



# Clinical effectiveness of Ya-Tha-Pra-Sen remedy for pain relief: A systematic review and meta-analysis of randomized controlled trials

Wiraphol Phimarn<sup>1\*</sup>, Siraporn Mahakoat<sup>2</sup>, Sujaree Panomhet<sup>2</sup>, Bunleu Sungthong<sup>3</sup><sup>1</sup>Social Pharmacy Research Unit, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham 44150, Thailand<sup>2</sup>Kamalasai Hospital, Kalasin, 46130, Thailand<sup>3</sup>Integrative Pharmaceuticals and Innovative Pharmaceutical Technology Research Unit, Faculty of Pharmacy, Mahasarakham University, Khamriang, Kantharawichai, Maha Sarakham, Thailand 44150

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## ABSTRACT

**Introduction:** Ya-Tha-Pra-Sen (YTPS) is a traditional Thai remedy commonly used to alleviate osteoarthritis and musculoskeletal pain. Despite its longstanding use, its clinical effectiveness has not been clearly established, and a comprehensive synthesis of available evidence is lacking. This study aimed to systematically review and meta-analyze the clinical efficacy of YTPS for pain management.**Methods:** Two independent reviewers conducted a systematic search of Thai and international databases (PubMed, Scopus, ScienceDirect, ThaiJo, and Thai Thesis) through February 2025. Search strategies were developed using Medical Subject Headings (MeSH) and related terms, including “Ya-Tha-Pra-Sen,” “YTPS,” and “Thai traditional medicine.” Effect sizes were pooled using a random-effects model, and statistical heterogeneity was evaluated.**Results:** Five randomized studies from Thailand (total n = 261) with treatment durations of six days to four weeks met inclusion criteria. Compared with placebo, YTPS significantly reduced pain intensity (standardized mean difference [SMD] = -1.95; 95% CI: -2.65 to -1.24;  $P < 0.001$ ). Pain reduction did not differ significantly between YTPS and topical analgesics (SMD = -0.22; 95% CI: -0.56 to 0.12;  $P = 0.21$ ). However, YTPS produced significantly greater improvement in physical function than topical comparators (SMD = -0.68; 95% CI: -1.03 to -0.34;  $P < 0.001$ ). No serious adverse events were reported.**Conclusion:** YTPS appears to be a safe and potentially effective alternative to conventional topical analgesics for musculoskeletal and knee osteoarthritis pain. Nonetheless, conclusions are tempered by small sample sizes, short follow-up periods, and variability in formulation and standardization across studies.

### Implication for health policy/practice/research/medical education:

This meta-analysis suggests that Ya-Tha-Pra-Sen remedy may serve as a promising alternative to conventional topical analgesics in the management of musculoskeletal pain and knee osteoarthritis.

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## Introduction

Pain constitutes a major global health challenge, exerting substantial effects on individual well-being, occupational performance, and overall quality of life (1). Epidemiological data indicate that more than 60% of adults report experiencing bodily pain (2), while

approximately 10% develop chronic pain each year (3). Frequently affected regions include the shoulders, ankles, upper back, and head. The intensity and clinical expression of pain are shaped by a complex interplay of factors, including genetic susceptibility, general health status, coexisting medical conditions, psychological and

\*Corresponding author: Wiraphol Phimarn,  
Email: wiraphol.p@msu.ac.th

cognitive influences, early-life pain exposure, and broader social and cultural contexts (4).

Pain is commonly categorized according to duration: acute pain persists for less than three months, subacute pain lasts three to six months, and chronic pain extends beyond six months (5). Effective pain control generally requires an integrated, multidisciplinary strategy incorporating pharmacologic treatment, interventional procedures, physical rehabilitation, and psychological support. For mild to moderate pain, first-line pharmacotherapy typically includes non-opioid agents such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (6). NSAIDs act primarily through inhibition of cyclooxygenase (COX) enzymes and suppression of prostaglandin synthesis; however, their use may be constrained by gastrointestinal, hepatic, and renal adverse effects, limiting suitability in certain populations (7). These safety concerns have stimulated interest in alternative therapies with anti-inflammatory activity and improved tolerability.

Pain management also frequently involves self-care and conservative modalities, including topical preparations (8), massage (9), physical therapy (10), heat application (11), and structured exercise programs (12). Traditional medical systems have historically contributed to organized therapeutic frameworks. During the Ayutthaya era, the Na-Rai traditional medicine compendium consolidated Thai pharmacological knowledge. Among its recorded formulations, Ya-Tha-Pra-Sen (YTPS) holds particular historical and therapeutic relevance (13).

Documented as the 58<sup>th</sup> formulation in the Na-Rai text, YTPS has been traditionally employed for musculoskeletal and circulatory disorders, including muscle strain, paralysis, angina, cramps, and fatigue (14). The preparation consists of 13 medicinal plants (Table 1), notably *Piper nigrum* L., *Alpinia galanga* (L.) Willd., and *Boesenbergia rotunda* (L.) Mansf. Several constituents exhibit established pharmacological activities (15). *Piper nigrum* contains piperine, which demonstrates analgesic, anti-inflammatory, and antioxidant effects (16). *Allium sativum* provides flavonoids capable of modulating pro-inflammatory pathways (17), while *Aloe vera* possesses recognized anti-inflammatory properties (18). Experimental investigations indicate that YTPS tincture exhibits anti-inflammatory and antioxidant activity without significant toxicity (19). Clinical evidence has also suggested benefit in knee osteoarthritis (20), supporting its potential role in musculoskeletal management.

Despite emerging research in osteoarthritis and muscle pain, the clinical efficacy of YTPS has not been comprehensively synthesized, and its therapeutic value remains incompletely defined. Therefore, this study conducted a systematic review and meta-analysis to critically evaluate the effectiveness of YTPS for pain relief.

## Materials and Methods

### Data sources and search strategies

This systematic review and meta-analysis was undertaken in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure transparency and methodological integrity (48). The review protocol was prospectively registered with PROSPERO (CRD420251070217). Two investigators (W.P. and B.S.) independently carried out an extensive search of electronic databases, including PubMed, Scopus, ScienceDirect, ThaiJo, and Thai Thesis, covering all records from database inception through February 2025. The search strategy incorporated controlled vocabulary and relevant keywords related to pain management and the intervention of interest, such as “Ya-Tha-Pra-Sen,” “YTPS,” and “Thai traditional medicine.” To maximize completeness, the reference lists of pertinent reviews and eligible studies were manually screened to identify additional publications not retrieved through database searches. No limitations were placed on language or study design to maintain broad inclusivity. Furthermore, experts in the field were consulted to help identify any potentially relevant studies that might have been overlooked.

### Study selection

Study identification and selection were conducted using a predefined and structured methodology. Following database retrieval, duplicate citations were eliminated. Titles and abstracts were then evaluated for relevance, after which potentially eligible studies underwent full-text review to determine final inclusion. Only articles meeting the established eligibility criteria were incorporated into this systematic review. Studies were considered eligible if they: (i) examined the effects of YTPS in the context of pain management; (ii) reported quantifiable clinical outcomes; and (iii) employed a randomized controlled trial (RCT) design. Publications without primary research data including editorials, correspondence, narrative reviews, meta-analyses, and case reports were excluded. Studies were also excluded if they lacked an interventional framework or did not present outcome data suitable for quantitative analysis. In addition to electronic database searches, reference tracking and conference materials were reviewed to identify further relevant studies. All stages of screening and study selection were independently performed by two reviewers to enhance methodological robustness and reduce the risk of selection bias.

### Outcome measures

The primary endpoint was pain intensity, evaluated using the Visual Analogue Scale (VAS), a widely accepted instrument for quantifying pain severity. The VAS generally comprises a 100-mm horizontal line anchored

**Table 1.** Pharmacologically active compounds and mechanisms of action of the Ya-Tha-Pra-Sen (YTPS) remedy

| Scientific name                                 | Thai name    | Part used | Major active compounds                | Known pharmacological effects  | Biological activities                                      | References |
|---|--------------|-----------|---------------------------------------|--|--|------------|
| <i>Piper nigrum</i> L.                          | Prik-Thai    | Fruit     | Piperine                              | Inhibits COX-2 and TNF- $\alpha$ ; enhances $\beta$ -endorphin release | Anti-inflammatory, analgesic                               | (21–23)    |
| <i>Alpinia galanga</i> (L.) Willd.              | Kha          | Rhizome   | Galangin, 1'-Acetoxychavicol acetate  | Inhibits iNOS and NF- $\kappa$ B activation                            | Anti-inflammatory, analgesic                               | (24–26)    |
| <i>Boesenbergia rotunda</i> (L.) Mansf.         | Kra-Chai     | Rhizome   | Pinostrobin, Panduratin A             | Suppresses NO and prostaglandin E2                                     | Anti-inflammatory  | (27,28)    |
| <i>Allium ascalonicum</i> L.                    | Hom-Daeng    | Bulb      | Organosulfur compounds                | Modulates NF- $\kappa$ B and cytokine pathways                         | Anti-inflammatory  | (29,30)    |
| <i>Allium sativum</i> L.                        | Kra-Tiam     | Bulb      | Allicin, S-allylcysteine              | Inhibits prostaglandin synthesis and NF- $\kappa$ B                    | Anti-inflammatory, rheumatoid arthritis                    | (31,32)    |
| <i>Ferula assa-foetida</i> L.                   | Ma-Ha-Hing   | Resin     | Ferulic acid, Sesquiterpene coumarins | Inhibits COX enzymes, reduces TNF- $\alpha$                            | Anti-inflammatory, anti-nociceptive                        | (33,34)    |
| <i>Aloe vera</i> (L.) Burm.f.                   | Ya-Dam       | Resin     | Acemannan, Aloin                      | Inhibits IL-1 $\beta$ , IL-6, TNF- $\alpha$ ; promotes wound healing   | Anti-inflammatory  | (35)       |
| <i>Cymbopogon nardus</i> (L.) Rendle            | Ta-Khrai-Hom | Leaves    | Citronellal, Geraniol                 | Inhibits cytokines and prostaglandins                                  | Anti-inflammatory, analgesic                               | (36,37)    |
| <i>Senna siamea</i> (Lam.) Irwin & Barneby      | Khi-lek      | Leaves    | Barakol                               | Inhibits serotonin uptake; antioxidant                                 | Anti-inflammatory, analgesic                               | (38)       |
| <i>Baliospermum solanifolium</i> (Burm.) Suresh | Tong-Taek    | Leaves    | Phorbol esters                        | Reduces edema and cytokine expression                                  | Anti-inflammatory  | (39)       |
| <i>Tamarindus indica</i> L.                     | Ma-Kham      | Leaves    | Tannins, Flavonoids                   | Inhibits COX and LOX enzymes   | Anti-inflammatory, analgesic,                              | (40–42)    |
| <i>Melia azedarach</i> L.                       | Lian         | Leaves    | Limonoids, Triterpenoids              | Suppresses NF- $\kappa$ B and MAPK pathways                            | Anti-inflammatory, rheumatic pain                          | (43,44)    |
| <i>Putranjiva roxburghii</i> Wall.              | Ma-Kham-Kai  | Leaves    | Putranjivain A, Flavonoids            | Anti-nociceptive via opioid receptors, antioxidant                     | Anti-inflammatory, joint pain rheumatism, anti-nociceptive | (45–47)    |

Abbreviations: COX-2: cyclooxygenase-2; TNF- $\alpha$ : tumor necrosis factor-alpha;  $\beta$ -endorphin: beta-endorphin; iNOS: inducible nitric oxide synthase; NF- $\kappa$ B: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; IL-1 $\beta$ : interleukin-1 beta; IL-6: interleukin-6; LOX: lipoxygenase; MAPK: mitogen-activated protein kinase

by descriptors indicating the extremes of pain. Participants marked the point that best reflected their perceived pain level, and the score was calculated by measuring the distance in millimeters from the origin to the selected point (49). Pain associated with osteoarthritis was further assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a validated questionnaire measuring pain, stiffness, and physical function. The WOMAC includes 24 items distributed across three domains: pain (5 items), stiffness (2 items), and physical function (17 items). For consistency and comparability, total scores are commonly normalized to a 0–100 scale (50). Secondary outcomes comprised reported adverse events, allowing additional evaluation of the safety profile of the interventions examined.

#### Data extraction

Two reviewers independently screened abstracts and subsequently evaluated full-text articles to determine eligibility. Data extraction was also conducted independently to ensure accuracy and consistency. Extracted information included study design, country of origin, pain classification (based on duration and clinical context), sample size per treatment arm, and participant characteristics such as sex distribution and mean age. Baseline pain scores assessed by the VAS and WOMAC score were also documented. The methodological rigor of included RCTs was appraised using the Jadad scale, categorizing studies as lower quality (score <2) or higher quality (score ≥3) (51). Risk of bias was further evaluated according to established criteria and classified as low, unclear, or high risk (52). Any disagreements regarding study eligibility, data extraction, or quality assessment were resolved through discussion and consensus.

#### Data synthesis and analysis

Pooled effect sizes and corresponding 95% confidence intervals (CIs) were calculated using the DerSimonian–Laird random-effects model, which accounts for between-study variability in meta-analytic synthesis (53). Potential publication bias was initially explored through visual inspection of funnel plots, following established methodological guidance (54). Heterogeneity was evaluated from both clinical and statistical perspectives. Clinical heterogeneity was examined by comparing differences in participant characteristics, interventions, comparators, outcomes, study design (PICOS framework), and assessment methods. Statistical heterogeneity was quantified using the  $\chi^2$  (Chi-square) test and the  $I^2$  statistic. The  $I^2$  value was derived from Cochrane's  $Q$  statistic and degrees of freedom, with thresholds of ≤25%, 25–75%, and ≥75% representing low, moderate, and high heterogeneity, respectively. For the  $\chi^2$  test, a  $P$  value <0.10 was considered indicative of significant heterogeneity.

Funnel plot asymmetry was further assessed using Egger's regression test (55,56). All analyses were performed using Review Manager (RevMan) version 5.3 and STATA version 14 (StataCorp, Texas, USA). Statistical significance was defined as  $p < 0.05$ . Sensitivity analyses employing a fixed-effects model were conducted to evaluate the stability and robustness of the pooled estimates.

## Results

### Study selection

A total of 25 records were retrieved through the systematic search. Following removal of 14 duplicates, the remaining titles and abstracts were screened for relevance. Three studies were excluded at this stage due to non-human designs or the absence of pain-related outcomes. Eight articles proceeded to full-text assessment. Of these, three were excluded: one employed a pre–post design, one was a review article, and one compared different YTPS formulations without meeting inclusion criteria. Ultimately, five studies satisfied the predefined eligibility criteria and were included in the meta-analysis (Figure 1).

### Study characteristics

Most of the included studies employed RCT designs, with one trial conducted in Thailand specifically implemented as a double-blind study (total  $n=261$ ) (19,20,57–59). The investigated clinical conditions primarily comprised knee osteoarthritis and muscle pain. Pain outcomes were measured using the VAS and the WOMAC. Key study characteristics—including participant age, YTPS formulation, comparator interventions, treatment duration, and outcome measures are presented in Table 2.

Overall methodological quality was acceptable. Three RCTs demonstrated moderate to high quality, with Jadad scores of 3 and 5, whereas two studies were rated as lower quality (Jadad score <2). Risk of bias was assessed across standard methodological domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other potential sources of bias. Each domain was categorized as having low, unclear, or high risk (Figure 2).

### VAS score

The analysis revealed no substantial statistical heterogeneity ( $I^2 < 50\%$ ), indicating reasonable consistency among the included studies. Compared with placebo, YTPS was associated with a significant reduction in VAS pain scores (SMD =  $-1.95$ ; 95% CI:  $-2.65$  to  $-1.24$ ;  $P < 0.001$ ). In contrast, no statistically significant differences were detected when YTPS was compared with topical analgesics (SMD =  $-0.22$ ; 95% CI:  $-0.56$  to  $0.12$ ;  $P = 0.21$ ) or with Plai herbal compress (SMD =  $-0.20$ ; 95% CI:  $-0.82$

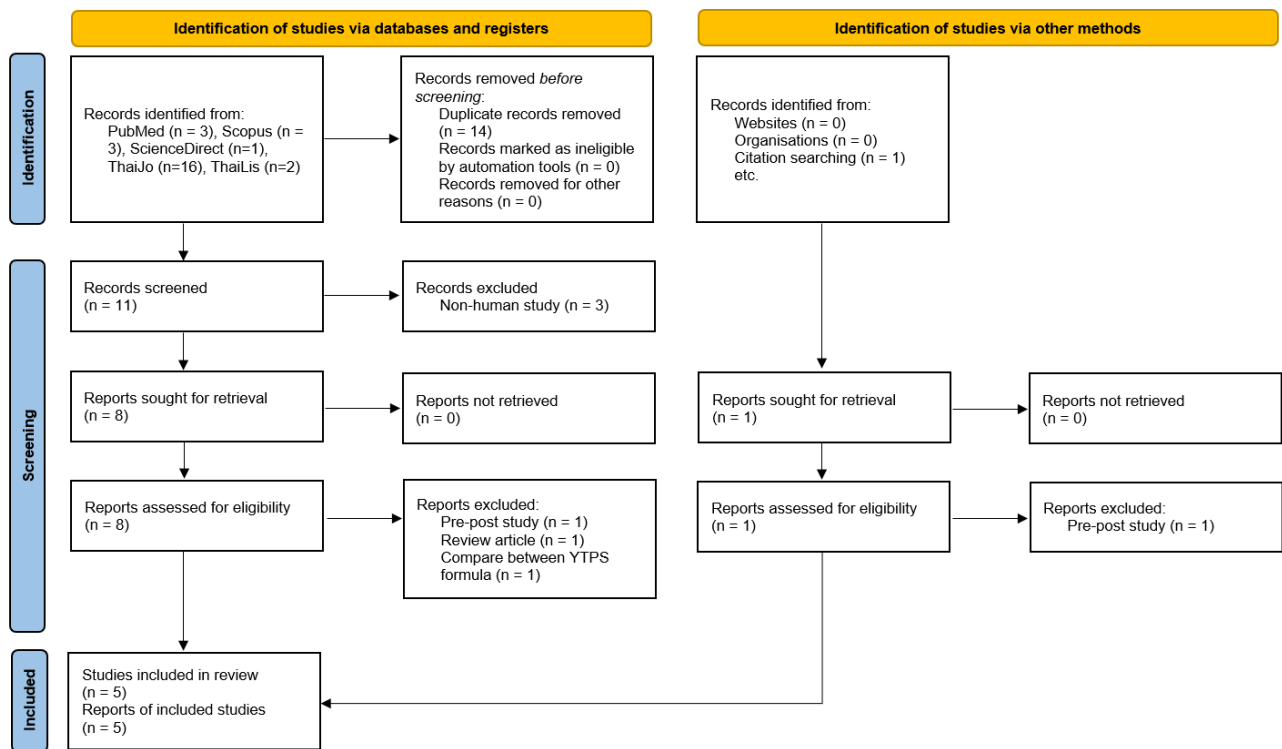


Figure 1. Flow diagram showing how the studies considered in this analysis were selected.

to 0.43;  $P = 0.54$ ). These results suggest that the analgesic effect of YTPS is broadly comparable to that of established topical and herbal therapies (Figure 3).

**WOMAC score**

WOMAC outcomes were reported in only two studies

(20,58). Pooled analyses showed no statistically significant differences between YTPS and comparator interventions for the pain domain (SMD = -0.39; 95% CI: -1.04 to 0.26;  $P = 0.24$ ) or stiffness domain (SMD = -0.48; 95% CI: -1.29 to 0.33;  $P = 0.24$ ). These findings indicate variability across studies evaluating these components. In contrast,

Table 2. Characteristics of the included studies

| First author, year       | Design | Age (year) | Population                 | Intervention  | Comparators   | Outcomes  | Jadad score |
|--------------------------|--------|------------|----------------------------|---|---|---|-------------|
| Naroiet, 2019 (19)       | DRCT   | 60-69      | Osteoarthritis of the knee | YTPS topical, applied 2 mL to the knee, 3 times a day, for 7 days (n=25)  | Placebo topical, applied 2 mL to the knee, 3 times a day, for 7 days (n=25)           | VAS, WOMAC, extension, flexion  | 3           |
| Sittiprom, 2023 (57)     | RCT    | 20-60      | Muscle pain                | YTPS topical, applied approximately 2.5 g twice daily, for 6 days (n=15)  | Placebo (n=15), applied approximately 2.5 g twice daily for 6 days                    | VAS, range of motion (ROM)  | 2           |
| Kanokkangsdal, 2020 (20) | RCT    | 45-80      | Osteoarthritis of the knee | YTPS topical, applied 6 mL to the knee 3 times a day, for 14 days (n=33)  | Analgesic cream, apply 1 g to the knee 3 times a day, for 14 days (n=33)              | VAS, WOMAC, 100 m walk, liver function test, renal function test, AEs | 3           |
| Pheangsalud, 2022 (58)   | RCT    | >50        | Osteoarthritis of the knee | YTPS topical, applied 2 mL to the knee, 3 times a day, for 4 weeks (n=38) | Diclofenac sodium topical, applied 2 mL to the knee 3 times a day, for 4 weeks (n=37) | VAS, WOMAC, AEs   | 2           |
| Saei, 2018 (59)          | RCT    | 15-59      | Muscle pain                | YTPS topical, applied 2 mL to the knee, 3 times a day, for 2 weeks (n=20) | Plai Herbal compression remedy, apply 3 times a day, for 2 weeks (n=20)               | Pain score, muscle strain   | 3           |

Abbreviations: DRCT: double-blind randomized controlled trial; YTPS: Ya-Tha-Pra-Sen; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; RCT: randomized controlled trial; AEs: adverse events

|                      | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------------|---|---|---|---|--|--------------------------------------|------------|
| Kanokkangsadal, 2020 | +   | -                                       | -   | -   | +  | +                                    | ?          |
| Na roiet, 2019       | ?   | +                                       | +   | +   | +  | +                                    | ?          |
| Pheangsalud, 2022    | ?   | -                                       | -   | -   | +  | +                                    | ?          |
| Saei, 2018           | +   | -                                       | -   | -   | +  | +                                    | ?          |
| Sittiprom, 2023      | -   | -                                       | ?   | ?   | +  | +                                    | ?          |

**Figure 2.** Comprehensive assessment of the risk of bias, presenting the authors' evaluations across individual bias domains for each included study. (+: low risk; -: high risk; ?: unclear).

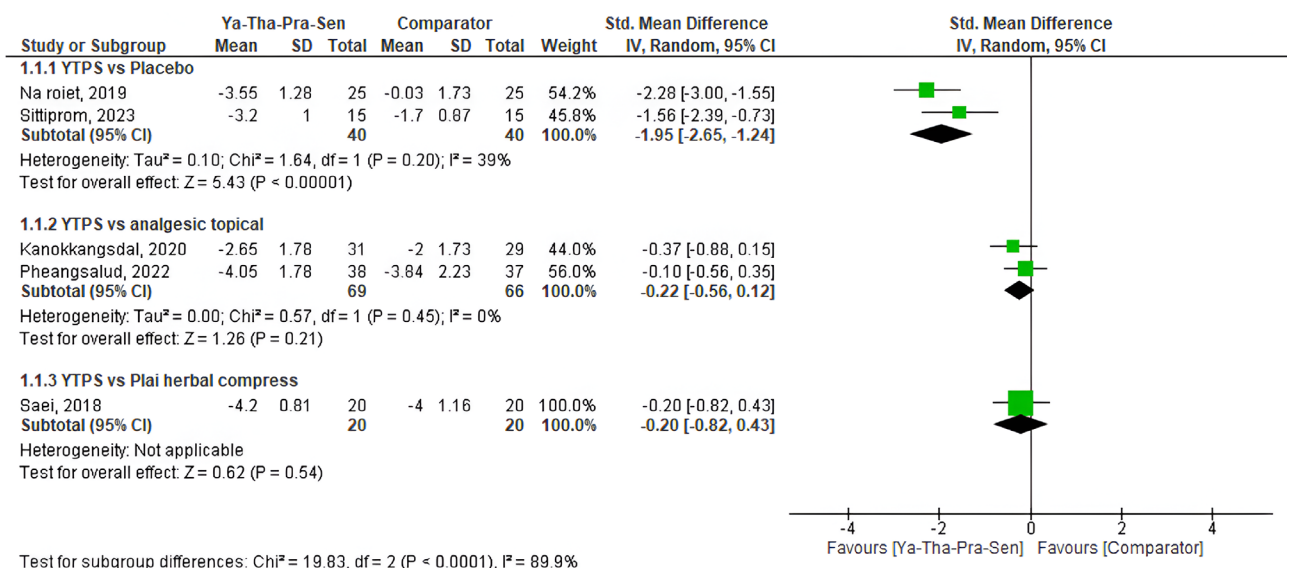
YTPS was associated with a significant improvement in the physical function subscale compared with topical analgesics (SMD = -0.68; 95% CI: -1.03 to -0.34;  $P < 0.001$ ), suggesting a potential advantage in enhancing mobility and functional performance (Figure 4).

**Adverse effect**

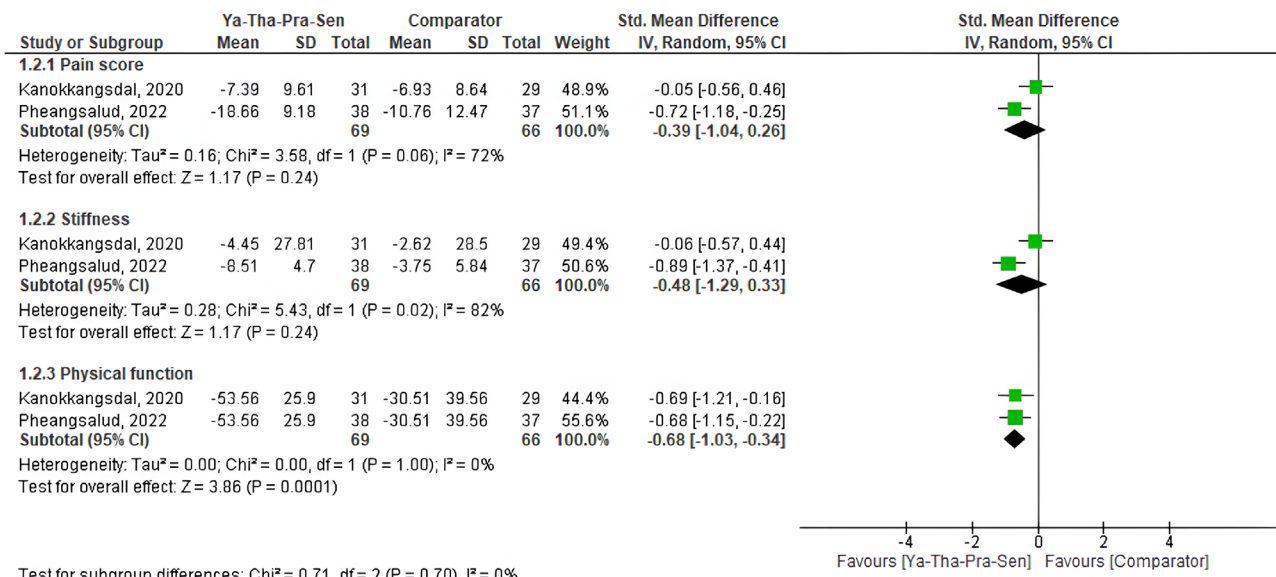
In the study by Kanokkangsadal et al (20), mild local reactions were observed in both treatment arms. Two participants in the YTPS group (6.45%) and two in the comparator pain cream group (6.89%) developed minor application-site symptoms such as erythema, pruritus, rash, and irritation. Laboratory monitoring demonstrated no clinically or statistically significant alterations in renal or hepatic function in either group. All kidney function indicators remained within normal reference ranges, and no meaningful pre- to post-treatment differences were detected. Similarly, Pheangsalud and Kamoltham (58) reported an absence of adverse events among the 40 participants receiving YTPS. In contrast, two individuals in the diclofenac gel group (n = 40) experienced localized discomfort, including burning and pain at the application site during the initial phase of treatment, which persisted for approximately 13 days. These participants also reported temporary knee weakness. Importantly, neither study documented serious adverse events or persistent complications after discontinuation of therapy.

**Sensitivity analysis**

Sensitivity analysis findings are summarized in Table 3. A fixed-effects model was applied to evaluate the stability of the pooled estimates. The primary outcome clinical efficacy assessed by VAS remained consistent with the original random-effects analysis, supporting the robustness of the main results. In contrast, changes were observed in the WOMAC domains. Under the fixed-effects model, improvements in the stiffness and physical function subscales shifted from non-significant to statistically significant, indicating that these outcomes



**Figure 3.** Forest plot of standardized mean differences (SMD) in visual analogue scale (VAS) pain scores comparing Ya-Tha-Pra-Sen to the comparator across three studies. SD: standard deviation; CI: confidence interval.



**Figure 4.** Forest plot of standardized mean differences (SMD) in WOMAC scores comparing Ya-Tha-Pra-Sen to placebo across three studies. WOMAC: The Western Ontario and McMaster Universities Arthritis Index; SD: standard deviation; CI: confidence interval.

may be sensitive to the analytical approach used.

**Publication bias**

Publication bias was assessed through visual inspection of a funnel plot (Figure 5). The observed symmetry of the plot indicated no apparent evidence of significant publication bias.

**Discussion**

This systematic review and meta-analysis found that YTPS did not demonstrate superior efficacy to placebo in the management of musculoskeletal pain. However, its clinical effects were comparable to those of standard topical analgesics and Plai herbal compresses across the studied populations. With respect to safety, short-term use of YTPS showed a similar incidence of adverse events to topical analgesic creams. Both interventions

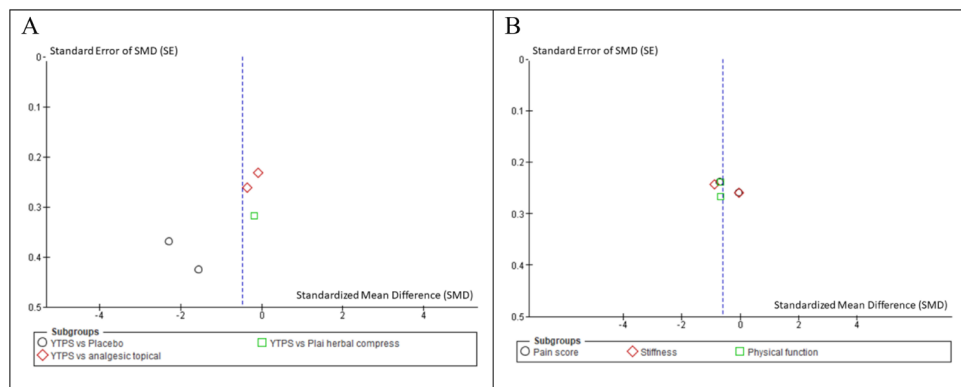
were associated primarily with mild cutaneous reactions, such as rash, erythema, pruritus, and localized irritation at the application site. Although herbal therapies are often perceived as safer than synthetic medications, the present findings indicate that YTPS and conventional topical analgesics exhibit comparable short-term safety profiles. This similarity may reflect overlapping pharmacodynamic actions, as experimental studies have demonstrated that both YTPS and standard topical agents suppress inflammatory mediators, including nitric oxide (NO), prostaglandin E2 (PGE2), interleukins (ILs), and tumor necrosis factor (TNF), potentially contributing to analogous adverse event patterns (60).

The present analysis indicates that YTPS, a traditional Thai herbal preparation, exhibits clinically meaningful analgesic activity. These findings align with prior pharmacological research on its individual botanical

**Table 3.** Sensitivity analysis results compared the main analysis for VAS and WOMAC scores

| Outcomes                     | Main analysis<br>N; SMD [95%CI]; I <sup>2</sup> | Sensitivity analysis<br>N; SMD [95%CI]; I <sup>2</sup> | References |
|------------------------------|---|--|------------|
| <b>VAS</b>                   |   |  |            |
| YTPS vs Placebo              | 80; -1.95 [-2.65, -1.24]; 39%*                  | 80; -1.97 [-2.51, -1.42]; 39%*                         | (19,57)    |
| YTPS vs analgesic topical    | 135; -0.22 [-0.56, 0.12]; 0.0%                  | 135; -0.22 [-0.56, 0.12]; 0.0%                         | (20,58)    |
| YTPS vs Plai herbal compress | 40; -0.20 [-0.82, 0.43]; N/A                    | 40; -0.20 [-0.82, 0.43]; N/A                           | (59)       |
| <b>WOMAC score</b>           |   |  |            |
| Pain score                   | 135; -0.39 [-1.04, 0.26]; 72.0%                 | 135; -0.41 [-0.75, -0.07]; 72.0%*                      | (20,58)    |
| Stiffness                    | 135; -0.48 [-1.29, 0.33]; 82.0%                 | 135; -0.50 [-0.85, -0.16]; 82.0%*                      | (20,58)    |
| Physical function            | 135; -0.68 [-1.03, -0.34]; 0.0%*                | 135; -0.68 [-1.03, -0.34]; 0.0%*                       | (20,58)    |

SMD: standardized mean difference; CI: confidence interval; I<sup>2</sup>: heterogeneity statistic; YTPS: Ya-Tha-Pra-Sen remedy; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; N/A: not available due to inclusion of a single study. \* Indicates significant findings based on the 95% CI, excluding the null hypothesis.



**Figure 5.** Funnel plots assessing potential publication bias. (A) Funnel plot for studies reporting Visual Analogue Scale (VAS) pain scores and (B) funnel plot for studies reporting Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

components, many of which possess documented anti-inflammatory and pain-relieving properties.

Makham Kai (*Putranjiva roxburghii*), the predominant ingredient in the formulation, has been shown to suppress NO production, thereby contributing to anti-inflammatory effects (61). Related plant species within the same botanical family have demonstrated comparable activity in experimental models (62). Piperine, the principal active compound of long pepper (*Piper longum*), reduces inflammatory responses and nociception through inhibition of NO, PGE<sub>2</sub>, and cyclooxygenase-2 (COX-2), mechanisms similar to those of conventional NSAIDs (63). Galangin, a flavonoid derived from *Alpinia galanga*, also exhibits anti-inflammatory and analgesic properties (64). In addition, anthraquinone constituents present in darker herbal components of YTPS are known to promote gastrointestinal motility and support bowel function (65).

Angsusing et al (66) evaluated the antioxidant and anti-inflammatory properties of an ethanolic extract of YTPS, with particular emphasis on its principal bioactive constituents,  $\beta$ -amyryn and stigmaterol. Quantitative profiling identified concentrations of 70.30 nM for  $\beta$ -amyryn and 605.76 nM for stigmaterol within the extract. Antioxidant capacity was demonstrated through ABTS and DPPH radical scavenging assays, with half-maximal inhibitory concentration (IC<sub>50</sub>) values of 144.50  $\pm$  2.82  $\mu$ g/mL and 31.85  $\pm$  0.18  $\mu$ g/mL, respectively. At 1000  $\mu$ g/mL, the extract produced a significant anti-inflammatory response ( $P < 0.01$ ), reflected by reduced secretion of interleukin-6 (IL-6) and TNF- $\alpha$  in lipopolysaccharide (LPS)-stimulated systems. NO generation was suppressed by approximately 50% at concentrations of 24.76  $\pm$  1.48  $\mu$ g/mL for the YTPS extract, 55.52  $\pm$  24.40  $\mu$ M for  $\beta$ -amyryn, and greater than 570  $\mu$ M for stigmaterol. Moreover, both  $\beta$ -amyryn and stigmaterol significantly attenuated LPS-induced release of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in THP-1-derived macrophages, highlighting plausible mechanisms underlying their anti-inflammatory activity.

Mangmool et al (67) investigated the molecular

basis of the anti-inflammatory activity of YTPS. Their study demonstrated that ethanolic extracts of YTPS, as well as several of its individual herbal constituents, suppressed LPS-induced PGE<sub>2</sub> release and NO production in a concentration-dependent manner. In RAW264.7 macrophages, exposure to YTPS extract at 50  $\mu$ g/mL significantly reduced LPS-stimulated mRNA expression of key pro-inflammatory mediators, including TNF- $\alpha$ , COX-2, inducible nitric oxide synthase (iNOS), and nuclear factor- $\kappa$ B (NF- $\kappa$ B). Among the tested components, *Podocarpus roxburghii* leaf extract most effectively inhibited TNF- $\alpha$  and iNOS expression, whereas *Tamarindus indica* leaf extract showed the strongest suppression of COX-2 and NF- $\kappa$ B. Phytochemical characterization of *P. roxburghii* identified three bioflavonoids putraflavone, podocarpusflavone A, and amentoflavone—which significantly attenuated LPS-induced PGE<sub>2</sub> and NO production in RAW264.7 cells. Of these compounds, amentoflavone exhibited the most pronounced anti-inflammatory activity, markedly downregulating TNF- $\alpha$ , COX-2, and iNOS expression.

The present results are aligned with the conceptual principles of traditional Thai medicine, in which pain and inflammation are attributed to imbalances or stagnation of the wind element (Vayo Dhatu) and the fire element (Tejo Dhatu). Therapeutic strategies such as laxation are believed to restore elemental balance, promote circulatory flow, and relieve symptoms. From a pharmacological perspective, anthraquinone compounds contained in certain YTPS constituents exhibit notable anti-inflammatory activity. These effects resemble those of diacerein, a synthetic anthraquinone derivative employed in contemporary clinical practice as an alternative analgesic, particularly for patients who cannot tolerate NSAIDs (68,69).

Although the present findings suggest that YTPS demonstrates efficacy and short-term safety comparable to conventional topical analgesics in the management of musculoskeletal pain and knee osteoarthritis, it may represent a reasonable alternative to topical NSAIDs.

As a preparation grounded in traditional Thai medicine and supported within national health initiatives, YTPS carries particular policy relevance in Thailand. Moreover, its domestic manufacture by local pharmaceutical producers and hospital dispensaries reduces reliance on imported active pharmaceutical ingredients, such as NSAIDs. This approach may contribute to strengthening the local pharmaceutical sector, promoting economic sustainability, and improving access to treatment for the wider Thai population.

Although the meta-analysis showed a statistically significant reduction in VAS scores with YTPS compared with placebo (SMD =  $-1.95$ ,  $P < 0.001$ ), statistical significance does not necessarily equate to clinical importance. To determine practical relevance, the results were interpreted in light of established minimal clinically important differences (MCIDs) for both VAS and WOMAC outcomes. For the VAS, the accepted MCID for chronic musculoskeletal pain is approximately 1.0–2.0 cm on a 10-cm scale (70,71). The observed effect size (SMD =  $-1.95$ ) falls within or slightly above this range, indicating that the reduction in pain intensity is likely to be clinically meaningful. With respect to the WOMAC physical function domain, reported MCID values range from  $-0.50$  to  $-0.80$  (SMD), depending on study population and intervention (72). The pooled estimate in this analysis (SMD =  $-0.68$ ) represents a moderate effect and suggests a clinically relevant improvement in functional performance.

A key strength of this study is its rigorous synthesis of available evidence on herbal medicine using systematic review and meta-analytic techniques, which are widely regarded as providing a high level of evidence. This approach enables a structured and reliable evaluation of comparative effectiveness, including assessment of non-inferiority, which is particularly pertinent in this setting. Importantly, systematic reviews within the field of complementary and alternative medicine remain relatively limited (73), and this analysis helps address that gap. Emphasizing non-inferiority is methodologically appropriate, as standard clinical management typically involves active treatments rather than placebo controls. Accordingly, comparing herbal interventions with established topical analgesics offers clinically relevant and practice-oriented insights.

Although the available evidence suggests that YTPS provides consistent analgesic effects and appears non-inferior to conventional topical analgesics, several important limitations warrant consideration. A major concern relates to the absence of phytochemical standardization in herbal formulations, including YTPS (74). The content and potency of bioactive constituents may vary considerably depending on geographic source, cultivation conditions, harvesting period, and preparation techniques (75). Notably, none of the included studies

quantified or reported the concentrations of active compounds within the YTPS preparations administered. This lack of chemical characterization may partly explain variability in clinical outcomes and represents a significant methodological constraint.

In terms of safety, no serious adverse events were documented in the included trials. However, the concurrent use of YTPS with other topical analgesics has not been systematically investigated. Accordingly, careful use is advisable pending further high-quality safety data.

To enhance the consistency and quality of YTPS formulations, bioactive compounds such as piperine and galangin recognized for their analgesic and anti-inflammatory activities should be adopted as marker constituents in both extract and powdered preparations. Evidence regarding dose–response relationships remains limited, particularly with respect to standardized extract concentrations or quantified active ingredients. The absence of phytochemical standardization across the included trials may have contributed to clinical heterogeneity and restricted definitive conclusions regarding therapeutic efficacy. Future RCTs should therefore incorporate rigorous quality control procedures, including high-performance liquid chromatography or thin-layer chromatography fingerprinting and quantitative analysis of marker compounds, to improve reproducibility and scientific reliability. Establishing clearly defined and standardized dosing regimens will also be essential to guide appropriate clinical application.

In addition, several included studies demonstrated methodological limitations, such as inadequate randomization, insufficient allocation concealment, and lack of blinding. Although the present review adhered to PRISMA standards to ensure a structured and transparent synthesis of evidence, these trial-level weaknesses necessitate cautious interpretation of the findings. Finally, the relatively small sample sizes of most included studies further limit the generalizability of the results.

Future RCTs should be designed and reported in accordance with established methodological standards, such as the CONSORT guidelines, to strengthen the credibility and interpretability of findings. Well-designed, adequately powered, multicenter studies are needed to confirm and extend the current evidence. Increasing sample sizes would improve statistical precision, decrease the likelihood of type II error, and enhance the generalizability and external validity of results across broader patient populations and varied clinical contexts.

## Conclusion

Available evidence indicates that YTPS may represent a viable alternative to conventional topical analgesics for the treatment of musculoskeletal pain and knee osteoarthritis, particularly within the context of traditional Thai medicine. Incorporation into clinical practice could

also offer socioeconomic advantages by promoting locally manufactured herbal products and reinforcing the domestic healthcare sector in Thailand. However, concomitant use of YTPS with standard topical analgesics is not advisable due to the potential for overlapping adverse effects. Although early findings are encouraging, limitations in methodological quality and relatively short follow-up durations preclude firm conclusions regarding long-term efficacy and safety. Accordingly, further well-designed RCTs are warranted, with emphasis on standardized dosing strategies, dose–response evaluation, and comprehensive long-term safety assessment. In clinical situations where NSAIDs are contraindicated or unavailable, YTPS may provide a culturally appropriate and potentially effective alternative or adjunct for pain management.

### Authors' contribution

**Conceptualization:** Wiraphol Phimarn and Bunleu Sungthong.

**Data collection:** Wiraphol Phimarn, Siraporn Mahakoat, Sujaree Panomhet and Bunleu Sungthong.

**Formal analysis:** Wiraphol Phimarn and Bunleu Sungthong.

**Funding acquisition:** Wiraphol Phimarn.

**Investigation:** Wiraphol Phimarn and Bunleu Sungthong.

**Methodology:** Wiraphol Phimarn, Siraporn Mahakoat, Sujaree Panomhet and Bunleu Sungthong.

**Project administration:** Wiraphol Phimarn.

**Resources:** Wiraphol Phimarn, Siraporn Mahakoat, Sujaree Panomhet, and Bunleu Sungthong.

**Software:** Wiraphol Phimarn and Bunleu Sungthong.

**Supervision:** Bunleu Sungthong.

**Visualization:** Wiraphol Phimarn, Bunleu Sungthong.

**Writing—original draft:** Wiraphol Phimarn.

**Writing—review & editing:** Wiraphol Phimarn, Siraporn Mahakoat, Sujaree Panomhet and Bunleu Sungthong.

### Conflict of interests

The authors declare no conflicts of interest.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, and double publication) were considered and addressed by the authors. The protocol was performed in accordance with the PRISMA guidelines.

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