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# Efficacy and safety of *Derris scandens* (Roxb.) Benth. for musculoskeletal pain treatment: A Systematic Review and Meta-analysis of randomized controlled trials.

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**Abstract**

**Ethnopharmacological relevance:**

*Derris scandens* (Roxb.) Benth. has been used as active ingredient in Thai traditional medicine recipes for pain treatment. Dry stem powder and ethanolic extract also recommended in Thailand National List of Essential Medicines (NLEMs) for musculoskeletal pain treatment as herbal medicine. However, no summarization of clinical effect and safety has been evaluated.

**Objective**

Our study aimed to determine the clinical effects and safety of *D. scandens* for musculoskeletal pain treatment compared with standard regimen,nonsteroidal anti-inflammatory drugs (NSAIDs).

**Methods**

International and Thai databases were searched from inception through August 2015. Comparative randomized controlled trials investigating oral *D. scandens* for musculoskeletal pain were included. Outcomes of interest included level of pain and adverse event. Mean changes of the outcomes from baseline were compared between *D. scandens* and NSAIDs by calculating mean difference.

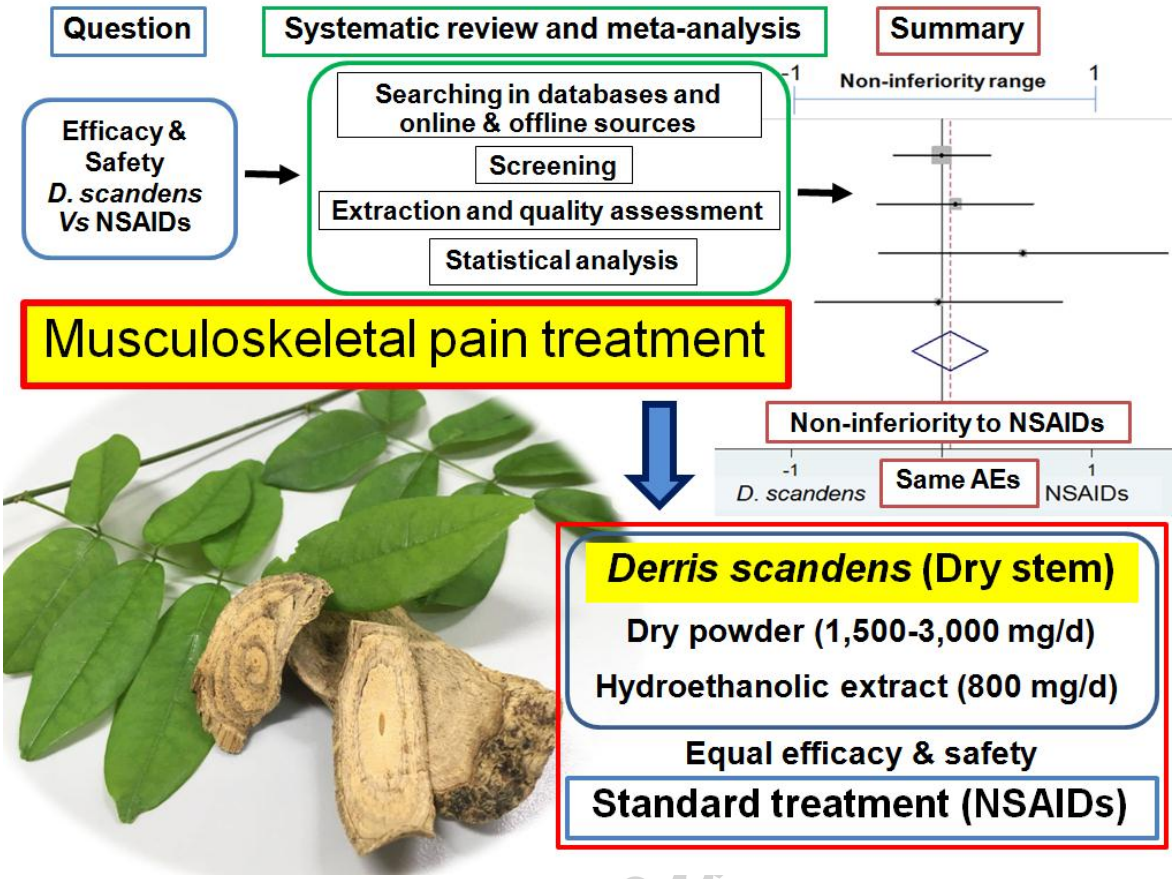
**Results**

From 42 articles identified, 4 studies involving a total of 414 patients were included for efficacy analysis. The effects of oral *D. scandens* on reducing pain score were no different from those of non-steroidal anti-inflammatory drugs at any time points (3, 7, 14 days and overall). The overall pain reduction in the *D. scandens* group was not inferior to treatment with NSAIDs (weighted mean difference 0.06; 95% CI:-0.20, 0.31) without evident of heterogeneity ($I^2$=0.00%, p=0.768). When compared, the adverse events (AEs) of *D. scandens* showed no different relative risk with NSAIDs. The major adverse events were gastrointestinal symptoms.

**Conclusion**

*D. scandens* may be considered as an alternative for musculoskeletal pain reduction.

**Graphical abstract**






***Abbreviations***

NLEMs, National List of Essential Medicines; NSAIDs, Nonsteroidal anti-inflammatory drugs (NSAIDs); COX-1, Cyclooxygenase 1; LTB4, Leukotriene-B4; AEs, Adverse events; RCT, Randomized controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses' VAS, visual analog score; OA, Osteoarthritis; HPLC, High performance liquid chromatography

***Keywords***

*Derris scandens*; alternative medicine; pain; musculoskeletal; nonsteroidal anti-inflammatory drugs; non-inferiority

## 1. Introduction

*Derris scandens* (Roxb.) Benth. (Fabaceae), *Brachypterum scandens* Benth. (synonym), Jewel vine or Thao-Wan-Priang (Thai name) is well–known medical plant in Asia and South East Asia. *D. scandens* stem or vine was traditionally used as a diuretic, antitussive, expectorant, antidysentery, and muscle pain treatment. It is also claimed as cancer prevention, and health promotion herb in cardiovascular patients and postmenopausal women (Sriwanthana and Chavalittumrong, 2001; Kuptniratsaikul et al., 2011).

*D. scandens* dried powder (dose 0.5-1 g immediately after meal three times a day) and 50% hydroethanolic extract (dose 400 mg immediately after meal two times a day) were included in the List of Herbal Medicinal Products in the Thailand National List of Essential Medicines for musculoskeletal pain treatment (National drug committee, 2015, www.nlem.in.th). Active ingredients of *D. scandens* for anti-inflammatory effect are genisteinglycoside derivatives (isoflavones). The major active substance of antioxidant and anti-inflammation is genistein-7-O-[$\gamma$-rhamnopyranosyl-(1$\rightarrow$6)-$\beta$-glucopyranoside] (Laupattarakasem et al., 2003; Kuptniratsaikul et al., 2011; Wongsinkongman et al., 2013). *D. scandens* extract exhibited good anti-inflammatory effect by inhibition of cyclooxygenase 1 (COX-1) and leukotriene-B4 (LTB4) generation, reduction of eicosanoid synthesis via both cyclooxygenase and lipoxygenase pathways and myeloperoxide release (Wongsinkongman et al., 2013; Kuptniratsaikul et al., 2011; Mahabusarakam et al., 2004; Laupattarakasem et al., 2004).

Musculoskeletal pain is a major medical problem commonly found in all countries (Mense, 2008; Hong, 2002). It is caused by the activation of nociceptive receptors leading to

releasing important endogenous inflammatory mediators such as prostaglandin E2. This mediator is important to produce local oedema, inflammation, and pain (Mense, 2008; Hong, 2002; Basbuam and Jessell, 2000). Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) which block prostaglandin synthesis are most commonly used for the treatment of musculoskeletal pain (Mense, 2008; Galer, 2001). However, causes of many adverse events such as gastrointestinal ulcer, allergy, heart failure and renal failure limit the use of NSAIDs. *D. scandens* has become a potentially viable option for pain management, since a number of research studies have evaluated the effects of *D. scandens*in a variety of clinical conditions especially for the treatment of musculoskeletal pain. However, there remains a gap in the literature with no summarization of evidence on the clinical benefits and safety of *D. scandens* for pain management. Although, there has been systematic reviews that provide evidence on oral herbal therapies for treating osteoarthritis, such as *Boswellia serrata* and avocado-soya bean unsaponifiables, the use of *D. scandens* has not been evaluated (Cameron and Chrubasik, 2014). The objective of this study is therefore to systematically review the literatures and conduct a meta-analysis to determine the efficacy and safety of oral *D. scandens* on pain management compared with NSAIDs.

## 2. Methods

This systematic review was conducted according to the Cochrane Collaboration framework guidelines(Higgins and Green; 2011),and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009).

### 2.1 Search strategies and study selection

The following databases were used to search for original research articles from inception to December 2015: AMED, CINAHL, Cochrane Central Register of clinical trial, EMBASE, Health Science Journals in Thailand, PubMed, Thai Index Medicus, Thai Library Integrated System, Thai Medical Index, Thai Thesis Database, WHO registry, and

www.clinicaltrial.gov. Strategic search terms used were *Derris scandens* OR Jewel vine OR Hog creeper OR Malay jewel vine OR "Thao-Wan-Priang" OR etc. For other sources, online and offline sources such as Journal of Thai Traditional & Alternative Medicine, libraries and references of papers derived for full text review were scanned to identify potential studies not indexed in the above databases. The experts were also contacted for additional trials.

Research articles were included if they met the following inclusion criteria: 1) randomized controlled trial (RCT) in patients with musculoskeletal pain and 2) evaluating clinical effects and/or safety of *D. scandens* for pain reduction treatment. There was no language restriction. PP scanned all the titles and abstracts to determine whether the studies assessed the effects of *D. scandens*. Full-text articles of the potential studies were subsequently assessed by PP and RS. Disagreements and uncertainties regarding eligibility were resolved by discussions with NC, when necessary.

**2.2 Data extraction and quality assessment**

Data extraction was undertaken by PP and RS using a data extraction form in accordance with the CONSORT statement for reporting herbal medicinal interventions (Gagnier et al., 2006). The data extracted included: study design; number of participants; age of participants; pain score of participants; characteristics of the intervention; and outcome measurement. The outcome measure is pain score at the end of the studies. Studies included in this review were assessed for methodological quality by PP and RS using the Cochrane risk of bias tool (Higgins and Green; 2011), and JADAD score (Jadad et al., 1996). The Cochrane risk of bias evaluates bias in intervention studies based on a number of criteria including: sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting; and other sources of bias. Studies in which baseline characteristics were different among studies groups were considered as high risk for the domain of 'other risk of bias'. Each study was classified as having low risk (low risk of bias for all key domains), high risk (high risk of bias for one or more key domains), or unclear

risk (unclear risk of bias for one or more key domains). Overall JADAD score of <3 or >3 indicates low or high methodological quality, respectively. Disagreements between the reviewers were settled through discussion and consensus.

### 2.3 Statistical analysis

Data from all studies were pooled in a meta-analysis to determine the overall effect size with 95% confidence interval. Pooled effects were calculated and stratified according to indications of *D. scandens* and its comparators (NSAIDs). Mean of the outcome at variables time for each treatment arm were calculated. Pooled standard deviations ($S_{pooled}$) of the mean were used. Then mean of the outcome variables were compared between intervention and comparator arms by calculating the overall mean differences, which could be weighted mean difference (WMD) for visual analog pain score. For pain reduction indication, the weighted mean difference value above 0 indicated that *D. scandens* was less effective in reducing pain or alleviating difficulties in performing activities compared to comparators (NSAIDs).

Statistical heterogeneity between studies was assessed using the chi-squared test and $I^2$ (Higgins et al., 2003). Thresholds of $I^2$ were interpreted in accordance with the magnitude and direction of effects and strength of evidence of heterogeneity (eg. p-value) as follows: might not be important (0%-30%); moderate heterogeneity (30%-50%); substantial heterogeneity (50%-75%); and considerable heterogeneity (75%-100%) (Higgins and Green, 2011). The Dersimonian and Laird random-effects model was employed for all analyses (Dersimonian and Laird, 1986). Meta-analyses were conducted using STATA® version 11 (STATA Corp, College Station, TX, USA). We also calculated the sample size required for testing non-inferiority between *D. scandens* and NSAIDs (Zhong, 2009) to determine whether the studies were of sufficient power to demonstrate non-inferiority. The non-inferiority was tested with marginal difference of pain score of ± 1 score out of 10 scores of VAS based on previous study (Kuptniratsaikul et al., 2011).

## 3. Results

### 3.1 Study selection

Of the 42 articles found from the various databases searched and 7 articles identified through other sources (reference lists of retrieved articles or contact content expert for additional articles), 49 articles were eligible for screening after duplication removal. Based on title and abstract screened, 8 articles were selected for full text review. Four articles were excluded as two studies were not clinical studies and another two studies were safety studies in healthy volunteers. Four randomized controlled trials which involved a total of 414 patients were included in this systematic review and meta-analysis (Fig. 1).

### 3.2 Study characteristics

Information extracted from the included studies was generally complied with the requirement in the CONSORT statement for reporting herbal medicinal interventions. All four RCTs (Table 1) were conducted in Thailand to investigate the effects of oral *D. scandens* on musculoskeletal pain reduction compared with NSAIDs. All of included articles reported Latin binomial of ingredient herbs. Method of authentication of raw material was also reported in 2 studies (Srimongkol et al., 2007; Kuptniratsaikul et al., 2010). Only one study explained quantitative description and quantitative testing of *D. scandens* and presented sample size calculation for non-inferiority (Kuptniratsaikul et al., 2010). Duration of studies of all RCTs ranged from 7 to 28 days.

The included studies were conducted in patients with primary osteoarthritis (OA) of knees (Kuptniratsaikul et al., 2010; Benchakanta et al., 2012), low back pain (Srimongkol et al., 2007) and chronic arthralgiafrom chikungunya (Maneenual et al., 2010) (Table 2). All patients were diagnosed by a medical doctor and confirmed by some laboratory test. Patients aged over 50 years were specified as the subjects of investigation in one study

(Kuptniratsaikul et al., 2010).The age of subjects in the remaining studies were ranged from 18-60 years (Srimongkol et al., 2007;Maneenual et al., 2010;Benchakanta et al., 2012). The pain duration before entering the trial was reported in 3 studies ranging from less than 30 days (acute pain) (Benchakanta et al., 2012) to 40 months (chronic pain) (Kuptniratsaikul et al., 2010).

*D. scandens* dried powder and hydroethanolic extract (reflux using 50% ethanol in water) of *D. scandens* in capsule were used as intervention in the different dose and dosage forms. Two studies used 1,500 mg/day (Maneenual et al., 2010) and 3,000 mg/day (Benchakanta et al., 2012) of *D. scandens* dried powder while another two studies used 600 mg/day (Srimongkol et al., 2007) and 800 mg/day (Kuptniratsaikul et al., 2010) of hydroethanolic *D. scandens* extract. All *D. scandens* preparations were prepared following the NLEM recommendation. The dose regimens used in 3 RCTs (Maneenual et al., 2010; Kuptniratsaikul et al., 2010; Benchakanta et al., 2012) were aligned with the recommended dose of *D. scandens* dried powder (1,500-3,000 mg/day) and hydroethanolic extract (800 mg/day) in the NLEM (National drug committee, 2015, www.nlem.in.th). One study used *D. scandens* hydroethanolic extract lower than the recommendation dose in NLEM (Srimongkol et al., 2007). Two RCTs stated that hydroethanolic extract were standardized extract using genistein-7-O-[γ-rhamnopyranosyl-(1→6)-β-glucopyranoside] (Srimongkol et al., 2007; Kuptniratsaikul et al., 2010) as bioactive marker but no study reported the amount of standard reference in the extract or dried powder. The comparators of all included RCTs were NSAIDs including diclofenac 75 mg/day(Srimongkol et al., 2007; Maneenual et al., 2010), naproxen 500 mg/day (Kuptniratsaikul et al., 2010) and ibuprofen 1,200 mg/day (Benchakanta et al., 2012)(Table 1).

All included studies measured VAS of pain in the similar rating scale, 0 to 10, at different time points (Table 2). Two studies evaluated VAS of pain at 0, 3 and 7 days (Srimongkol, 2007; Benchakanta, 2012).In chronic pain studies, VAS of pain was measured at 0, 14 days (Maneenual et al., 2010), and at 0, 14 and 28 days, respectively

(Kuptniratsaikul et al., 2010). Zero score of VAS represents no pain whereas 10 score represents the worst pain. A higher score indicates greater pain intensity. The average baseline VAS of pain (mean±SD) in all included studies varied from 4.90±1.72 (Maneenual, 2010) to 6.56±0.91 (Srimongkol, 2007). These scores were categorized as moderate pain (Jones, 2007).

### 3.3 Quality of included studies

Based on Cochrane's risk of bias criteria, all of included studies were rated high risk of bias. All RCTs were rated high risk of bias in blinding domain because they used different dosage forms for intervention and comparator. Two studies were rated high risk of bias in sequence generation and allocation concealment domains (Maneenual et al., 2010; Benchakanta et al., 2012) because they used inappropriate method for randomization and allocation concealment. None of included studies showed bias in incomplete outcome data, selective outcome reporting and other sources of bias. JADAD score of all included studies was also examined. The methodological quality of included trials was low to medium with JADAD score ranging from 1 to 3 of a total score of 5 (Table 3).

### 3.4 Clinical effects of *D. scandens* on musculoskeletal pain reduction

All included RCT studies investigated the use of *D. scandens* or NSAIDs in patients with musculoskeletal pain, by measuring the level of pain using a visual analogue scale (VAS) of pain (Appendix 1). Based on meta-analysis using WMD of VAS of pain at the end of study, the pain level in subjects receiving *D. scandens* for musculoskeletal pain treatment was not statistically different from that of NSAIDs (WMD 0.06; 95% CI -0.20, 0.31) (Fig. 2). In subgroup analysis, no significant difference was identified for the effect of *D. scandens* on pain reduction when compared with NSAIDs at day 3 (WMD, 0.13; 95%CI -0.34, 0.59), day 7 (WMD, 0.06; 95%CI -0.38, 0.50), and day 14 (WMD, 0.28; 95%CI -0.02, 0.58). Form 285 OA knee patients group, *D. scandens* exhibited non-inferiority for reducing VAS of pain to NSAIDs group (WMD 0.21; 95%CI -0.06, 0.48). Furthermore, *D. scandens* also alleviated

VAS of pain not lower than diclofenac 75 mg/day (WMD 0.22; 95%CI -0.41, 0.84) (Table 4). All meta-analysis results provided very low heterogeneity across studies ($I^2$=0.00%). The very low heterogeneity supported the consistency effect of *D. scandens* compared with NSAIDs between all included studies.

### 3.5 Adverse effects of *D. scandens*

Safety outcomes of *D. scandens* compared with NSAIDs were reported in 3 studies (Kuptniratsaikul et al., 2010; Maneenual et al., 2010; Benchakanta et al., 2012). No serious adverse events were reported in any of the studies. There was no significant different risk ratio (pooled effect) of adverse events from ether group (Table 5). Kuptniratsaikul V, et al reported that dyspepsia and GI irritation events in naproxene group were higher than those in *D. scandens*group (Kuptniratsaikul et al., 2010). On the other hand, Benchakanta S, et al reported GI irritation events in ibuprofen group were lower than those in*D. scandens*group (Benchakanta et al., 2012).The major adverse events were gastrointestinal (GI) symptoms such as dyspepsia, GI irritation, constipation, andnausea/vomiting (Table 5). Central nervous system (CNS) and others adverse symptoms were also reported from *D. scandens* and comparator groups.

## 4. Discussion

This systematic review and meta-analysis provides the efficacy of *D. scandens* arm in musculoskeletal pain were not inferior to that of standard drugs (NSAIDs) in all musculoskeletal pain patients at the end of each study and among knee OA patients.

Furthermore, adverse events among patients using *D. scandens* and NSAIDs in a short period were comparable. The result showed the same rate of adverse events including gastrointestinal, central nerves system and others symptoms in both group. Normally, people usually use herbal medicine instead of chemical drug to avoid the adverse event or complication but the uses of *D. scandens* in a short period show similar adverse events of NSAIDs especially for gastrointestinal complications. Since previous *in vivo* and *in vitro*

studies reported that both *D. scandens* and NSAIDs can inhibit cyclooxygenase 1 (COX-1) and leukotriene-B4 (LTB4) generation in the same manner, similar AEs of both can be produced (Wongsinkongman et al., 2013; Kuptniratsaikul et al., 2011; Mahabusarakam et al., 2004; Laupattarakasem et al., 2004). In Thailand National List of Essential Medicines (NLEMs), *D. scandens* should be used with caution in peptic ulcer patients because it may irritate the gastrointestinal mucosa. *D. scandens* is also prohibited in pregnant females. From our results, the combination of *D. scandens* with NSAIDs which usually prescribed in Thailand hospital for musculoskeletal pain should be avoided due to their AEs.

Although this study reveals that efficacy and safety *D. scandens* and NSAIDs for musculoskeletal pain seem similar. We suggest *D. scandens* as an alternative option of NSAIDs for musculoskeletal pain because *D. scandens* is Thai traditional medicine that is promoted to be used by Thai government. This herbal medicine can be produced by Thai company or hospital without any require imported chemical like NSAIDs. It results in stimulation of Thai economy and most of Thai people have easy access to this medicine. Moreover, NSAIDs have more other adverse effects such as increase risk of hypertension, cardiovascular diseases and kidney disease while these effects were not reported in the use of *D. scandens* (Kuptniratsaikul et al., 2010; Benchakanta et al., 2012; Srimongkol et al., 2007; Maneenual et al., 2010; Chavalittumrong et al., 2008; Sriwathana et al., 2009). In addition, for long-term study we found that dyspepsia and GI irritation events of NSAIDs were higher than those of *D. scandens* (Kuptniratsaikul et al., 2010). Therefore, we believe that *D. scandens* may be safer than NSAIDs in long-term use or when concerned about other adverse events.

The strength of our study is that it is a comprehensive summary of herbal medicine by using systematic reviews and meta-analyses which is at the top in the hierarchy of the clinical evidence and can answer the non-inferiority question. This study is one of a few systematic review and meta-analysis studies conducted in the field of complementary and alternative medicine (Schneider et al., 2005). The non-inferiority question is appropriate and

relevant for this context since the usual care is active comparator rather than placebo. The comparison of an herbal product to active comparator is very justified.

Even though the evidence on pain reduction is quite consistent across studies and non-inferior the effect of NSAIDs, a number of limitations should be mentioned. First, standardization method and bioactive marker content in herbal products including *D. scandens* preparations are very important step for clinical evaluation of herbal medicines (Gagnier et al., 2006). Since active ingredients in herbal products are influenced by several factors such as place, season or preparation, this may result in different clinical effects (Puttarak and Panichayupakaranant, 2012). All of included studies did not report amount of active compound in *D. scandens* preparations which may also be a limitation of this study and may lead to different of clinical outcomes. To ensure the quality of products, Genistein-7-O-[γ-rhamnopyranosyl-(1→6)-β-glucopyranoside](a flavonoid compound as anti-inflammatory and analgesic activity) should be used as a biomarker compound in hydroalcoholic extract or dry powder of *D. scandens*. Second, there are no data about dose response effect of *D. scandens* for pain reduction especially for dose of active constituents or standardized extract. Dose of standardized *D. scandens* is needed and should be investigated in future studies for the proper use of *D. scandens*. Third, the low quality of all included studies, because they did not employ a suitable randomization, concealment approach and blinding. However, this study provides current evidence based medicine of *D. scandens* on musculoskeletal pain by using systematic review and meta-analysis according to PRISMA guideline which is a widely acceptable method for drawing conclusions of clinical evidence of interventions. Therefore, taking into account the relatively low quality of included studies, caution should be made when interpreting or applying the results derived from these studies. Futures RCTs should be conducted as high quality trials and report according to CONSORT.

## 5. Conclusion

Current evidence suggested that *D. scandens* might be considered as a potential alternative for NSAIDs for the treatment of musculoskeletal pain since its use, as traditional medicine and listed product in NLEM. The use of *D. scandens* as alternative medicine could support local economy system in Thailand and it might be safer than NSAIDs in long-term use. Concomitant use of *D. scandens* and NSAIDs, should be avoided due to their similar AEs. However, given that the overall quality of current studies is low with short period of follow-up, firm conclusions on the efficacy and safety of *D. scandens* cannot be drawn. Interpretation of current evidence should be done with caution and further studies with higher quality remain needed. In addition, dose response effect and long-term use of standardized *D. scandens* products should be further investigated.

**Conflict of interest**

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.



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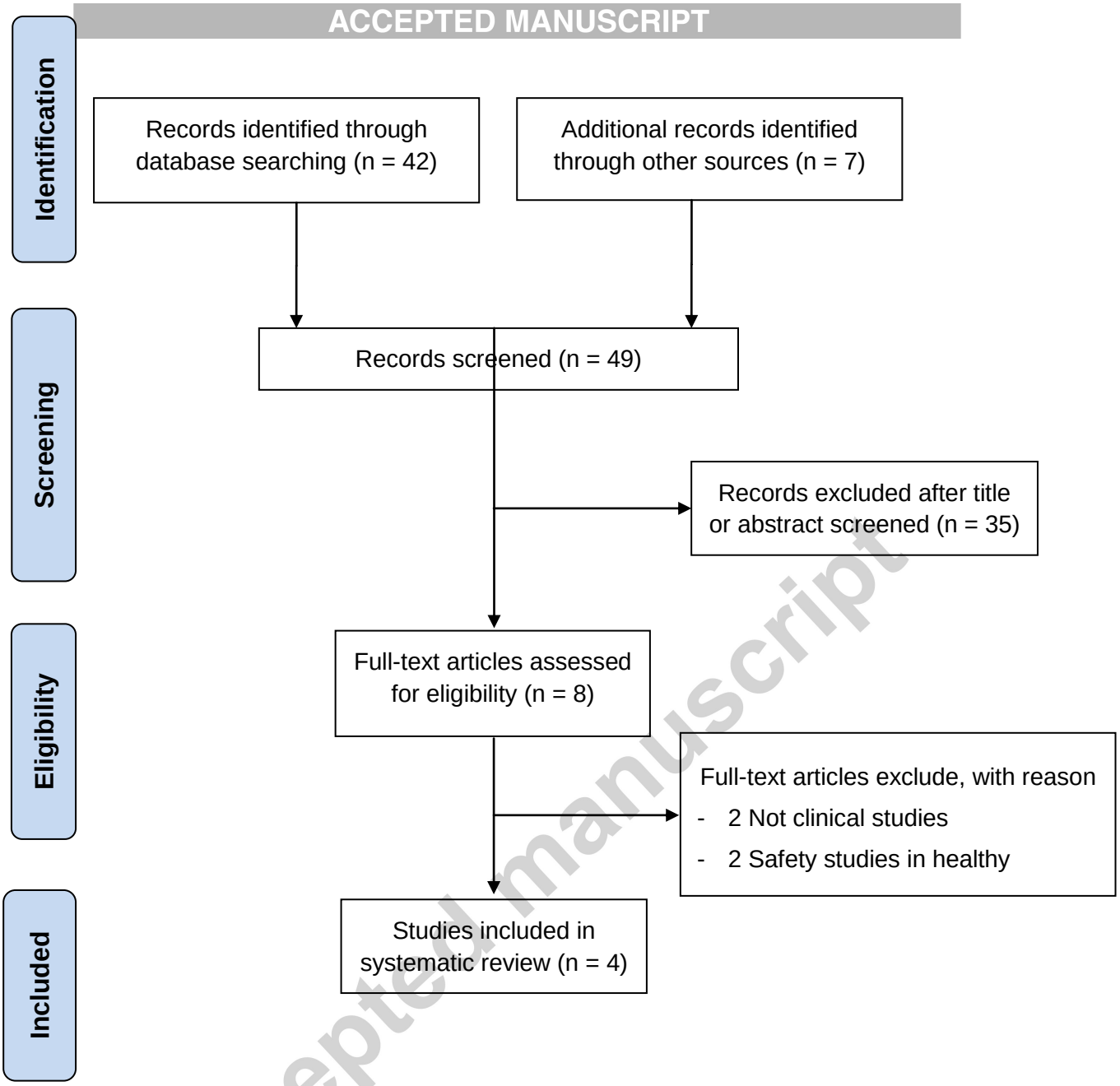


**Figure 1 Flow diagram of study selection**

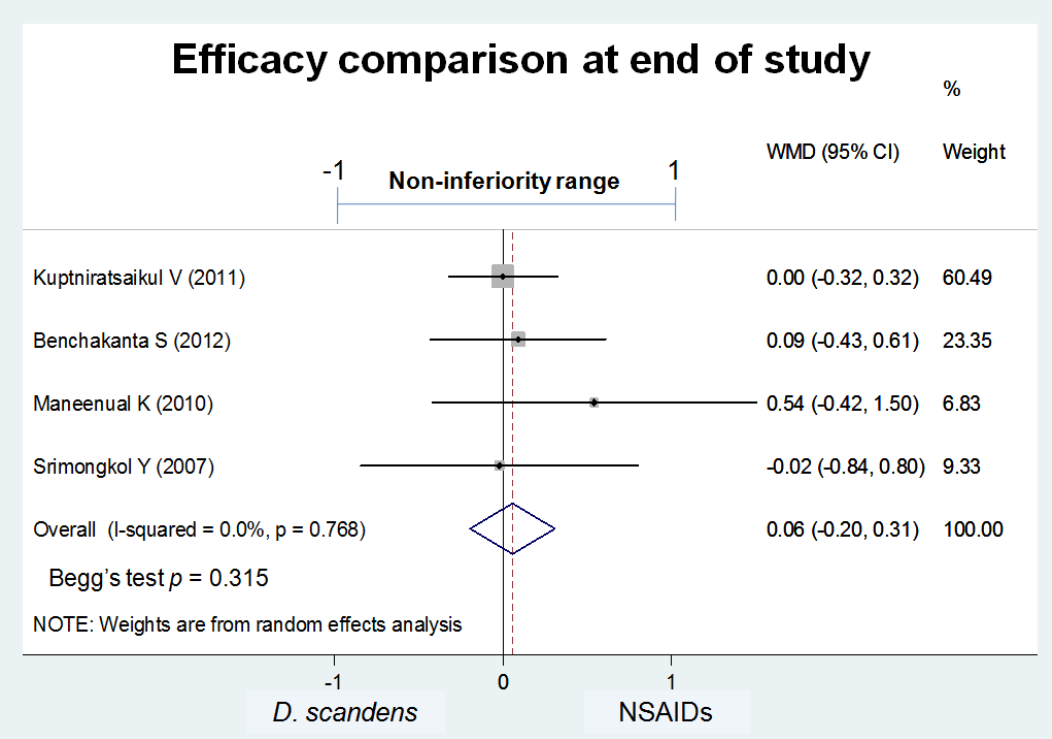


**Figure 2 Efficacy comparisons of *Derris scandens* (Roxb.) Benth. and NSAIDs for pain reduction at end of study**

**Table1 Characteristics of *Derris scandens* (Roxb.) Benth. in included studies**

| Author | Plant part | Preparation | Extraction method | Standardization | Dose/day (mg) | Standard compound |
|---|---|---|---|---|---|---|
| Srimongkol, 2007 | Vine | Extract | Reflux method using 50% ethanol | Yes | 600 | Genistein* |
| Kuptniratsaikul, 2010 | Stem | Extract | Reflux method using 50% ethanol | Yes | 800 | Genistein* |
| Maneenual, 2010 | Vine | Dry powder | N/A | No | 1,500 | NR |
| Benchakanta, 2012 | Vine | Dry powder | N/A | No | 3,000 | NR |

N/A = Not applicable, NR = not report, * genistein-7-O-[γ-rhamnopyranosyl-(1→6)-β-glucopyranoside]

**Table 2 Characteristics of included studies**

| **Author** | **RCTs method** | **Patients** | **Groups** | **No. Patients** | **Pain duration (months)** | **Mean age; or [Range] (Years)** | **Treatment duration (Days)** | **M:F** | **BMI** | **Baseline pain score** |
|---|---|---|---|---|---|---|---|---|---|---|
| Srimongkol, 2007 | Double blind | Low back pain | *D. scandens* 200 mg TID | 37 | NR | NR; [20-60] | 7 | 5:32 | No overweight | 6.41±1.12 |
| | | | Diclofenac 25 mg TID | 33 | | | | 6:27 | | 6.56±0.91 |
| Kuptniratsaikul, 2010 | Open label | Primary OA knee | *D. scandens* 400 mg BID | 63 | 39.8±49.3 | 59.4±7.0 | 28 | 8:47 | 26.3±3.8 | 5.10±1.40 |
| | | | Naproxen 250 mg BID | 62 | 36.2±34.5 | 60.5±8.2 | | 10:42 | 26.6±3.6 | 5.60±1.70 |
| Maneenual, 2010 | Double blind | Chronic arthralgia* | *D. scandens* 500 mg TID | 29 | < 12 | NR; [18-60] | 14 | 1:28 | NR | 4.90±1.72 |
| | | | Diclofenac 25 mg TID | 30 | | | | 5:25 | | 5.03±1.63 |
| Benchakanta, 2012 | Double blind | Primary OA knee | *D. scandens*1,000 mg TID | 94 | ≤ 1 | 48.1±7.8 | 7 | 15:73 | 25.5±4.0 | 4.92±1.97 |
| | | | Ibuprofen 400 mg TID | 94 | | 49.2±7.2 | | 17:73 | 25.6±3.5 | 4.99±1.84 |

RCT = Randomized controlled trials, NR = Not report, *Chikungunya patients (positive: antibody IgM) with fever >4 days

**Table 3 Methodological quality assessment of the included studies**

| Author | Risk of bias domain | | | | | | | | JADAD Score |
|---|---|---|---|---|---|---|---|---|---|
| | Sequence generation | Allocation concealment | Blinding | | Incomplete outcome data | Selective outcome reporting | Other sources of bias | Overall risk of bias | |
| | | | Investigator | Patient | | | | | |
| Srimongkol, 2007 | L | U | U | H | L | L | L | H | 3 |
| Kuptniratsaikul, 2010 | L | U | L | H | L | L | L | H | 3 |
| Maneenual, 2010 | H | H | U | H | L | L | L | H | 1 |
| Benchakanta, 2012 | H | H | L | H | L | L | L | H | 1 |

L = Low risk, U = Unclear, H = High risk

**Table 4 Subgroup analysis results of *Derris scandens* (Roxb.) Benth. compared with NSAIDs**

| Study | N | Mean difference [95% Confident interval] | p-value | Heterogeneity test | | % $I^2$ |
|---|---|---|---|---|---|---|
| | | | | $X^2$ | p-value | |
| **Efficacy at various time point** | | | | | | |
| Srimongkol, 2007 | 70 | 0.35 [-0.46, 1.16] | | | | |
| Benchakanta, 2012 | 178 | 0.02 [-0.54, 0.58] | | | | |
| **Pool effect at 3 days** | **248** | **0.13 [-0.34, 0.59]** | **0.593** | **0.43** | **0.513** | **0.00** |
| Srimongkol, 2007 | 70 | -0.02 [-0.84, 0.80] | | | | |
| Benchakanta, 2012 | 178 | 0.09 [-0.43, 0.61] | | | | |
| **Pool effect at 7 days** | **248** | **0.06 [-0.38, 0.50]** | **0.794** | **0.05** | **0.825** | **0.00** |
| Kuptniratsaikul, 2010 | 107 | 0.25 [-0.06, 0.56] | | | | |
| Maneenual, 2010 | 59 | 0.54 [-0.42, 1.50] | | | | |
| **Pool effect at 14 days** | **166** | **0.28 [-0.02, 0.58]** | **0.068** | **0.32** | **0.574** | **0.00** |
| **Effect on primary OA knee pain** | | | | | | |
| Kuptniratsaikul, 2010 | 107 | 0.25 [-0.06, 0.56] | | | | |
| Benchakanta, 2012 | 178 | 0.09 [-0.43, 0.61] | | | | |
| **Pool effect** | **285** | **0.21 [-0.06, 0.48]** | **0.130** | **0.27** | **0.606** | **0.00** |
| **Effect of *D. scandens* comparewithdiclofenac (75 mg/day)** | | | | | | |
| Srimongkol, 2007 | 70 | -0.02 [-0.84, 0.80] | | | | |
| Maneenual, 2010 | 59 | 0.54 [-0.42, 1.50] | | | | |
| **Pool effect** | **129** | **0.22 [-0.41, 0.84]** | **0.497** | **0.75** | **0.386** | **0.00** |

**Table5 Adverse events (AEs) of *Derris scandens* (Roxb.) Benth. compared with NSAIDs**

| Adverse events | Study | Total events/group (%) | | Risk ratio | $I^2$ |
|---|---|---|---|---|---|
| | | *D. scandens* | NSAIDs | (95% CI) | (%) |
| **Overall AEs** | | | | | |
| | Benchakanta, 2012 | 32/90 (35.55) | 35/88 (39.77) | 0.85 (0.61, 1.31) | |
| | Kuptniratsaikul, 2010 | 22/63 (34.9) | 29/62 (46.8) | 0.75 (0.49, 1.15) | |
| | | | | **0.83 (0.62, 1.10)** | **0.0** |
| **Gastrointestinal (GI) symptoms** | | | | | |
| Dyspepsia | Benchakanta, 2012 | 12/90 (13.33) | 5/88 (5.68) | 2.35 (0.86, 6.39) | |
| | Kuptniratsaikul, 2010 | 3/63 (4.80) | 18/62 (29.0) | 0.16 (0.05, 0.53) | |
| | Maneenual, 2010 | 2/29 (3.33) | 3/30 (0.00) | 0.69 (0.12, 3.83) | |
| | | | | **0.65 (0.11, 3.79)** | **82.8** |
| GI irritation | Benchakanta, 2012 | 15/90 (16.67) | 5/88 (5.68) | 2.93 (1.11, 7.73) | |
| | Kuptniratsaikul, 2010 | 2/63 (3.20) | 14/62 (22.6) | 0.14 (0.03, 0.59) | |
| | | | | **0.67 (0.03, 13.88)** | **91.8** |
| Nausea | Benchakanta, 2012 | 2/90 (2.22) | 1/88 (1.14) | 1.96 (0.18, 21.18) | |
| | Kuptniratsaikul, 2010 | 1/63 (1.60) | 1/62 (1.60) | 0.96 (0.66, 15.39) | |
| | | | | **1.46 (0.24, 8.82)** | **0.0** |
| Vomiting | Benchakanta, 2012 | 0/90 (0.00) | 1/88 (1.14) | 0.33 (0.01, 7.90) | |
| | Kuptniratsaikul, 2010 | 0/63 (0.00) | 1/62 (1.60) | 0.33 (0.01, 7.90) | |
| | | | | **0.33 (0.03, 3.11)** | **0.0** |
| Flatulence | Benchakanta, 2012 | 4/90 (4.44) | 4/88 (4.54) | 0.98 (0.25, 3.79) | |
| | Maneenual, 2010 | 4/29 (13.8) | 0/30 (0.00) | 9.30 (0.52, 165.4) | |
| | | | | **2.14 (0.24, 18.96)** | **51.9** |
| Constipation | Benchakanta, 2012 | 4/90 (4.44) | 1/88 (1.14) | 3.91 (0.45, 34.31) | |
| | Kuptniratsaikul, 2010 | 2/63 (3.20) | 1/62 (1.60) | 1.97 (0.18, 21.15) | |
| | Maneenual, 2010 | 4/29 (13.8) | 0/30 (0.00) | 9.30 (0.52, 165.4) | |
| | | | | **3.78 (0.93, 15.34)** | **0.0** |
| Loose stool | Kuptniratsaikul, 2010 | 3/63 (4.80) | 2/62 (3.20) | **1.48 (0.26, 8.52)** | **-** |
| Melena | Kuptniratsaikul, 2010 | 0/63 (0.00) | 1/62 (1.60) | **0.33 (0.01, 7.90)** | **-** |
| Dry mouth/throat | Maneenual, 2010 | 1/29 (3.45) | 1/30 (3.33) | **1.03 (0.07, 15.77)** | **-** |
| **Central nerves system (CNS)symptoms** | | | | | |
| Dizziness | Benchakanta, 2012 | 5/90 (5.55) | 7/88 (7.95) | 0.70 (0.23, 2.12) | |
| | Maneenual, 2010 | 1/29(3.45) | 5/30 (16.67) | 1.48 (0.44, 4.98) | |
| | Kuptniratsaikul, 2010 | 6/63 (9.50) | 4/62 (6.50) | 0.21 (0.03, 1.67) | |
| | | | | **0.76 (0.31, 1.90)** | **25.4** |
| Headache | Benchakanta, 2012 | 7/90 (7.78) | 5/88 (5.68) | 1.37 (0.45, 4.15) | |
| | Maneenual, 2010 | 1/29(3.45) | 5/30 (16.67) | 1.48 (0.26, 8.53) | |
| | Kuptniratsaikul, 2010 | 3/63 (4.80) | 2/62 (3.20) | 0.21 (0.03, 1.67) | |
| | | | | **0.94 (0.32, 2.71)** | **27.3** |
| Drowsiness | Benchakanta, 2012 | 9/90 (10.00) | 10/88 (11.36) | **0.88 (0.38, 2.06)** | **-** |
| **Others symptoms** | | | | | |
| Appetite increased | Benchakanta, 2012 | 4/90 (4.44) | 1/88 (1.14) | **3.91 (0.45, 34.31)** | **-** |
| Sweating | Benchakanta, 2012 | 4/90 (4.44) | 3/88 (3.41) | **1.30 (0.30, 5.66)** | **-** |
| Rash | Kuptniratsaikul, 2010 | 2/63 (3.20) | 1/62 (1.60) | **1.97 (0.18, 21.15)** | **-** |

**Appendix 1 Outcomes**

| Author | Treatment | VAS of pain score (Mean±SD) | | | | |
|---|---|---|---|---|---|---|
| | | Day 0 | Day 3 | Day 7 | Day 14 | Day 28 |
| Srimongkol, 2007 | *D. scandens* | 6.41±1.12 | 3.41±1.38 | 1.73±1.43 | N/A | N/A |
| | Diclofenac | 6.56±0.91 | 3.06±2.00 | 1.75±2.00 | N/A | N/A |
| Kuptniratsaikul, 2010 | *D. scandens* | 5.10±1.40 | N/A | N/A | 3.75±0.80 | 3.35±0.80 |
| | Naproxen | 5.60±1.70 | N/A | N/A | 3.50±0.85 | 3.35±0.90 |
| Maneenual, 2010 | *D. scandens* | 4.90±1.72 | N/A | N/A | 2.21±1.99 | N/A |
| | Diclofenac | 5.03±1.63 | N/A | N/A | 1.67±1.77 | N/A |
| Benchakanta, 2012 | *D. scandens* | 4.92±1.97 | 3.71±1.84 | 2.63±1.73 | N/A | N/A |
| | Ibuprofen | 4.99±1.84 | 3.69±1.96 | 2.53±1.81 | N/A | N/A |

N/A = Not applicable