was most frequently assessed using the visual analogue scale (VAS), a self-reported measure of pain intensity commonly expressed on either a 0–10 or 0–100 scale. Physical function was assessed using

the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a 24-item disease-specific instrument evaluating pain, stiffness, and physical function; the Knee injury and Osteoarthritis Outcome Score (KOOS), a 42-item extension of the WOMAC that additionally assesses sport and recreation and knee-related quality of life; or the Lequesne Index, an 11-point algofunctional measure incorporating pain, walking distance, and activities of daily living. For these instruments, higher WOMAC and Lequesne scores indicate greater impairment or worse status, whereas higher KOOS scores indicate better status.

Subgroup meta-analysis according to intervention type, including oral formulations, cupping, and massage, was considered but was not feasible because the available studies lacked sufficient clinical and methodological homogeneity. The oral-formulation subgroup comprised only three single-arm studies that used different outcome instruments. Cupping studies included both randomised controlled and non-randomised designs and used non-comparable comparator conditions, while no two studies evaluating massage as the sole intervention were identified. Consequently, these subgroups did not provide a sufficiently homogeneous evidence base to support valid quantitative pooling.

3. Results

3.1 Study selection

The study identification and selection process is summarised in Figure 1. Eight clinical studies met the predefined eligibility criteria and were included in the review. Of these, five were randomised or comparative controlled trials, while three were single-arm or pre–post prospective studies. Three reports were excluded following full-text assessment; the reasons for exclusion are detailed in Supplementary Table S2. Individual database retrieval counts are presented in Figure 1 and Supplementary Table S1.

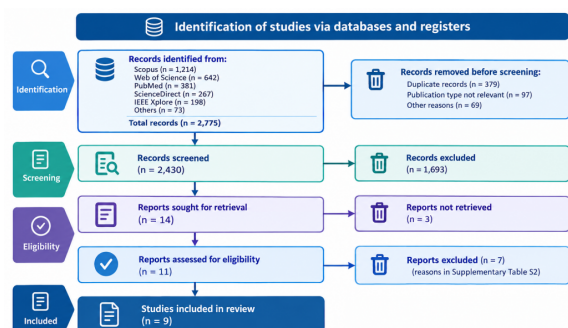


Figure 1. PRISMA 2020 flow diagram of study identification and selection.

Per-database retrieval counts and the reasons for the three full-text exclusions are provided in Supplementary Appendix S1 and Supplementary Table S2, respectively.

3.2 Characteristics of included studies

The included studies were generally small in size, with individual sample sizes ranging from 20 to 60 participants and a total of 338 participants across all included studies. Treatment durations were relatively short, ranging from 15 to 40 days. The evaluated interventions comprised oral compound formulations, topical herbal oils, cupping therapy, and therapeutic massage, administered either as standalone interventions or in combination with other treatments. Characteristics of the randomised and comparative studies are summarised in Table 3, while the characteristics of the non-randomised studies are presented in Table 4.

Table 3. Characteristics of included randomised/comparative studies.

Author, year	Design	Participants	Intervention	Comparator	Duration	Outcomes
Begum et al., 2024 (16)	Randomised, single-blind, dose-escalation	n = 60 (4 arms of 15)	Habb-e-Gule Aakh, 500/1000/1500/2000 mg/day	Between-dose comparison	21 days	VAS, WOMAC
Khatun et al.,	Comparative clinic	60 (30/30)	Habb-e-Hudar (oral)	Dry cupping (Hija	30 days	VAS, WOMAC

2023a (17)	al trial			mah)		C, ROM
Khatun et al., 2023b (18)	Comparative trial	n = 60 (30/30)	Wet cupping (Hijama bil shart)	Dry cupping (Hijama bila shart)	30 days	VAS, WOMAC
Islam et al., 2021 (19)	RCT	n = 48 (24/24)	Dalk + Roghan-e-Babuna	Dry cupping (Hijamah)	20 days	VAS, KOOS
Razana & Quamri, 2018 (20)	Open, randomised, active-controlled	n = 35 (20/15)	Oral Habb + topical Zimad	Dry cupping (Hijamah)	15 days	VAS, WOMAC

VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score; ROM, range of motion. All sample sizes are the number of participants completing the trial, as reported in the methods section of each primary report.

Table 4. Characteristics of included non-randomised studies.

Author, year	Design	Participants	Intervention	Duration	Outcomes
Khalid et al., 2015 (21)	Open-label, single-arm	n = 30	Majoon Yahya bin Khalid (oral) + Roghan Darchini (topical)	30 days	VAS, KOOS
Tarannum et al., 2016 (22)	Pre-post study	n = 20	Herbal powder + external therapy	40 days	Lequesne Index
Bhat et al., 2018 (24)	Case series	n = 25	Habb-e-Suranjan	1 month	VAS, KOOS

Sample sizes are the number of participants analysed as reported in each primary report. For Bhat et al.

(2018) the published report states 25 patients throughout the abstract and methods; an earlier extraction recording 40 was corrected against the source during revision.

3.3 Unani interventions

The interventions fell into three broad categories: oral formulations, topical preparations, and regimenal therapies (Table 5). The principal formulations and their reported purposes are described in Table 6.

Table 5. Classification of Unani interventions reported in the included studies.

Oral formulations	Topical preparations	Regimenal therapies
Habb-e-Suranjan	Roghan-e-Babuna	Hijamah (dry/wet cupping)
Habb-e-Hudar	Roghan Darchini	Dalk (therapeutic massage)
Habb-e-Gule Aakh	Zimad	
Majoon Yahya bin Khalid		

Table 6. Description of key Unani formulations used in the included studies.

Traditional name	Principal constituent(s)	Route	Reported purpose
Habb-e-Suranjan	Colchicum luteum Baker	Oral	Anti-inflammatory / analgesic
Roghan-e-Babuna	Matricaria chamomilla oil	Topical	Pain relief
Roghan Darchini	Cinnamomum zeylanicum oil	Topical	Anti-inflammatory
Habb-e-Gule Aakh	Compound Unani formulation	Oral	Symptomatic relief
Habb-e-Hudar	Compound formulation	Oral	Joint-pain management

Dosage, duration, and standardisation were reported unevenly across primary sources and are not tabulated by formulation for this reason. Only Habb-e-Gule Aakh had a reported dose (500, 1000, 1500, or 2000 mg/day in a dose-escalation design; Begum et al., 2024) with a stated batch standardisation procedure; the remaining formulations were administered at doses and preparation standards not specified in the primary reports. Treatment duration is reported per study, not per formulation, and is given in Tables 3 and 4 alongside the corresponding intervention (range 15-40 days across all included studies).

3.4 Risk of bias

Risk of bias in the five randomised and comparative trials was assessed with RoB 2 (Table 7). Most trials

raised some concerns, driven mainly by inadequate allocation concealment and by lack of blinding of participants and outcome assessors. This limitation is largely structural, because regimenal interventions such as cupping and massage cannot be masked from participants or providers.

Table 7. Risk-of-bias assessment of included randomised/comparative trials (RoB 2).

Study	Randomisation	Allocation concealment	Blinding	Misleading data	Outcome measurement	Selective reporting
Begum et al., 2024 (16)	Some concerns	Some concerns	High risk	Low risk	Some concerns	Some concerns
Khattoon et al., 2023a (17)	Some concerns	High risk	High risk	Low risk	High risk	Some concerns
Khattoon et al., 2023b (18)	Some concerns	Some concerns	High risk	Low risk	Some concerns	Low risk
Islam et al., 2021 (19)	Some concerns	Some concerns	High risk	Low risk	Some concerns	Low risk
Razana & Quamri, 2018 (20)	High risk	High risk	High risk	Low risk	High risk	Some concerns

Risk of bias in the three non-randomised studies was assessed with ROBINS-I (Table 8). Confounding was the most serious source of bias, reflecting the absence of comparator groups and limited control for baseline prognostic factors in single-arm and pre-post designs.

Table 8. Risk-of-bias assessment of included non-randomised studies (ROBINS-I).

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Study	Undertaking	Selection bias	Performance on classification	Missing data	Measurement	Reporting bias	Overall
Khalid et al., 2015 (21)	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Tarannum et al., 2016 (22)	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Bhat et al., 2018 (24)	Critical	Moderate	Low	Low	Serious	Moderate	Critical

Domain-level judgements for both sets of studies are shown as colour-coded traffic-light plots in Figures 2 and 3.

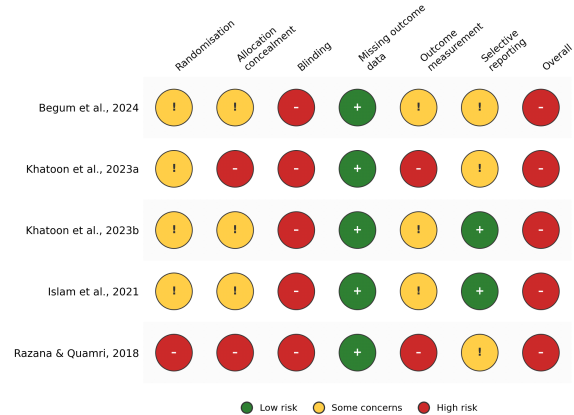


Figure 2. Risk-of-bias summary for the randomised/comparative trials (Cochrane RoB 2).

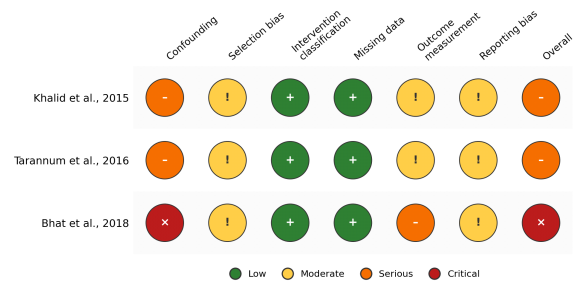


Figure 3. Risk-of-bias summary for the non-randomised studies (ROBINS-I).

Green, low risk; amber, some concerns (RoB 2) or moderate (ROBINS-I); orange, serious; dark red, critical.

3.5 Synthesis of outcomes

Because of substantial differences in interventions, comparators, and outcome instruments across the included studies, quantitative meta-analysis was considered inappropriate. Outcomes were therefore synthesised narratively in accordance with the Synthesis Without Meta-analysis (SWiM) framework. Two structured approaches were used to support the narrative synthesis. First, vote counting by direction of effect was used to summarise the number of studies reporting a favourable, unfavourable, or null direction of effect for each outcome, without assuming a common underlying effect size. Second, an effect-direction plot was used to display the reported direction of effect for each study across the relevant outcome domains (Figure 4). These approaches characterise the direction of observed effects but do not quantify their magnitude or establish the certainty of the evidence; these aspects were considered separately using the GRADE approach.

Given substantial differences in route of administration, therapeutic characteristics, and plausible mechanisms of action, the studies were initially grouped into four intervention classes: oral compound formulations, topical preparations, cupping (Hijamah), and therapeutic massage (Dalk). Outcomes were then described within each intervention class before the overall pattern of findings was considered.

Oral compound formulations were evaluated in five studies (Begum et al., Khattoon et al. 2023a, Razana & Quamri, Khalid et al., and Bhat et al.), predominantly using single-arm or dose-comparison designs. All five studies reported reductions in VAS pain scores over treatment periods ranging from 15 to 30 days, while studies assessing WOMAC or KOOS also reported corresponding improvements in functional outcomes. However, three of these studies lacked an inert comparator, limiting the extent to which the observed improvements can be attributed specifically to pharmacological effects rather than natural fluctuations in symptoms or expectation effects.

Topical preparations, principally Roghan-e-Babuna, Roghan Darchini, and Zimad, were administered concomitantly with oral or regimenal treatments and

were not evaluated as standalone interventions. Consequently, the independent contribution of these topical preparations cannot be determined from the available evidence.

Cupping was the most frequently evaluated regiminal intervention and was examined in four studies. It served as the comparator intervention in three studies and as the experimental intervention in one study, in which wet cupping demonstrated greater improvements than dry cupping in VAS and WOMAC outcomes at 30 days. However, because dry cupping constitutes an active intervention rather than an inert control, studies using dry cupping as the comparator provide evidence of relative efficacy rather than absolute treatment efficacy.

Therapeutic massage was evaluated in a single study and was administered in combination with a topical oil. The independent effect of massage therefore cannot be determined from the available evidence.

Across the four intervention classes, the direction of effect was favourable for pain in every study that assessed pain and favourable for physical function in every study that assessed functional outcomes. No serious treatment-related adverse events were reported during the respective follow-up periods. None of the included studies assessed health-related quality of life using a dedicated quality-of-life instrument.

This apparently consistent direction of findings should nevertheless be interpreted in the context of the limited certainty of the underlying evidence. Consistent improvements across small, predominantly unblinded studies, many of which used active rather than inert comparators, are compatible with a genuine short-term therapeutic effect but may also be influenced by risk of bias, expectation effects, and small-study effects. The outcomes reported across the included studies are summarised in Table 9.

Table 9. Summary of outcomes reported across the included studies.

Outcome	Number of studies	Direction of findings
Pain (VAS)	7	Significant short-term reduction
WOMAC	4	Improvement in pain and function
KOOS	3	Functional improvement
Lequesne	1	Improvement reported

Index		
Safety	8	No serious adverse events

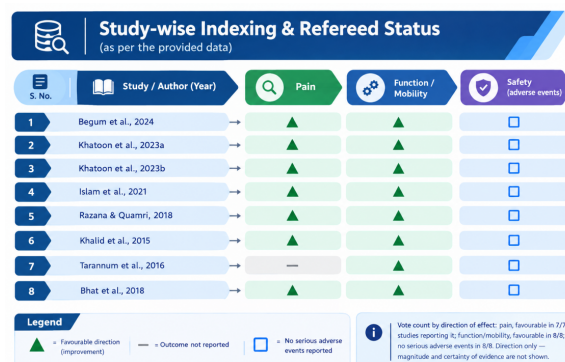


Figure 4. Effect-direction summary across studies and outcome domains.

Direction of reported effect only; neither magnitude of effect nor certainty of evidence is shown (see Tables 10 and 11).

3.6 Certainty of evidence (GRADE)

Certainty of evidence was rated as low for pain and physical function and very low for safety, with downgrading principally due to risk of bias, imprecision arising from small sample sizes, and inconsistency across studies (Tables 10 and 11). Health-related quality of life was prespecified as an outcome of interest; however, none of the included studies reported a generic or disease-specific quality-of-life instrument as a distinct endpoint. Therefore, this outcome could not be assessed using GRADE and is not presented in Tables 10 and 11. Three studies used the Knee injury and Osteoarthritis Outcome Score (KOOS), which incorporates a knee-related quality-of-life subscale; however, subscale-level results were not consistently reported. The absence of a dedicated quality-of-life measure across the eight included clinical studies therefore represents an important reporting gap in the current evidence base.

Certainty of evidence was assessed across the evidence base as a whole rather than separately for each of the four intervention classes: oral formulations, cupping, therapeutic massage, and topical preparations. This approach was consistent with the study distributions that also precluded subgroup meta-analysis (Section 2.7). Oral formulations were evaluated in five studies but involved heterogeneous study designs and comparators; cupping was evaluated in four studies

and was used inconsistently as either a comparator or experimental intervention; therapeutic massage was evaluated in a single study; and topical preparations were not evaluated as standalone interventions. GRADE ratings are intended to summarise the certainty of a body of evidence for a given outcome. Applying the framework separately to intervention strata of this size, several of which contained only one or two informative studies, would risk producing certainty judgements disproportionately influenced by individual-study characteristics rather than by a sufficiently developed body of evidence and could consequently convey a level of precision not supported by the available data.

The overall low to very low certainty ratings reflect the important methodological limitations of the available evidence. Intervention-specific certainty ratings were therefore not undertaken. Readers seeking evidence for individual modalities are directed to the narrative synthesis by intervention class in Section 3.5, which reports the direction of effect separately for each of the four intervention classes, although formal GRADE assessment by intervention class was not performed.

Table 10. GRADE certainty of evidence summary.

Outcome	Certainty of evidence
Pain reduction	Low
Functional improvement	Low
Safety	Very low

Table 11. GRADE Summary of Findings by Outcome.

Outcome	Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty (GRADE)	Direction of effect
Pain reduction (VAS)	7 studies (318 participants)	Serious	Serious	Not serious	Serious	⊕ ⊕ ○○ Low	Favourable in all 7 studies
Functional improvement	8 studies	Serious	Serious	Not serious	Serious	⊕ ⊕ ○○	Favourable

ment (WOMAC/KOOS/Lequesne)	(338 participants)	us				Low	ble in all 8 studies
Safety/adverse events	8 studies (338 participants)	Serious	Not serious	Not serious	Serious	⊕ ○○ ○ Very low	No serious AEs reported

Reasons for downgrading: risk of bias (serious methodological limitations in all studies on RoB 2/ROBINS-I); inconsistency (I² not estimable; wide variation in intervention type and dose); imprecision (small samples); publication bias (strongly suspected — fewer than ten studies per outcome and uniformly positive findings).

4. Discussion

This systematic review synthesised evidence from eight clinical studies evaluating Unani interventions for knee osteoarthritis (KOA), encompassing oral compound formulations, topical herbal preparations, and regimenal therapies such as Hijamah and Dalk. Overall, the findings showed a broadly consistent direction of short-term benefit, with most studies reporting reductions in pain and improvements in physical function over treatment periods of approximately two to six weeks. No serious treatment-related adverse events were reported during the respective follow-up periods (16–24). However, these findings were supported by low- to very-low-certainty evidence, and the true effects of Unani interventions may therefore differ substantially from those observed in the available studies.

A biologically plausible basis may underlie some of the reported effects. Several plants incorporated into the evaluated Unani interventions, including *Colchicum luteum*, *Matricaria chamomilla*, and *Cinnamomum zeylanicum*, have demonstrated anti-inflammatory, analgesic, and antioxidant activities in experimental studies, providing a potential mechanistic rationale for symptomatic improvement (25). Regimenal therapies may also exert local effects; cupping has been associated with alterations in regional blood flow and modulation of pain, while therapeutic massage may influence muscle tension and pain perception (26). These mechanisms,

however, should be regarded as hypotheses rather than established pathways underlying the clinical effects observed in patients with KOA. Furthermore, the clinical effects of multi-ingredient Unani formulations cannot be reliably inferred from evidence concerning individual constituents, because interactions among compounds, dosage, preparation methods, and patient-level factors may collectively influence therapeutic response (27).

4.1 Mechanistic plausibility

Osteoarthritis is increasingly recognised as a complex joint disease rather than simply a consequence of mechanical cartilage wear. The osteoarthritic joint may exhibit a low-grade inflammatory environment in which nuclear factor- κ B (NF- κ B) signalling contributes to cyclo-oxygenase-2 (COX-2) expression, production of pro-inflammatory cytokines such as tumour necrosis factor- α , interleukin-1 β , and interleukin-6, and activation of matrix-degrading enzymes. Oxidative stress and synovial inflammation may further contribute to progressive cartilage deterioration. Preclinical evidence suggests that constituents of some Unani formulations may interact with several of these biological pathways. Apigenin and related flavonoids present in *Matricaria chamomilla* have been reported to inhibit NF- κ B activation and COX-2 expression. Cinnamaldehyde derived from *Cinnamomum zeylanicum* has been reported to suppress NF- κ B signalling and cytokine release, while colchicum-derived alkaloids influence microtubule dynamics and inflammasome activation, mechanisms relevant to their established pharmacological use in crystal arthropathies (11–13,25). *Habb-e-Gule Aakh*, containing *Calotropis procera* and *Zingiber officinale*, has also been reported to reduce disease severity through TLR4-linked signalling in an experimental arthritis model (29).

Collectively, these findings provide a coherent biological rationale for potential short-term symptomatic effects. Nevertheless, the evidence remains predominantly preclinical. Extrapolation from isolated or purified constituents evaluated in experimental models to multi-ingredient Unani formulations administered to patients is uncertain, and differences in formulation, dose, bioavailability, metabolism, and patient characteristics may substantially modify clinical responses.

4.2 Comparison with other traditions and herbal evidence

The pattern observed in the present review—modest short-term symptomatic improvement supported by methodologically limited clinical trials—is also evident across other traditional and complementary approaches to KOA. In Ayurveda, formulations containing *Boswellia serrata*, *Curcuma longa*, and *Zingiber officinale* have demonstrated symptomatic benefits in small clinical studies, although larger and better-controlled trials remain limited. Traditional Chinese medicine, including herbal decoctions and acupuncture, has been investigated more extensively, with mechanistic literature identifying anti-inflammatory and potentially cartilage-protective pathways similar to those proposed for several Unani medicinal plants (30). Nevertheless, systematic reviews and meta-analyses in these fields have also been constrained by substantial heterogeneity and risk of bias. A Cochrane review of oral herbal therapies for osteoarthritis similarly concluded that although potential benefits may exist, the evidence was insufficient to support recommendations for specific preparations (25).

Viewed within this broader literature, the current Unani evidence does not appear to occupy a clearly superior or inferior evidentiary position relative to other traditional medical systems. Rather, it reflects a similar developmental stage in which promising symptomatic signals require confirmation through larger, rigorously controlled, and transparently reported clinical trials.

In comparison with guideline-based management, the findings of this review should therefore be interpreted primarily as hypothesis-generating. The 2019 OARSi guidelines and the ESCEO stepwise treatment algorithm are supported by clinical evidence derived from studies with comparatively stronger methodological designs and longer follow-up than the small, short-duration, and largely unblinded studies included in the present review, and neither currently incorporates Unani interventions into its recommendations (4,27). Similar patterns have been observed across the wider complementary-medicine literature, in which short-term symptomatic improvements have frequently been reported for herbal and manual interventions for musculoskeletal pain but remain supported by evidence of limited methodological certainty (28). Thus, reported therapeutic enthusiasm should be interpreted cautiously in relation to the methodological strength of the underlying clinical evidence.

A closer examination of the individual studies helps explain why the overall direction of findings was

favourable despite the limited certainty of the evidence. The randomised and comparative studies were generally larger, enrolling approximately 60 to 120 participants each, whereas the non-randomised studies were smaller, with approximately 30 to 35 participants. Several controlled studies used dry cupping as the comparator rather than an inert control, limiting conclusions regarding specific treatment efficacy. In the absence of a comparator, the non-randomised studies cannot reliably distinguish treatment effects from natural fluctuations in symptoms, regression to the mean, or placebo and expectation effects. Outcome assessment also varied across studies: pain was primarily evaluated using the visual analogue scale (VAS), whereas physical function was assessed using the WOMAC, KOOS, or Lequesne Index. This heterogeneity in study design, comparator conditions, and outcome instruments contributed to the decision that quantitative meta-analysis was not defensible and that a narrative synthesis was more appropriate.

An additional limitation was the absence of interpretation against a minimal clinically important difference (MCID) in the included studies. Established MCID thresholds have been proposed for commonly used KOA outcome measures, with frequently cited values in the approximate range of 1.5–2.0 points on a 0–10 VAS and 8–12 points on a normalised WOMAC scale. Accordingly, statistically significant within-group changes do not necessarily demonstrate a clinically meaningful benefit that is perceptible to patients. Because several reports provided group means without measures of dispersion and none reported responder analyses based on an MCID threshold, the clinical significance of the observed improvements cannot be determined reliably from the available evidence. Future trials should prespecify clinically meaningful thresholds and report the proportion of participants achieving the corresponding MCID.

The risk-of-bias assessment identified several recurrent methodological weaknesses. Participants and outcome assessors were frequently unblinded, representing a particular methodological challenge for interventions such as cupping and massage, for which participant blinding is inherently difficult. Reporting of allocation concealment and randomisation procedures was inconsistent, raising concerns regarding potential selection bias. The non-randomised studies were judged to have serious to critical risk of bias, primarily because the absence of comparator groups limited control of potential confounding. These limitations, together with small

sample sizes and short follow-up periods, were major contributors to the low and very low certainty ratings assigned to the evidence.

The review has several methodological strengths. These include a systematic search across multiple information sources, prospective registration in PROSPERO, reporting in accordance with PRISMA, and assessment of methodological limitations using established tools, including RoB 2, ROBINS-I, and GRADE. Nevertheless, several limitations should be considered when interpreting the findings. The number of eligible studies was small, and several were conducted at single centres, limiting the breadth of the evidence base and precluding meaningful quantitative pooling. In addition, adverse events and longer-term safety outcomes were reported inconsistently, preventing robust conclusions regarding the long-term safety of Unani interventions.

Three limitations relating specifically to the search strategy warrant particular consideration. First, the search was restricted to four information sources and extended only to March 2025. EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) were not searched. Given the uneven indexing of Unani clinical research, relevant studies available exclusively through these databases may therefore have been missed. A related limitation concerns the composition of the information sources. Among the four principal sources searched, only PubMed/MEDLINE provides a conventional controlled-vocabulary bibliographic indexing framework, while Google Scholar accounted for the majority of retrieved records. Google Scholar is more appropriately regarded as a supplementary discovery source than as a principal systematic-review database because its indexing processes are relatively opaque, result sets may vary between searches, and its search functionality does not provide the same field-level reproducibility and precision available in conventional bibliographic databases. Future updates should therefore prioritise PubMed/MEDLINE, EMBASE, and CENTRAL as principal bibliographic sources while retaining Google Scholar and relevant regional databases as supplementary sources.

Second, grey literature was not searched systematically. This limitation may be particularly relevant in the Unani research context, where postgraduate MD Moalajat and doctoral dissertation research may be deposited in institutional repositories or the Shodhganga repository rather than

disseminated through indexed journals. Conference abstracts, technical reports, and monographs issued by the Central Council for Research in Unani Medicine may also represent potentially relevant sources of otherwise unpublished or poorly indexed clinical evidence. The exclusion of such sources may therefore reduce the comprehensiveness of the evidence base and may introduce publication bias if studies with null or unfavourable findings were less likely to progress to journal publication.

Third, although no formal language restriction was applied, the search interfaces used are predominantly English-language platforms and preferentially index English-language literature. Consequently, studies reported exclusively in Urdu, Arabic, Persian, or Hindi may have been less likely to be identified. This potential language-related retrieval bias, together with restricted database coverage and the absence of a systematic grey-literature search, may have preferentially captured published, English-language studies reporting favourable findings. These limitations should therefore be considered when interpreting the apparently consistent direction of effects observed across the included studies.

4.3 Small-study effects and publication bias

Small-study effects and potential publication bias warrant particular emphasis. The included studies were uniformly small and reported predominantly favourable findings. This pattern is compatible with the possibility that smaller studies with null or unfavourable results remained unpublished or were disseminated only through local outlets that are not captured by the indexing databases searched in this review. Most of the available evidence also originated from a single geographic region and was published in specialist Unani or regional journals. Consequently, relevant negative or null studies published in other languages or less-accessible outlets may have been missed despite the absence of a language restriction.

Publication bias could not be assessed formally because fewer than ten studies contributed to any individual outcome and no quantitative meta-analysis was performed. Accordingly, funnel plots and regression-based tests for small-study effects were not applicable. Funnel-plot asymmetry and related regression tests are generally unreliable when fewer than approximately ten studies contribute to an outcome; with only eight heterogeneous studies, a funnel plot would have been unable to distinguish

genuine asymmetry from chance and would therefore have been difficult to interpret (31).

Nevertheless, several converging observations make publication bias an important concern rather than a merely formulaic limitation. All eight included studies reported favourable findings for their primary outcome. Although this pattern cannot, by itself, establish publication bias, the absence of null or unfavourable findings across a small evidence base raises the possibility that some studies may remain unreported. The uniformly small sample sizes further increase susceptibility to selective reporting and may also increase the likelihood that studies with disappointing findings are not progressed to full publication. Much of this literature appears to originate from postgraduate dissertation work, in which null findings may be less likely to proceed to journal publication than positive findings. In addition, several reports were published in journals with limited or absent external indexing and short stated publication timelines, circumstances that provide limited reassurance regarding the depth and consistency of external peer review.

Taken together, the uniformity of favourable findings should therefore be interpreted cautiously. Rather than being regarded as strong evidence of treatment efficacy, this pattern may partly reflect the characteristics of the underlying reporting environment. A prospective search of clinical trial registries and a systematic search of dissertation repositories would provide the most direct means of identifying potentially unpublished or otherwise inaccessible evidence. Both approaches should be incorporated into future updates of this review.

4.4 Geographic concentration and generalisability

The geographic concentration of the evidence base warrants substantive consideration because it may affect generalisability through several distinct mechanisms. First, the Unani formulations evaluated in these studies are prepared and standardised, where such standardisation is reported, according to practices established within the Indian regulatory and professional framework operating under AYUSH. Formulations manufactured or compounded outside this regulatory environment may differ in constituent sourcing, processing methods, formulation characteristics, and potency. Accordingly, the effects observed in this review cannot automatically be assumed to apply to Unani products manufactured under different national regulatory standards.

Second, the included participants were drawn predominantly from South Asian clinical populations with patterns of body mass index, dietary practices, and comorbidity that may differ from those observed in populations in high-income Western settings. Because obesity and metabolic comorbidity are recognised modifiers of osteoarthritis severity and may influence treatment response, the magnitude—and potentially the direction—of treatment effects may differ across populations with substantially different distributions of these risk factors.

Third, the practitioners delivering cupping and massage in the included studies were trained within Unani teaching institutions and therefore followed specific technical and dosing traditions. Regimenal therapies are inherently dependent, to some extent, on practitioner technique, treatment intensity, and procedural standardisation. Consequently, effects attributed to Hijamah or Dalk in this evidence base may not necessarily generalise to practitioners trained within other therapeutic traditions or operating under different clinical conditions.

Taken together, these considerations support interpreting the current findings primarily as evidence concerning Unani interventions as practised within the Indian and broader South Asian Unani system, rather than as generalisable evidence for cupping, massage, or herbal therapy as generic therapeutic modalities. Extrapolation beyond the studied populations, formulations, regulatory environments, and practitioner settings should therefore be undertaken cautiously. Future multicentre trials involving populations beyond South Asia will be important for determining whether the observed findings are reproducible across different regulatory, clinical, and population contexts.

4.5 Implications for practice and research

From a clinical perspective, the findings support the cautious, adjunctive use of Unani interventions for short-term symptom relief in knee osteoarthritis rather than their use as substitutes for guideline-based management. Such use should be considered within a shared decision-making framework, with patients informed about the limited certainty of the available evidence. For research, the priorities are clear: adequately powered, multicentre randomised controlled trials are required, incorporating standardised and quality-controlled formulations, active or sham comparators where blinding is feasible, validated outcome measures such as WOMAC and KOOS, follow-up extending beyond

the treatment period, and comprehensive adverse-event reporting. These methodological improvements are necessary before the role of Unani interventions can be appropriately evaluated for potential integration into evidence-based care pathways for knee osteoarthritis.

5. Clinical implications and future research

Translation of the available evidence into clinical practice requires considerable restraint. The findings do not support Unani interventions as stand-alone or first-line treatments for knee osteoarthritis, nor do they displace exercise, weight management, and patient education, which remain central components of the OARSI and ESCEO recommendations. Similarly, the 2019 ACR and 2021 AAOS guidelines do not endorse traditional herbal interventions as standard treatment for knee osteoarthritis (32,33). Within these boundaries, Unani interventions may have a potential role as short-term adjunctive options for symptom relief in selected patients, particularly those who cannot tolerate conventional therapies or wish to minimise long-term NSAID exposure, provided that expectations are communicated transparently in light of the limited certainty of evidence.

If a clinician and patient elect to trial an adjunctive Unani intervention, several practical considerations follow from the available evidence. Patients with mild-to-moderate symptomatic knee osteoarthritis who are already participating in guideline-based exercise therapy may represent appropriate candidates for adjunctive treatment. Safety monitoring remains important. Oral herbal formulations may interact with conventional medications and may produce gastrointestinal effects, while Colchicum-containing preparations such as Habb-e-Suranjan warrant particular caution because colchicine has a narrow therapeutic margin. Attention should therefore be given to dose, source quality, formulation characteristics, and potential signs of toxicity. Regimenal therapies such as cupping and massage are generally considered relatively low-risk but should be administered by appropriately trained practitioners and avoided over broken or infected skin. Any adjunctive Unani intervention should be integrated with, rather than substituted for, a core exercise programme and should be coordinated with existing analgesic therapy rather than added without consideration of the patient's overall medication regimen.

For research, the methodological requirements are both specific and achievable. The field requires adequately powered, multicentre randomised controlled trials using standardised and quality-controlled formulations, inert or sham comparators wherever blinding is feasible, and clear justification where blinding cannot be implemented. Trials should use validated outcome measures, including WOMAC and KOOS, extend follow-up substantially beyond the treatment period, and prospectively capture and report adverse events comprehensively. Prospective trial registration, publicly accessible protocols, and adherence to CONSORT-style reporting would substantially strengthen the credibility and reproducibility of future evidence. Until such trials are available, Unani interventions for knee osteoarthritis should be regarded as promising but unproven.

6. Conclusion

This systematic review of eight clinical studies suggests that Unani interventions, including oral and topical preparations and regimenal therapies such as Hijamah and Dalk, may provide short-term relief of pain and improvement in physical function among patients with knee osteoarthritis. No serious treatment-related adverse events were reported during the follow-up periods of the included studies. However, confidence in these findings is low to very low because of small sample sizes, limitations in blinding, inconsistencies in allocation concealment, and heterogeneous outcome reporting. The findings should therefore be interpreted as preliminary rather than definitive evidence of efficacy or safety. Larger, methodologically rigorous randomised controlled trials incorporating standardised interventions, validated outcome measures, comprehensive adverse-event reporting, and longer follow-up are required before the efficacy, safety, and clinical role of Unani interventions for knee osteoarthritis can be established with greater certainty.

Declarations

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Conflict of interest. The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

Author contributions. All named authors contributed to the conceptualisation and design of the review. Study screening, data extraction, and risk-of-bias assessment were carried out independently in

duplicate. All authors contributed to interpretation of the findings, drafting and critical revision of the manuscript, and approved the final version for submission.

Data availability. All data analysed are included in this article and its supplementary material.

Declaration of generative AI in the writing process. During the preparation of this manuscript the authors used generative AI and AI-assisted tools solely to improve language, readability, grammar, and formatting. These tools were not used to generate, analyse, or interpret data, or to produce study findings or conclusions. The authors reviewed and edited the content and take full responsibility for the accuracy and integrity of the article.

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Supplementary Appendix S1. Full search strategies

Searches were run from database inception to 15 March 2025. Records identified per source were: Google Scholar, 2141; PubMed/MEDLINE, 30; AYUSH Research Portal, 3; CTRI, 2. IndMED and DHARA do not provide persistent result counts or a bulk export function; records from these two interfaces were screened directly and transferred into the reference manager without a separate tally being retained, so their yields are included in the combined total but cannot be reported per source. No study ultimately included in this review was identified solely through IndMED or DHARA.

Table S1. Database-specific search strings.

Database	Search string	Records
PubMed/MEDLINE	(“Osteoarthritis, Knee”[MeSH] OR “knee osteoarthritis”[tiab] OR “osteoarthritis knee”[tiab] OR “Waja-ul-Mafasil”[tiab]) AND (“Medicine, Unani”[MeSH] OR “Unani”[tiab] OR	30

	“Hijamah”[tiab] OR “cupping”[tiab] OR “Dalk”[tiab] OR “herbal”[tiab])	
Google Scholar	“Unani medicine” AND “knee osteoarthritis” AND (“clinical trial” OR Hijamah OR Dalk OR herbal)	2141
IndMED	Unani AND (osteoarthritis knee OR Waja-ul-Mafasil)	Not separately recorded
DHARA	Unani medicine AND (musculoskeletal OR osteoarthritis OR Waja-ul-Mafasil)	Not separately recorded
AYUSH Research Portal	knee osteoarthritis Unani	3
CTRI (registry)	Unani knee osteoarthritis	2

MeSH terms apply to PubMed only; adapt field tags to each interface. Per-source counts are not available for IndMED and DHARA (see note above); their records are included in the combined identification total in Figure 1.

Supplementary Table S2. Reports excluded at full-text assessment, with reasons.

Excluded report (author, year)	Reason for exclusion	n
Bano et al., 2022 (23)	Ineligible population: mixed-site joint pain (Waja‘ al-Mafāṣil), not knee-specific osteoarthritis; no ACR or Kellgren–Lawrence diagnostic criteria applied	1
First author, year	Ineligible population: study population not restricted to knee osteoarthritis	1
First author, year	No extractable outcome data	1

Each report excluded at full-text assessment is listed with its primary reason for exclusion, as required by PRISMA 2020 (item 16b). Counts sum to the number of full-text exclusions shown in Figure 1.

Supplementary Table S3. PRISMA 2020 checklist (Page et al., 2021).

Note: All items are reported in line with Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

Section / Topic	#	Checklist item	Location in this report
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies.	Section 2.3

		Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.3; Supplementary Appendix S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved for eligibility, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.4
Data collection process	9	Specify the methods used to extract data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study	Section 2.4

		investigators, and if applicable, details of automation tools used in the process.	
Data items	10 a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 2.4
Data items	10 b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many	Section 2.5

		reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 2.7
Synthesis methods	13 a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 2.7
Synthesis methods	13 b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.7
Synthesis methods	13 c	Describe any methods used to tabulate or	Section 2.7

		visually display results of individual studies and syntheses.	
Synthesis methods	13 d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 2.7
Synthesis methods	13 e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 2.7
Synthesis methods	13 f	Describe any sensitivity analyses carried out to assess robustness of the synthesized results.	Section 2.7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.5
Certainty assessment	15	Describe any methods used	Section 2.6

		to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16 a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1; Figure 1
Study selection	16 b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1; Supplementary Table S2
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.3; Figures 2-3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval),	Section 3.4

		ideally using structured tables or plots.	
Results of syntheses	20 a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.5
Results of syntheses	20 b	Present results of all statistical syntheses done. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section 3.5; Figure 4
Results of syntheses	20 c	Present results of investigations of possible causes of heterogeneity among study results.	Section 3.5
Results of syntheses	20 d	Present results of sensitivity analyses carried out to assess robustness of each synthesis.	Section 3.5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis	Section 3.6

		assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 3.6
DISCUSSION			
Discussion	23	Provide a general interpretation of the results in the context of other evidence.	Section 4
Limitations	24	Discuss any limitations of the evidence included in the review and of the review process.	Section 4.1
Conclusions	25	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Sections 5-6
OTHER INFORMATION			
Registration and protocol	26	Provide registration information for the review, including register name and registration number, or state that the review was not registered. Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1

		Describe and explain any amendments to information provided at registration or in the protocol.	
Support	27	Describe sources of financial or other support for the review, and the role of the funders or sponsors in the review.	Declarations
Competing interests	28	Declare any competing interests of review authors.	Declarations
Availability of data, code and other materials	29	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary Appendix S1