science, engineering and health studies

Research Article

Science, Engineering and Health Studies
https://lio1.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Clinical effectiveness of Sahasthara remedy for relief of musculoskeletal pain: a systematic review and meta-analysis of randomized controlled trials

Sontaya Sookying[1], Mutita Piromyapron[2], Panupong Puttarak[3], Sornkanok Vimolmangkang[4] and Surasak Saokaew[1,2,5,6,7,8]*

[1] Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand
[2] Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand
[3] Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla 90110, Thailand
[4] Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand
[5] Unit of Excellence on Clinical Outcomes Research and Integration (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand
[6] Unit of Excellence on Herbal Medicine, School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand
[7] Biofunctional Molecule Exploratory Research Group, Biomedicine Research Advancement Centre, School of Pharmacy, Monash University Malaysia, Bandar Sunway 47500, Malaysia
[8] Novel Bacteria and Drug Discovery Research Group, Microbiome and Bioresource Research Strength, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Malaysia

***Corresponding author**:
Surasak Saokaew
surasak.sa@up.ac.th

Received: *20 May 2020*
Revised: *19 November 2020*
Accepted: *23 November 2020*
Published: *22 July 2021*

Citation:
Sookying, S., Piromyapron, M., Puttarak, P., Vimolmangkang, S., and Saokaew, S. (2021). Clinical effectiveness of Sahasthara remedy for relief of musculoskeletal pain: a systematic review and meta-analysis of randomized controlled trials. Science, Engineering and Health Studies, 15, 21050007.

ABSTRACT

Sahasthara (SHT) has been used for more than thirty years for reducing pain. The remedy has been listed in the Thailand national list of essential medicines. Evidence on the clinical benefits of SHT has never been summarized and documented. Its effectiveness is still limited and unclear. This study aims to systematically review and meta-analyze the clinical effects of SHT for pain reduction. Studies were eligible if they measured pain intensity. Ninety-nine identified studies were systematically searched and two of those were included into the synthesis and analysis. Quality of articles was assessed using the Jadad scale and risk of bias tool. This study was performed and reported in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Two publications included in this meta-analysis were randomized control trials that compared the efficacy of SHT to diclofenac, a standard drug used for pain. SHT shows significant differences in pain reduction compared to diclofenac. Our findings indicated the potential of SHT as a pain reliever that is superior to diclofenac. Safety data, however, were not reported systematically, although the studies provided safety information compared to NSAIDs. Longitudinal studies on the efficacy and safety of SHT are needed.

Keywords: Sahasthara; Thai traditional medicine; pain; osteoarthritis; visual analogue scale; meta-analysis

1. INTRODUCTION

Pain is a problem associated with uncomfortable feelings, and causes suffering for populations worldwide. The symptoms affect work and daily life. Globally, it is estimated that 56% and 23% of adults suffer from body pain and head pain, respectively (Boros, 2017): in each year, new chronic pain is diagnosed at about 10% (Goldberg and McGee, 2011). The most frequent pain sites were shoulders, ankles, upper back, and head. The severity of pain depends on many factors including genetic characteristics, general health status and comorbidities, the emotional and cognitive context, pain experiences in childhood, and cultural and social factors (Keeratitanont et al., 2015).

Categorization of pain can be done in many ways, including differentiation by duration of pain. Acute, sub-acute, and chronic pain have been defined as pain with a duration less than 3 months, between 3 and 6 months, and longer than 6 months, respectively (Pearson, 2012).

Treatment approaches for pain relief consist of pharmacological and interventional measures, physical therapy and exercise, and psychological procedures. For pharmacological therapy, the first line drugs recommended for mild to moderate pain are non-opioids such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) (HCANJ, 2017).

NSAIDs exhibit their pharmacological effects by inhibiting prostaglandins and cyclooxygenase (COX) enzymes, yielding many side effects such as peptic ulcers, liver dysfunction, and renal dysfunction so that there are limitations of usage in some patients. Therefore, the alternative medicines, which possessed anti-inflammatory activity with fewer side effects may play a potential role in the treatment of pain.

Thai traditional medicine (TTM) is alternatively used for pain therapy with treatments, including Thai traditional massage, hot herbal compression, and topical and oral herbal medicines. One popular TTM formula for pain relief is called “Sahasthara” (SHT), which is a well-known drug that has been used to treat muscle and joint pain in Thailand for around thirty years (Kakatum et al., 2012).

The SHT is a traditional Thai formula indicated in the Thailand national list of essential medicine since 2011. It is composed of twenty-one plants (Table 1). Among these, pepper (*Piper nigrum* L.) is the main ingredient (DMSIC, 2019). The mechanism of SHT for anti-inflammatory activity is like that of NSAID according to the *in vitro* study. The SHT showed anti-inflammatory activity by inhibiting nitric oxide (NO) release and COX-II activity (IC_{50} = 2.81 and 16.97 mcg/mL, respectively) (Jaiaree and Itharat, 2012; Kakatum, 2011). SHT also showed its abilities to inhibit interleukin-1β (IL-1β)-induced cellular reactive oxygen species (ROS) formation in human dermal fibroblasts as well as the inhibition of tumor necrosis factor-α gene expression (Thamsermsang et al., 2017). Moreover, SHT extract has shown antimutagenic activity against three standard mutagens in standard antimutagenicity tests (Sripanidkulchai et al., 2007).

The SHT is found to be safe. The mutagenicity and toxicity of SHT extract were investigated. SHT extract had no mutagenic activity on *Salmonella typhimurium* TA98 and TA100 in the modified Ames test (Sripanidkulchai et al., 2007). *In vivo* toxicity testing in animal models showed that an oral administration dose range of SHT, which was translated from the dose used in patients, did not affect the biochemical parameters of liver and renal function involving BUN, creatinine, AST, and ALT (Booranasubkajorn et al., 2017). Besides, in clinical trials, the adverse effect reported by patients receiving SHT capsules was abdominal discomfort, which was also reported in the diclofenac group. Other biochemical parameters representing renal and liver functions were found to be normal and did not increase compared to baseline values as ALP, AST, and ALT increased in the group receiving diclofenac (Nootim et al., 2013; Pinsornsak et al., 2015). From efficacy and safety data, SHT might be considered as an alternative for pain management.

There are studies that were performed to evaluate the effect of SHT in various clinical conditions such as osteoarthritis (OA) and muscle pain (Nootim et al., 2013; Pinsornsak et al., 2015; Singtong et al., 2016). However, evidence on the clinical advantages of SHT has not yet been summarized. Its effectiveness is still limited and unclear. Thus, the aim of this study was to systematically review and meta-analyze the clinical effects of SHT for pain relief.

2. MATERIALS AND METHODS

2.1 Data sources and search strategy

Two authors (M. P. and S. Sa.) independently searched the electronic databases including AMED, CINAHL, Cochrane Central Register of clinical trials, EMBASE, WHO registry, PubMed, www.clinicaltrial.gov, Thai index medicus, health science journals in Thailand, Thai library integrated system, Thai medical index, and Thai thesis database. The relevant articles were searched from the inception to April 2020. For the search plan, strategic search terms used were *SHT, Sahasathara* or *Sahasatara* or *Sahasatara remedy* or *Thai traditional medicine* and *pain*. We also searched from references in the literature reviews and manuscripts that were published in journals but were not found in databases. There was no limitation of language and study design. In addition, the related researchers and experts were contracted to expound the articles.

2.2 Study selection

We searched articles and removed duplicates, screened titles and abstracts, then found full texts of each article. Finally, the acceptable articles were included in this systematic review. We included research classified as (i) studies of SHT that were related to pain; (ii) studies reporting measured outcomes; (iii) studies that were clinical studies. Excluded articles were those in which the data were not original articles such as comments, letters, reviews, meta-analyses, case-reports, editorials, not experimentation, or not reporting absolute outcomes for data analysis. After completion of the main search, a bibliographic search was performed by seeking articles from conference proceedings. These were independently conducted by two investigators.

2.3 Outcome measures

The primary outcomes were pain scores determined using a visual analogue scale (VAS) (pain assuagement). A horizontal line of 100 mm in length is usually used, anchored by word descriptors at each end. The patient marks on the line to point out their perception of their current state. The VAS score is made out by measuring a length from the left hand end of the line to the point

of the marks (Gould, 2001). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was also used to assess pain from OA. It comprises 24 items: 5 pain, 2 stiffness, and 17 physical function items. WOMAC provides three subscale scores (pain, stiffness, and physical function) and a total score. Total WOMAC score is commonly transformed to a 0-100 scale to ease the interpretation and comparison with different sources of data (Ackerman, 2009). In addition, secondary outcomes evaluated as adverse events were also measured.

Table 1. Medicinal plants in the Sahasthara remedy and their biological activities (DMSIC, 2019)

Scientific name	Thai name	Part used	Biological activities
Piper nigrum L.	Prik-Thai-Lon	Seed	Antioxidant (Kapoor et al., 2009) Anti-inflammation (Bang et al., 2009)
Plumbago indica L.	Jet-Ta-Mul-Plerng-Dang	Root	Anti-inflammation (Chan et al., 2008; Checker et al., 2009)
Terminalia chebula Retz.	Sa-Mhor-Thai	Fruit	Antioxidant (Hazra et al., 2010) Anti-inflammation (Reddy and Reddanna, 2009; Reddy et al., 2009)
Piper retrofractum Vahl.	Dee-Plee	Fruit	Antioxidant (Kusirisin et al., 2009)
Baliospermum solanifolium (Burm.) Suresh	Tong-Tak	Root	Antioxidant (Desai et al., 2008) Anti-inflammation (Desai et al., 2008)
Acorus calamus L.	Wan-Nam	Rhizome	Antioxidant (Mukherjee et al., 2007) Anti-inflammation (Kim et al., 2009; Mehrotra et al., 2003)
Kleinhovia hospita L.	Has-Sa-Khun-Tade	Root	N/A
Cinnamomum camphora (L.) J.Presl	Ka-Ra-Boon	Crystal	Antioxidant (Lee et al., 2006; Lin et al., 2007) Anti-inflammation (Lee et al., 2006; Lin et al., 2007)
Myristica fragrans Houtt.	Dok-Chan	Aril of seed	Antioxidant (Singh et al., 2005)
Myristica fragrans Houtt.	Luk-Chan	Seed	Anti-inflammation (Jin et al., 2005)
Lepidium sativum L.	Tien-Dang	Seed	Antioxidant (Rababah et al., 2011)
Anethum graveolens L.	Tien-Ta-Tuk-Ka-Tan	Fruit	Antioxidant (Chanwitheesuk et al., 2005; Ramos et al., 2003; Shyu et al., 2009)
Ferula asafoetida H.Karst.	Ma-Ha-Hing	Resin	Anti-inflammation (Abd El-Razek, 2007)
Pimpinella anisum L.	Tien-Sut-Ta-But	Fruit	Antioxidant (Gülçın et al., 2003) Anti-inflammation (Tabanca et al., 2007)
Cuminum cyminum L.	Tien-Khao	Fruit	Antioxidant (Satyanarayana et al., 2004; Thippeswamy and Naidu, 2005)
Merremia vitifolia (Burm. f.) Hallier f.	Jing-Jor	Root	N/A
Nigella sativa L.	Tien-Dum	Seed	Antioxidant (Burits and Bucar, 2000) Anti-inflammation (Al-Ghamdi, 2001)
Anacyclus pyrethrum (L.) Lag.	Kote-Kag-Kra	Root	Antioxidant (Surveswaran et al., 2007)
Atractylodes lancea (Thunb.) DC.	Kote-Ka-Mao	Rhizome	Antioxidant (Cai et al., 2004) Anti-inflammation (Chan et al., 2008; Fan et al., 2010; Resch et al., 1998)
Picrorhiza kurroa Royle ex Benth.	Kote-Kan-Prao	Root	Antioxidant (Rajkumar et al., 2011) Anti-inflammation (Engels et al., 1992; Zhang et al., 2004)
Terminalia chebula Retz. (gall)	Kote-Pung-Pla	Gall	Antioxidant (Manosroi et al., 2010a; Manosroi et al., 2010b) Anti-inflammation (Manosroi et al., 2010a)

Note: N/A: no data available

2.4 Data extraction

Two investigators independently reviewed each abstract and completed full text. Each of them also extracted data from each study to include into the analysis. Data extraction was performed on study characteristics (study design, country, pain classification by duration, and by clinical perspectives); the sample size of patients in each arm; patient characteristics (number of females, mean age); baseline pain score (VAS, WOMAC); and quality of studies (Jadad scale, risk of bias). The Jadad scale was used for the quality assessment of randomized control trials (RCTs) (Jadad score: ≤2 = low quality, ≥3 = high quality) (Chung et al., 2012; Jadad et al., 1996). Risk of bias (shown in terms of low risk, unclear risk, and high risk) was also analyzed (Higgins et al., 2011). Discrepancies were resolved by consensus.

2.5 Data synthesis and analysis

The pooled effect and 95% confidence intervals were analyzed by the DerSimonian-Laird random-effects models (DerSimonian and Laird, 1986). The statistical test of publication bias used in this study was the funnel plot (Sterne et al., 2011). Heterogeneity of the included studies was assessed by the determination of either clinical heterogeneity or statistical heterogeneity. Clinical heterogeneity was evaluated by determining PICO (patient, intervention, comparator, and outcome), sample study, measurement, comparators, and outcomes, while statistical heterogeneity was analyzed using the I^2 and X^2 tests. Percentage I^2 was calculated based on the following equation: $I^2=100\%$ (Q-*df*)/Q, where Q is Cochrane's heterogeneity statistic and *df* is degrees of freedom. The heterogeneity was determined as low, medium, and high by the cut-off value at 25%, 50%, and 75%, respectively. For the X^2 test, a *p*-value of less than 0.1 (significant) investigated the study of heterogeneity.

3. RESULTS

3.1 Study selection

Ninety-nine identified studies were systematically searched, and ten studies were removed due to duplication. After finishing the exclusion based on information in titles and abstracts, ten studies were discarded. Then, thirty-five were excluded due to interventions not including SHT (28 articles), no pain relief outcome (3 articles), published in peer-reviewed journals (2 articles), and being letters; reviews; meta-analyses, or editorials (1 article). The remaining two studies were assessed for eligibility and then were finally included into quantitative synthesis (meta-analysis) (Figure 1).

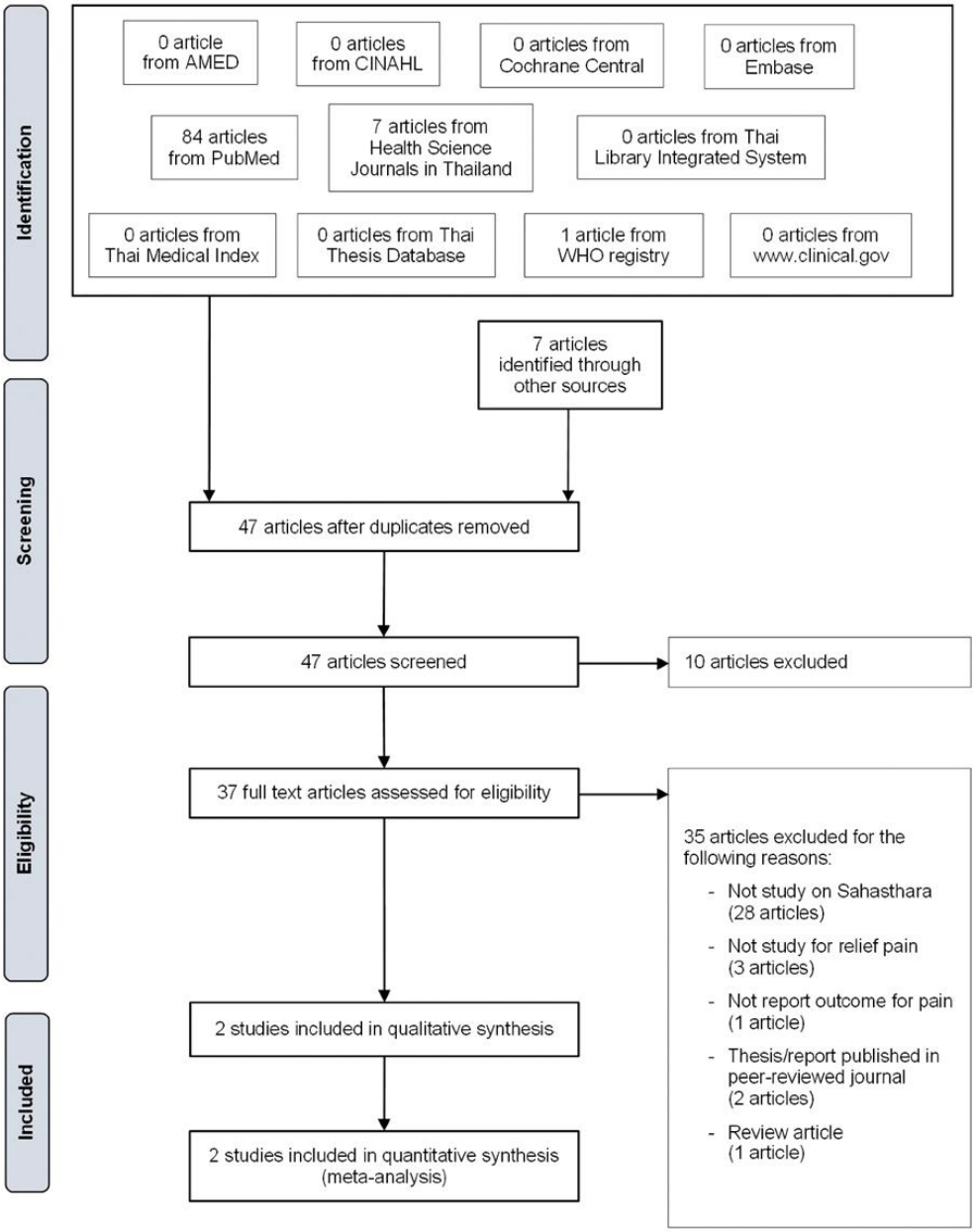

Figure 1. Flow diagram of literature identification, inclusion, and exclusion

3.2 Study characteristics

Both studies were randomized, controlled, double blind trials which were performed in Thailand (Nootim et al., 2013; Pinsornsak et al., 2015). Types of pain in the studies were OA of the knee (OA knee) and muscle pain. Pain scores were assessed using the VAS (horizontal line) and WOMAC. Baseline characteristics of both studies including mean age, number of females, and number of patients were similar (Table 2). The statistical test of publication bias using a funnel plot showed a narrow distribution and symmetry. Moreover, the methodological quality of the two RCTs included in this meta-analysis was high in both cases as shown by the Jadad scores of 3 and 5. In addition, risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and freedom from sources of bias were found to be low, unclear, and high risk (Figure 2).

3.3 Pain score (VAS score comparing the SHT remedy with diclofenac)

Our study demonstrated that heterogeneity was not found ($I^2 = 0.0\%$, $p = 0.985$) and the weight mean difference of the VAS score was -4.20 (95% CI; -5.73 to -2.67, $p<0.001$) comparing the SHT remedy with diclofenac (Figure 3). Therefore, it can be concluded that the efficacy on pain relief of SHT is better than that of diclofenac.

4. DISCUSSION

SHT is one of the well-known herbal medicines in TTM. This natural remedy has been used for a long time as a pain killer. The main mechanisms of action of the SHT remedy for pain reduction are as an antioxidant and anti-inflammatory agent. The antioxidant activity was reported in terms of free radical scavenging activity. The free radical scavenging effects of SHT and its plant components were determined using DPPH assay. The 30% inhibitory concentration (IC_{30}) of SHT was 19.62 µg/mL (IC_{30} of L-ascorbic acid, 3.32 µg/mL) (Thamsermsang et al., 2017). The main components that possessed anti-oxidative effects, *M. fragrans* (seed and aril of seed) and *T. chebula* (fruit and gall), were reported similarly in two independent studies (Kakatum et al., 2012; Thamsermsang et al., 2017). Thirteen active ingredients in SHT were identified as gallic acid, chebulic acid, digalloyl glucoside, caffeoylferuloylquinic lactone, galloylshikimic acid, trigalloyl glucoside, corilagin, chebulanin, chebulagic acid, dicaffeoylquinic lactone, dicaffeoyl quinic acid, ellagic acid rhamnoside, and ellagic acid (Nuengchamnong and Ingkaninan, 2017). Five of those: gallic acid, chebulic acid, corilagin, chebulagic acid, and ellagic acid, were major compounds found in *T. chebula* (Pfundstein et al., 2010).

The anti-inflammatory activity of SHT and its components was investigated in lipopolysaccharide (LPS) induced-NO production, IL-1β induced intracellular ROS production and gene expression, and COX-II inhibitory activity on PEG_2 release. It was found that SHT, *A. lancea*, *B. montanum,* and *T. chebula* (fruit) can inhibit LPS induced-NO production in RAW 264.7 cell lines by the IC_{50} of 2.81, 9.70, 12.55, and 3.3 µg/mL, respectively while the IC_{50} of standard indomethacin was 20.32 µg/mL (Jaiaree and Itharat, 2012; Kakatum et al., 2012). Pre-treatment of SHT extract and its major constituents, piperine and gallic acid, significantly attenuated IL-1β induced-ROS level while neither of them affected the ROS level in normal conditions. They can also modulate the gene expression profiles associated with inflammatory signaling mediated by IL-1β (Thamsermsang et al., 2017). In addition, the PEG_2 releasing inhibitory effect was studied to determine whether SHT can inhibit COX-II and the results showed that SHT, *M. fragrans* (seed), *P. nigrum,* and *P. retrofractum* exhibited the IC_{50} of 16.7, 16.99, 17.71, and 23.80 µg/mL, respectively (IC_{50} of indomethacin, 1.00 µg/mL) (Jaiaree and Itharat, 2012).

This systematic review and meta-analysis summarized the first comprehensive evidence from RCTs of SHT effectiveness on musculoskeletal pain reduction compared with standard drugs (diclofenac).

Our key findings revealed that the reduction of the VAS score in the SHT arm is superior to that of diclofenac. It suggests SHT as a potential pain reliever. Considering only the included studies, safety data were reported in only one study. More safety was found in the SHT arm. At present, the quality and quantity of the available evidence are limited. More high quality RCTs are suggested to be performed to support the potential of SHT as an alternative therapy for acute and chronic musculoskeletal pain. This result will lead to the recommendation of TTM as an alternative treatment.

Even though the evidence on pain reduction of SHT is quite consistent across studies and its superior effect to NSAIDs is demonstrated, several concerns need to be pointed out. First, it is important to note that there is no report on the amount of quantitative and qualitative analysis of active compounds in SHT preparations used in the studies (Nootim et al., 2013). There are many factors affecting the amount of bioactive constituent contents in herbal medicine such as the variety of plants, the part used, and the place and time of plant harvesting. These lead to variation of clinical effects and toxicity. Fingerprints or standardization of bioactive marker content in SHT preparations are a vital step for clinical evaluation. Further RCTs of SHT, standardization of SHT extract should be performed. Second, there are no data about the dose-response of SHT for the treatment of pain. It is better to report dose-response relationships by considering the standardized dose. Thus, the dose of standardized SHT needs to be investigated in further studies for the appropriate use of SHT. Third, the limitations of our review are the number of studies and the quality of included studies reported as a high risk of bias. Further studies should be performed as high-quality trials and reported according to the CONSORT statement.

Table 2. Baseline characteristics of included studies

Study ID	Author (year)	Study design	Country	Classification of pain		Interven-tion	Time of assess-ment (Days)	n ITT[A]	n complete	Female, number; n/N (%)	Age, years; Mean (SD)	Baseline Pain		Quality	
				By duration	By clinical perspec-tives							VAS, mm; Mean (SD)	Total WOMAC score; Mean (SD)	Jadad score	Risk of bias
1	Pinsornsak P. (2015)	RCT, double blind	Thailand	Chronic	OA knee	Sahasthara remedy	0, 14, 28	33	31	28/31 (90.3%)	60.38 (6.97)	44.1[B] (23.5)	42.65 (15.7)	5 (high quality)	Low risk
						vs									
						diclofenac		33	30	27/30 (90%)	58.23 (7.99)	43.5[B] (19.3)	43.13 (13.69)		
2	Nootim P. (2013)	RCT, double blind	Thailand	Acute	Muscle pain	Sahasthara remedy	0-7	36	31	23/31 (74.19%)	40.81 (1.94)	4.97[C] (0.32)	N/A[C]	3 (high quality)	High risk
						vs									
						diclofenac		36	31	24/31 (77.42%)	41.1 (1.72)	4.84[C] (0.27)	N/A[C]		

Note: [A]: Intention-to-treat assignment, [B]: VAS (horizontal line: mm from 100 mm), [C]: No assessment

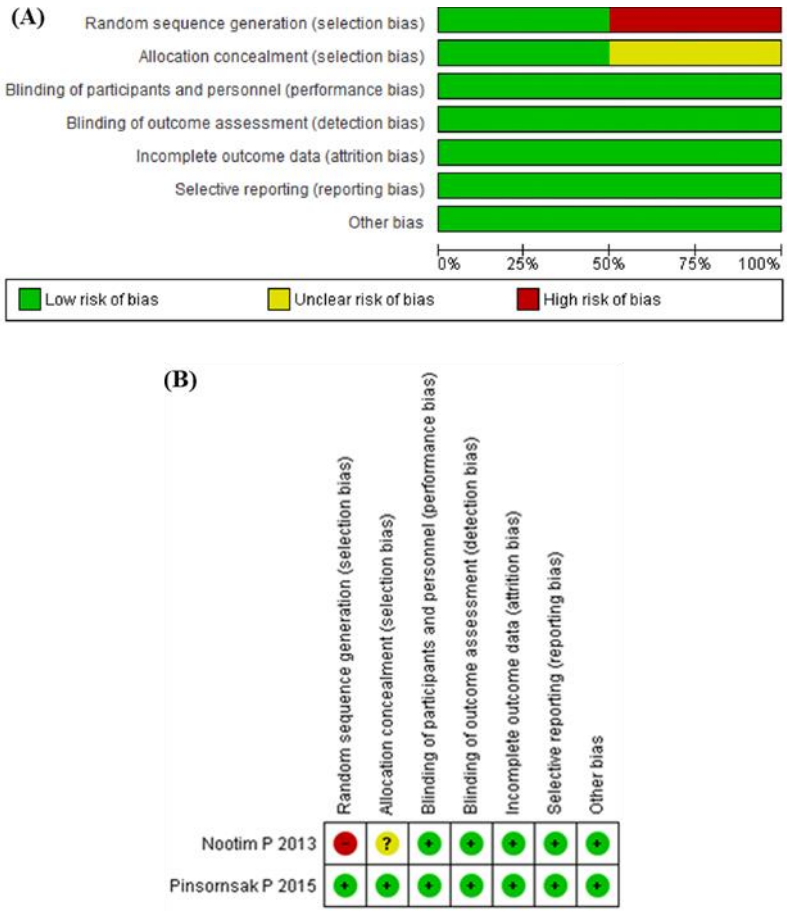

Figure 2. Risk of bias graph (A), and risk of bias summary (B) assessment of included randomized controlled trials

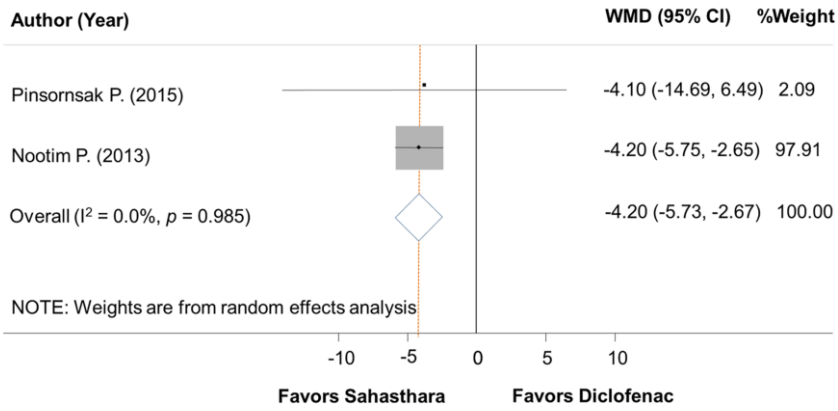

Figure 3. Meta-analysis of visual analogue scale scores comparing the Sahasthara remedy with diclofenac

5. CONCLUSION

This systematic review and meta-analysis found that the reduction of the VAS score in the Sahasthara (SHT) arm is superior to that of diclofenac. It suggests SHT as a potential pain reliever. More safety was found in the SHT arm. However, the quality and quantity of the available evidence are limited. More high quality RCTs are suggested to be performed to support the potential of SHT as an alternative therapy for acute and chronic musculoskeletal pain.

ACKNOWLEDGMENT

This work was supported by a grant from the Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN) [grant number: FF64-UoE003], School of Pharmaceutical Sciences, University of Phayao. The funding source had no role in the study design, the collection, analysis, and interpretation of the data.

REFERENCES

Abd El-Razek, M. H. (2007). A new ester isolated from *Ferula assa-foetida* L. *Bioscience, Biotechnology, and Biochemistry*, 71(9), 2300-2303.

Ackerman, I. (2009). Western Ontario and McMaster universities osteoarthritis index (WOMAC). *Australian Journal of Physiotherapy*, 55, 212-213.

Al-Ghamdi, M. S. (2001). The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*. *Journal of Ethnopharmacology*, 76(1), 45-48.

Bang, J. S., Oh, D. H., Choi, H. M., Sur, B., Lim, S., Kim, J. Y., Yang H., Yoo M. C., Hahm D. H., and Kim K. S. (2009). Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1β-stimulated fibroblast-like synoviocytes and in rat arthritis models. *Arthritis Research and Therapy*, 11(2), R49.

Booranasubkajorn, S., Huabprasert, S., Wattanarangsan, J., Chotitham, P., Jutasompakorn, P., Laohapand, T., Akarasereenont, P., and Tripatara, P. (2017). Vasculoprotective and vasodilatation effects of herbal formula (Sahatsatara) and piperine in spontaneously hypertensive rats. *Phytomedicine*, 24, 148-156.

Boros, L. (2017). GSK Global Pain Index 2017 Global Research Report. *GSK*. [Online URL: https://www.gsk.com/ media/ 3814/global-pain-index-2017-report.pdf] accessed on May 1, 2020.

Burits, M., and Bucar, F. (2000). Antioxidant activity of *Nigella sativa* essential oil. *Phytotherapy Research*, 14(5), 323-328.

Cai, Y., Luo, Q., Sun, M., and Corke, H. (2004). Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life Science*, 74(17), 2157-2184.

Chan, B. C. L., Hon, K. L. E., Leung, P. C., Sam, S. W., Fung, K. P., Lee, M. Y. H., and Lau H. Y. A. (2008). Traditional Chinese medicine for atopic eczema: PentaHerbs formula suppresses inflammatory mediators release from mast cells. *Journal of Ethnopharmacology*, 120(1), 85-91.

Chanwitheesuk, A., Teerawutgulrag, A., and Rakariyatham, N. (2005). Screening of antioxidant activity and antioxidant compounds of some edible plants of Thailand. *Food Chemistry*, 92(3), 491-497.

Checker, R., Sharma, D., Sandur, S. K., Khanam, S. K., and Poduval, T. B. (2009). Anti-inflammatory effects of plumbagin are mediated by inhibition of NF- kappaB activation in lymphocytes. *International Immunopharmacology*, 9(7-8), 949-958.

Chung, J. H., Kang, D. H., Jo, J. K., and Lee, S. W. (2012). Assessing the quality of randomized controlled trials published in the Journal of Korean Medical Science from 1986 to 2011. *Journal of Korean Medical Science*, 27(9), 973-980.

DerSimonian, R., and Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, 7, 177-188.

Desai, P. V., Wadekar, R. R., Kedar, G. H., and Patil, K. S. (2008). Free radical scavenging activity of aqueous extract of roots of Baliospermum montanum Muell-Arg. *International Journal of Green Pharmacy*, 2, 31-33.

Drug and Medical Supply Information Center (DMSIC). (2019). *The national lists of essential medicines 2019*. Drug and Medical Supply Information Center, Ministry of Public Health. [Online URL: http://dmsic.moph.go.th/index/data service/97/0] accessed on May 4, 2020. [in Thai]

Engels, F., Renirie, B. F., Hart, B. A., Labadie, R. P., and Nijkamp, F. P. (1992). Effects of apocynin, a drug isolated from the roots of *Picrorhiza kurroa*, on arachidonic acid metabolism. *FEBS letters*, 305(3), 254-256.

Fan, J., Liu, K., Zhang, Z., Luo, T., Xi, Z., Song, J., and Liu, B. (2010). Modified Si-Miao-San extract inhibits the release of inflammatory mediators from lipopolysaccharide-stimulated mouse macrophages. *Journal of Ethnopharmacology*, 129(1), 5-9.

Goldberg, D. S., and McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, 11, 770.

Gould, D. (2001). Visual analogue scale (VAS). *Journal of Clinical Nursing*, 10, 697-706.

Gülçın, I., Oktay, M., Kıreçcı, E., and Küfrevıoğlu, O. I. (2003). Screening of antioxidant and antimicrobial activities of anise (*Pimpinella anisum* L.) seed extracts. *Food Chemistry*, 83(3), 371-382.

Hazra, B., Sarkar, R., Biswas, S., and Mandal, N. (2010). Comparative study of the antioxidant and reactive oxygen species scavenging properties in the extracts of the fruits of *Terminalia chebula*, *Terminalia belerica* and *Emblica officinalis*. *BMC Complementary and Alternative Medicine*, 10, 20.

Health Care Association of New Jersey (HCANJ). (2017). *Best practice committee of the health care association of New Jersey*. HCANJ. [Online URL:https:// www.hcanj.org/files/ 2013/09/Pain-Management-Guidelines-_HCANJ-May-12-final.pdf.] accessed on May 4, 2020.

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savović, J, Schulz, K. F., Weeks, L., and Sterne, J. A. (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal*, 343, d5928.

Jadad, A. R., Moore, A., Carroll, D., Jenkinson, C, Reynolds, J. M., Gavaghan, D. J., and McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials*, 17(1), 1-12.

Jaiaree, N., and Itharat, N. (2012). Anti-inflammatory effect of a Thai traditional drug for muscle pain treatment via nitric oxide and COX-II inhibitor. *Planta Medica*, 78(11), PF23.

Jin, D. Q., Lim, C. S., Hwang, J. K., Ha, I., and Han, J. S. (2005). Anti-oxidant and anti-inflammatory activities of macelignan in murine hippocampal cell line and primary culture of rat microglial cells. *Biochemical and Biophysical Research Communications*, 331(4), 1264-1269.

Kakatum, N. (2011). *Anti-inflammatory activity of Thai traditional remedy extract for muscle pain treatment called Sahastara and its plant ingredients*. Master's thesis. Thammasat University, Thailand.

Kakatum, N., Jaiaree, N., Makchucit, S., and Itharat, A. (2012). Antioxidant and anti-inflammatory activities of Thai medicinal plants in Sahasthara remedy for muscle pain treatment. *Journal of the Medical Association of Thailand*, 95(Suppl1), S120-126.

Kapoor, I. P. S., Singh, B., Singh, G., Heluani, C. S., Lampasona, M. P., and Catalan, C. A. (2009). Chemistry and in vitro antioxidant activity of volatile oil and oleoresins of black pepper (*Piper nigrum*). *Journal of Agricultural and Food Chemistry*, 57(12), 5358-5364.

Keeratitanont, K., Jensen, M. P., Chatchawan, U., and Auvichayapat, P. (2015). The efficacy of traditional Thai massage for the treatment of chronic pain: a systematic review. *Complementary Therapies in Clinical Practice*, 21(1), 26-32.

Kim, H., Han, T. H., and Lee, S. G. (2009). Anti-inflammatory activity of a water extract of *Acorus calamus* L. leaves on

keratinocyte HaCaT cells. *Journal of Ethnopharmacology*, 122(1), 149-156.

Kusirisin, W., Srichairatanakool, S., Lerttrakarnnon, P., Lailerd, N., Suttajit, M., Jaikang, C., and Chaiyasut, C. (2009). Antioxidative activity, polyphenolic content and anti-glycation effect of some Thai medicinal plants traditionally used in diabetic patients. *Medical Chemistry*, 5(2), 139-147.

Lee, H. J, Hyun, E. A., Yoon, W. J., Kim, B. H., Rhee, M. H., Kang, H. K., Cho, J. Y., and Yoo, E. S. (2006). In vitro anti-inflammatory and anti-oxidative effects of *Cinnamomum camphora* extracts. *Journal of Ethnopharmacology*, 103(2), 208-216.

Lin, C. T., Chu, F. H, Tseng, Y. H., Tsai, J. B., Chang, S. T., and Wang, S. Y. (2007). Bioactivity investigation of Lauraceae trees grown in Taiwan. *Pharmaceutical Biology*, 45(8), 638-644.

Manosroi, A., Jantrawut, P., Akazawa, H., Akihisa, T., and Manosroi, J. (2010a). Biological activities of phenolic compounds isolated from galls of *Terminalia chebula* Retz. (Combretaceae). *Natural Product Research*, 24(20), 1915-1926.

Manosroi, A., Jantrawut, P., Akihisa, T., Manosroi, W., and Manosroi, J. (2010b). In vitro anti-aging activities of *Terminalia chebula* gall extract. *Pharmaceutical Biology*, 48(4), 469-481.

Mehrotra, S., Mishra, K. P., Maurya, R., Srimal, R. C., Yadav, V. S., Pandey, R., and Singh, V. K. (2003). Anticellular and immunosuppressive properties of ethanolic extract of *Acorus calamus* rhizome. *International Immunopharmacology*, 3(1), 53-61.

Mukherjee, P. K., Kumar, V., Mal, M., and Houghton, P. J. (2007). *Acorus calamus*: scientific validation of ayurvedic tradition from natural resources. *Pharmaceutical Biology*, 45(8), 651-666.

Nootim, P., Bunchuailua, W., and Kapol, N. (2013). Comparative efficacy of sahasthara capsule vs diclofenac tablet for the relief of muscle pain. *Journal of Thai Traditional & Alternative Medicine*, 11(1), 54-65. [in Thai]

Nuengchamnong, N., and Ingkaninan, I. (2017). An on-line LC-MS/DPPH approach towards the quality control of antioxidantive ingredient in Sahastara. *Songklanakarin Journal of Science and Technology*, 39(1), 123-129.

Pearson, N. (2012). Acute versus Chronic Pain: Understanding the difference and choosing appropriate treatment. *OrionHealth*. [Online URL:https://www.orionhealth.net/news/-/asset_publisher/Xvx6HtHyOTwg/content/acute-versus-chronic-pain-understanding-the-difference-and-choosing-appropriate-treatment?inheritRedirect=false.] accessed on May 5, 2020.

Pfundstein, B., Desouky, S. K., Hull, W. E., Haubner, R., Erben, G., and Owen, R. W. (2010). Polyphenolic compounds in the fruits of Egyptian medicinal plants (*Terminalia bellerica*, *Terminalia chebula* and *Terminalia horrida*): characterization, quantitation and determination of antioxidant capacities. *Phytochemistry*, 71(10), 1132-1148.

Pinsornsak, P., Kanokkangsadal, P., and Itharat, A. (2015). The clinical efficacy and safety of the Sahastara remedy versus diclofenac in the treatment of osteoarthritis of the knee: a double-blind, randomized, and controlled trial. *Evidence-Based Complementary and Alternative Medicine*, 2015, 103046.

Rababah, T. M., Ereifej, K. I., Esoh, R. B., Al-u'datt, M. H., Alrababah, M. A., and Yang, W. (2011). Antioxidant activities, total phenolics and HPLC analyses of the phenolic compounds of extracts from common Mediterranean plants. *Natural Product Research*, 25(6), 596-605.

Rajkumar, V., Guha, G., and Kumar, R. A. (2011). Antioxidant and anti-neoplastic activities of *Picrorhiza kurroa* extracts. *Food and Chemical Toxicology*, 49(2), 363-369.

Ramos, A., Visozo, A., Piloto, J., Garcia, A., Rodriguez, C. A, and Rivero, R. (2003). Screening of antimutagenicity via antioxidant activity in Cuban medicinal plants. *Journal of Ethnopharmacology*, 87(2-3), 241-246.

Reddy, D. B., and Reddanna, P. (2009). Chebulagic acid (CA) attenuates LPS-induced inflammation by suppressing NF-kappaB and MAPK activation in RAW 264.7 macrophages. *Biochemical and Biophysical Research Communications*, 381(1), 112-117.

Reddy, D. B., Reddy, T. C. M., Jyotsna, G., Sharan, S., Priya, N., Lakshmipathi, V., and Reddanna, P. (2009). Chebulagic acid, a COX-LOX dual inhibitor isolated from the fruits of *Terminalia chebula* Retz., induces apoptosis in COLO-205 cell line. *Journal of Ethnopharmacology*, 124(3), 506-512.

Resch, M., Steigel, A., Chen, Z. L., and Bauer, R. (1998). 5-Lipoxygenase and cyclooxygenase-1 inhibitory active compounds from *Atractylodes lancea*. *Journal of Natural Products*, 61(3), 347-350.

Satyanarayana, S., Sushruta, K., Sarma, G. S., Srinivas, N., and Subba Raju, G. V. (2004). Antioxidant activity of the aqueous extracts of spicy food additives-evaluation and comparison with ascorbic acid in *in-vitro* systems. *Journal of Herbal Pharmacotherapy*, 4(2), 1-10.

Shyu, Y. S., Lin, J. T., Chang, Y. T., Chiang, C. J., and Yang, D. J. (2009). Evaluation of antioxidant ability of ethanolic extract from dill (*Anethum graveolens* L.) flower. *Food Chemistry*, 15, 515-521.

Singh, G., Marimuthu, P., Heluani, C. S., and Catalan, C. (2005). Antimicrobial and antioxidant potentials of essential oil and acetone extract of *Myristica fragrans* Houtt. *Journal of Food Science*, 70(2), M141-148.

Singtong, P., Soonyarach, W., and Phaikhomnam, P. (2016). Effectiveness of traditional Thai massage with Sahasthara drug used for treatment of shoulder muscle pain. *Journal of Traditional Thai Medicinal Research*, 2(2), 13-24. [in Thai]

Sripanidkulchai B, Fangkratok, N., Saralamp, P., and Soonthornchoreonnon, N. (2007). Mutagenicity and antimutaginicity tests of extracts from Thai traditional medicines. *KKU Research Journal*, 12(4), 492-498. [in Thai]

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., Carpenter, J., Rücker, G., Harbord, R. M., Schmid, C. H., Tetzlaff, J., Deeks, J. J., Peters, J, Macaskil, P., Schwarzer, G., Duval, S., Altman, D. G., Moher, D., and Higgins, J. P. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, 343, d4002.

Surveswaran, S., Cai, Y. Z., Corke, H., and Sun, M. (2007). Systematic evaluation of natural phenolic antioxidants from 133 Indian medicinal plants. *Food Chemistry*, 102(3), 938-953.

Tabanca, N., Ma, G., Pasco, D. S., Bedir, E., Kirimer, N., Baser, K. H., Khan, I. A., and Khan S. I. (2007). Effect of essential oils and isolated compounds from *Pimpinella* species on NF-κB: a target for antiinflammatory therapy. *Phytotherapy Research*, 21(8), 741-745.

Thamsermsang, O., Akarasereenont, P., Laohapand, T., and Panich, U. (2017). IL-1β-induced modulation of gene expression profile in human dermal fibroblasts: the effects of Thai herbal Sahatsatara formula, piperine and gallic acid possessing antioxidant properties. *BMC Complement and Alternative Medicine*, 17(1), 32.

Thippeswamy, N. B., and Naidu, K. A. (2005). Antioxidant potency of cumin varieties —cumin, black cumin and bitter cumin—on antioxidant systems. *European Food Research and Technology*, 220, 472-476.

Zhang, Y., DeWitt, D. L., Murugesan, S., and Nair, M. G. (2004). Novel lipid-peroxidation- and cyclooxygenase-inhibitory tannins from *Picrorhiza kurroa* seeds. *Chemistry & Biodiversity*, 1(3), 426-441.