

## Review article

# Herbal medicine (Danggui Shaoyao San) for treating primary dysmenorrhea: A systematic review and meta-analysis of randomized controlled trials



Hye Won Lee<sup>a</sup>, Ji Hee Jun<sup>b</sup>, Ki-Jung Kil<sup>c</sup>, Byong-Seob Ko<sup>a</sup>, Choong Hwan Lee<sup>d</sup>,  
Myeong Soo Lee<sup>b,\*</sup>

<sup>a</sup> KM Convergence Research Division, Korea Institute of Oriental Medicine, Republic of Korea

<sup>b</sup> Clinical Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

<sup>c</sup> College of Oriental Medicine, Joongbu University, ChungNam, Republic of Korea

<sup>d</sup> Department of Bioscience and Biotechnology, Konkuk University, Seoul, Republic of Korea

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## ABSTRACT

Danggui Shaoyao San (DSS), a traditional herbal prescription, has long been used to treat menopause-related symptoms, including dysmenorrhea. We conducted a systematic review of randomized controlled trials to evaluate the efficacy of DSS for dysmenorrhea. We searched the following electronic databases through October 2015: PubMed; EMBASE; the Cochrane Library; AMED; five Korean databases (KoreaMed, DBPIA, OASIS, RISS, and KISS); three Chinese databases (CNKI, Wan Fang Database, and VIP), and one Japanese database (CiNii). The Cochrane criteria were used to assess the risk of bias for the individual studies. All randomized clinical trials (RCTs) of DSS or modified DSS were included. Data from all articles were extracted by two independent reviewers. Meta-analysis was used to pool the data. A total of 746 potentially relevant studies were identified, and four RCTs met our inclusion criteria. All of the included RCTs had a high risk of bias across their domains. Three RCTs showed favourable effects of DSS on response rate compared with conventional medicine, and a meta-analysis showed that DSS had superior effects compared to analgesics (RR: 1.31, 95%CI, 1.06–1.63,  $I^2 = 73%$ ). One RCT showed a beneficial effect of DSS on pain compared with placebo control. Our systematic review and meta-analysis provided suggestive evidence of the superiority of DSS over analgesics or placebo for dysmenorrhea. The quality of evidence for this finding was low to moderate because of a high risk of bias.

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\* Corresponding author at: Clinical Research Division, Korea Institute of Oriental Medicine, Daejeon 305-811, Republic of Korea. Fax: +82 42 868 9299.  
E-mail addresses: [drmslee@gmail.com](mailto:drmslee@gmail.com), [mslee@kiom.re.kr](mailto:mslee@kiom.re.kr) (M.S. Lee).

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## 1. Introduction

Primary dysmenorrhea is menstrual pain without pelvic pathology occurring with ovulatory menstrual cycle and is the most common gynaecologic problem in women [1–3]. The reported estimated prevalence of dysmenorrhea is from 25% to 95% [2,4–8]. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce moderate to severe pain compared with placebo, while simple analgesics including aspirin and paracetamol may also be beneficial [9]. Severe adverse events associated with such treatments lead patients to seek supportive complementary and alternative medicine (CAM) [10,11]. One systematic review showed that 32.9% of menopausal women were current CAM users and 47.7% had used CAM in the past 12 months [12]. Examples of CAM therapies for dysmenorrhea include acupuncture related therapies [13–17] and Chinese herbal medicine (CHM) [18–24]. In particular, CHM is a potential CAM therapy for dysmenorrhea that is widely used in East Asia [19,20,22,25]. Danggui Shaoyao San (DSS), a CHM, is a traditional medicinal prescription that has long been used for the treatment of menopause-related symptoms in East Asia [25,26]. DSS is composed of the following six herbs: *Paeoniae Radix*, *Cnidii Rhizoma*, *Alismatis Rhizoma*, *Angelicae Radix*, *Poria Sclerotium*, and *Atractylodis Rhizoma alba*. The mechanisms of DSS are believed to include improvement of ovarian hormones [27], oestrogenic action [28] and neurotoxicity effects [29] under postmenopausal conditions.

Only one systematic review (SR) of Chinese herbal medicine (CHM) for primary dysmenorrhea has been conducted. This SR included 39 randomized clinical trials (RCTs) comparing all types of CHM [18]. The findings of this review suggested that CHM was promising for managing primary dysmenorrhea. However, as this review included all types of CHM, a need remains for a study that focuses on specific type of prescription. Furthermore, there is a language bias because the literature search included only English and Chinese databases and this review is also outdated.

Therefore, the aim of this article was to update and provide a thorough, critical evaluation of the current evidence from RCTs of DSS for primary dysmenorrhea.

## 2. Methods

### 2.1. Study registration

The protocol for this SR was registered in PROSPERO 2015: CRD42015026423.

### 2.2. Data source

The following electronic databases were searched from their inception through October 2015: PubMed; Cochrane Library; EMBASE; five Korean medical databases (Korea Med, DBPIA, OASIS, Research Information Sharing Service [RISS], and Korean Stud-

ies Information Service System [KISS]); three Chinese medical databases (China National Knowledge [CNKI], Wan Fang Database, and Journal integration platform [VIP]); and one Japanese medical database (CiNii). We used following the search terms: (Dysmenorrhea OR period pain OR menstrual pain OR cramps) AND ((danggui shaoyao) OR (dangguijakyak) OR (dangguijakyaksan) OR (tokishakuyakusan)) in English, Korean and Chinese. No language restrictions were imposed. Only data available in complete papers were reviewed. A recursive manual search of the cited references in published trials was conducted to identify other relevant trials.

### 2.3. Study selection

#### 2.3.1. Types of studies

All RCTs and quasi-RCTs of any types of DSS compared with pain-relief anti-depressants in patients with depression were included. Case studies, case series, qualitative studies, and uncontrolled trials were excluded. Trials that failed to provide detailed results were also excluded.

#### 2.3.2. Types of participants

Women of reproductive age with primary dysmenorrhea and with no identifiable pelvic pathology as indicated by pelvic examination, ultrasound scan and laparoscopy or self-reporting were considered for inclusion. Participants with secondary dysmenorrhea were excluded.

#### 2.3.3. Types of interventions

Studies that used any type of DSS or a modified DSS were included, as were studies comparing the effects of DSS alone or combined with conventional medication (NSAID or OCP) to the effects of conventional medicine alone. DSS included the following six formulas: *Paeoniae Radix*, *Cnidii Rhizoma*, *Alismatis Rhizoma*, *Angelicae Radix*, *Poria Sclerotium*, and *Atractylodis Rhizoma alba*. Modified DSS formulas were included as well. A modified DSS was defined by practitioners as a DSS with no more than one of the original herbs, but which had the same action as the original DSS formula. We included all forms of this medication, such as extracts, tablets, capsules, pills, powders, and injections. Studies examining DSS combined with other herbal decoctions or with other types of therapy were excluded. Trials in which the DSS was used as an adjunct to conventional treatment, usual care, or standard care were included if the control group received the same concomitant treatment as the DSS group. The control groups received pain relief (NSAID or OCP), placebo, no treatment and usual or standard care.

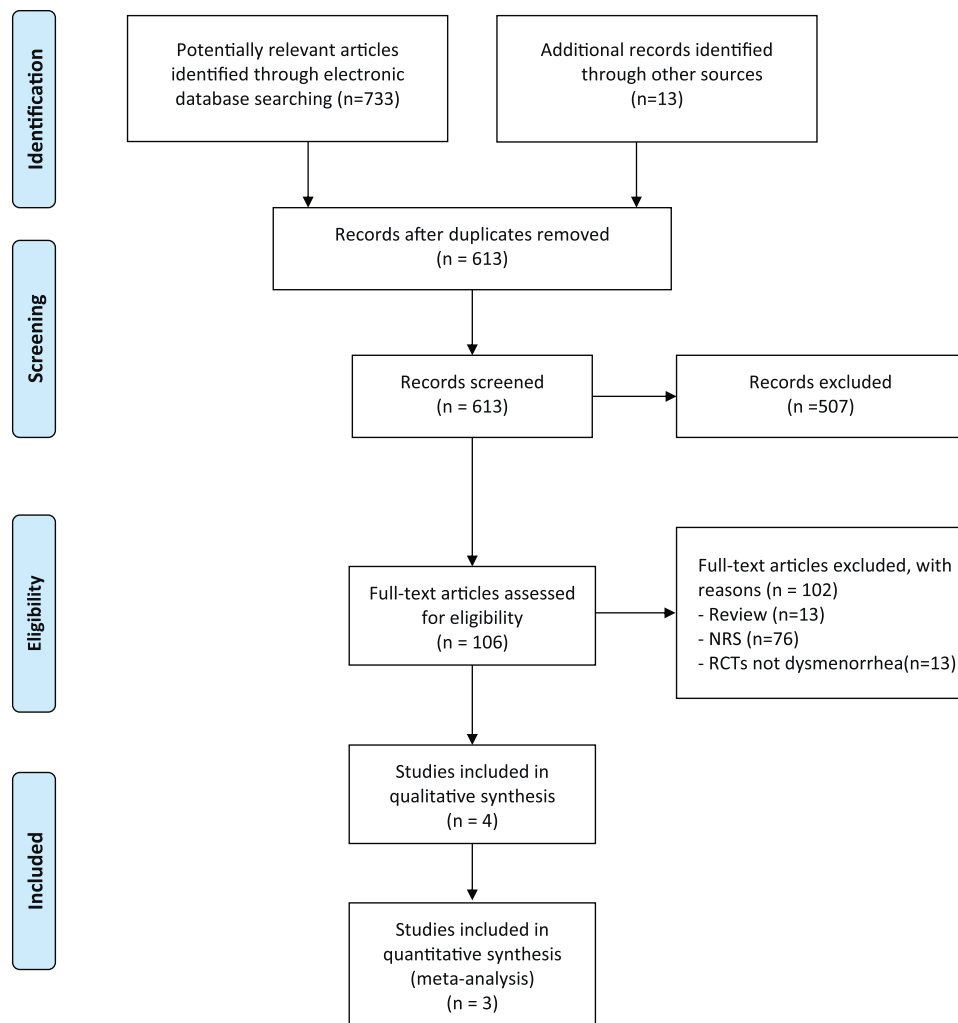
#### 2.3.4. Types of outcome measurements

The primary outcome measurements were reduction of menstrual pain only during the intervention as measured by visual analogue scale (VAS) or other validated scales and response rate of

**Table 1**  
Summary of randomized clinical studies of Danggui Shaoyao San (DSS) for primary dysmenorrhea.

First author (year) [Ref] Country	Sample size; age (yrs) duration of disease (yrs)	Intervention group (Regime)	Control group (Regime)	Main outcomes	Result	Authors' conclusion	Adverse events
Kotani (1997) [34] Japan	40 14–45 >1	(A) DSS (2.5 g, 3 times daily, 2 cycles, $n = 20$ ), plus p.r.n diclofenac (25 mg, upto 100 mg daily)	(B) Placebo (Oral, 2 cycles, $n = 20$ ), plus p.r.n diclofenac (25 mg, upto 100 mg daily)	1) Pain (10 VAS) 2) Diclofenac consumption	1) MD, $-2.31$ ( $-3.21$ to $-1.42$ ) 2) MD, $-4.47$ ( $-6.20$ to $-2.73$ )	'...DSS is effective for... dysmenorrhea...'	n.r.
Wu (2006) [33] China	90 (A) 19.3/ (B) 18.8 (A) 3.8/ (B) 4.2	(A) Modified DSS (300 ml, 2 time daily, 3 cycles, $n = 45$ )	(B) WM (Oral, ibuprofen, 200 mg, 3 times daily, 3 cycles, $n = 45$ )	Response rate	RR, 1.46 (1.15 to 1.87), $P = 0.002$	'Modified DSS for treating primary dysmenorrhea had good curative effect.'	n.r.
Peng (2010) [32] China	203 (A) 20.4; (B) 20.2 (A) 3.4/ (B) 3.5	(A) Modified DSS (n.r., 1 times daily, 3 cycles, $n = 102$ )	(B) WM (Oral, ibuprofen, 0.3 g, 2 times daily, 3 cycles, $n = 101$ )	Response rate	RR, 1.12 (1.00 to 1.26), $P = 0.04$	'...dysmenorrhea...with Modified DSS is remarkable and safely...'	Nausea (B:4); abdominal pain (B:5)
Ling (2011) [31] China	102 (A) 17.4/ (B) 18.2 (A) 5.2/ (B) 4.9	(A) Modified DSS (200 ml, 2 times day, 3 cycles) plus Moxa (30 min, once daily) ( $n = 51$ )	(B) WM (Oral, fenbide, 300mg, 2 times daily, 3 cycles, $n = 51$ )	Response rate	RR, 1.47 (1.17 to 1.84), $P = 0.001$	'Modified DSS on primary dysmenorrhea is significantly effective...'	n.r.

MD: mean difference; n.r.: not reported; RR: risk ratio; WM: western medicine.



**Fig. 1.** Flow chart of trial selection process. NRS: non randomized studies; RCT: randomized clinical trial.

symptom reduction. The secondary outcomes were adverse events (AEs), additional use of medication, and quality of life (QoL).

#### 2.4. Data extraction and risk of bias

All titles and abstracts of studies retrieved from the electronic searches were reviewed by three authors (HWL, JHJ and KJK), who selected the relevant articles by title and abstract. Hard copies of each publication were independently reviewed by the three authors to determine their inclusion based on the criteria (HWL, JHJ and THK). Additionally, we used GRADEpro software in the Cochrane Systematic Review to create a Summary of Findings table. Any disagreements were resolved by discussion among the three authors (HWL, JHJ and KJK) and an arbiter (MSL). The authors of the included studies were contacted for clarification, if necessary. Two authors (HWL and JHJ) extracted data from the included trials. The risk of bias was assessed using the assessment tool for “risk of bias” from the Cochrane Handbook version 5.1.0 [30], which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. We used L, U, and H as a key for the judgements, with “Low” (L) indicating a low risk of bias, “Unclear” (U) indicating that the risk of bias was unclear, and “High” (H) indicating a high risk

of bias. Another author (MSL) acted as an arbiter for unresolved disagreements.

#### 2.5. Data synthesis

All statistical analyses were performed using Rev Man (the Cochrane Collaboration) software, version 5.1.0. For dichotomous data, we present the treatment effect as relative risk with 95% confidence intervals (CIs). For continuous data, we use the mean difference (MD) with 95% CIs to present the treatment effect. We have converted other forms of data into MDs. If appropriate, we then pooled the data across the studies using random effects models. The chi-square test and the Higgins  $I^2$  test were used to assess heterogeneity.

### 3. Results

#### 3.1. Description of included trials

The searches identified 746 potentially relevant studies, of which three met our inclusion criteria (Fig. 1). The key data from all included RCTs are summarized in Table 1. Three RCTs originated from China [31–33] and one from Japan [34]. The three trials evaluated 435 women with primary dysmenorrhea. Modified DSS was used alone in three trials [31–33], and DSS was combined with

**Table 2**  
Composition of Danggui Shaoyao San (DSS) of included studies.

First author (year) [ref]	Formula	Composition of formula	
		Main composition of formula	Add-on composition of formula according to pattern identification/syndrome differentiation
Kotani (1997) [34]	DSS	Angelicae Radix Paeoniae Radix Poria Sclerotium Atractylodis Rhizoma alba Alismatis Rhizoma Cnidii Rhizoma (in the ratio: 3:4:4:4:4:3)	N/A
Wu (2006) [33]	Modified DSS	Angelicae Sinensis Radix 10–20 g, Cnidii Rhizoma 15–30g, Paeoniae Radix 15–30g, Paeoniae Radix Rubra 10–20 g, Poria Sclerotium 10–20 g, Alismatis Rhizoma 10–20 g, Atractylodis Rhizoma alba 10–20 g, Linderae Radix 10–20 g, Cyperii Rhizoma 10–20 g, Corydalis Tuber 10–20 g, Glycyrrhizae Radix et Rhizoma 5–10 g	Cold pain: Cinnamomi Cortex n.r., Foeniculi Fructus n.r. Blood stasis of pain: Persicae Semen 5–10 g, Carthami Flos 10–20 g, Distending pain: Curcumae longae Radix 10–20 g, Meliae Fructus 10–20 g Stabbing pain: Astragali Radix 10–20 g, Codonopsis Radix 10–20 g
Peng (2010) [32]	Modified DSS	Angelicae Sinensis Radix 15 g, Paeoniae Radix 20 g Cnidii Rhizoma 12 g, Atractylodis Rhizoma alba 15 g, Alismatis Rhizoma 10 g, Poria Sclerotium 15 g Cinnamomi Ramulus 10 g Cyperii Rhizoma 12 g Glycyrrhizae Radix et Rhizoma 8 g Codonopsis Pilosulae Radix 20 g	Yang deficiency with yin exuberance: Aconiti Lateralis Radix Preparata 10 g, Cinnamomi Cortex 6 g, Qi deficiency: Astragali Radix 30 g, Codonopsis Radix 20 g, Blood stasis: Persicae Semen 10 g, Carthami Flos 10 g, Yin deficiency with yang hyperactivity: Dioscoreae Rhizoma 20 g, Coicis Semen 20 g,
Ling (2011) [31]	Modified DSS	Paeoniae Radix 10–40 g, Cnidii Rhizoma 10–25 g Angelicae Sinensis Radix 10–25 g Poria Sclerotium 10–25 g Alismatis Rhizoma 10–25 g Atractylodis Rhizoma alba 10–25 g Leonuri Herba 10–30 g Linderae Radix 6–15 g Cyperii Rhizoma 6–15 g Glycyrrhizae Radix et Rhizoma 5–10 g	Pain: Paeoniae Radix n.r., Linderae Radix n.r. Blood stasis: Leonuri Herba n.r., Angelicae Gigantis Radix n.r. Dampness toxin: Hoelen n.r., Alismatis Rhizoma n.r. Distending pain: Cnidii Rhizoma n.r., Cyperi Rhizoma n.r. Corydalis yanhusuo n.r., Meliae Fructus n.r. Blood stasis, heat pattern: Paeoniae instead of Paeoniae Radix n.r., Field pennycress n.r., Sargendoxa Cuneate n.r., Taraxaci Herba n.r., Smilacis Rhizoma n.r. Blood stasis, cold pattern–Evodiae Fructus n.r., Foeniculi Fructus n.r., Cinnamomi Cortex n.r. Qi deficiency: Astragali Radix n.r., Codonopsis Radix n.r.

DSS: Danggui Shaoyao San; N/A: not available.

diclofenac in one trial [34]. The details of the formula compositions of DSS are listed in Table 2.

DSS was compared with two types of analgesic, including ibuprofen [32,33] and fentanyl [31] in three trials and one trial used placebo as a control [34]. The duration of the trials lasted from two to three menstruation cycles. Three RCTs [31–33] used the response rate for each intervention by practitioner and it was generally divided into four categories including (1) recovery, (2) marked improvement, (3) improvement, and (4) no change. One trial employed VAS to measure pain.

### 3.2. Risk of bias

The risk of bias was high in all of the included trials (Fig. 2). Only one trial was described as randomized [32], while two RCTs used sequence generated by admission order [31,33]. The other RCT did not report the random sequence generation method [34]. None of the RCTs mentioned allocation concealment or blinded outcome assessment. Most of the included trials had a high risk of bias due to not blinding patients and practitioners, except for one RCT [34]. Drop-out cases were reported by three RCTs [31,33,34], while the last trial did not report [32]. None of the trials had published protocols and they all had an unclear risk of bias in selective outcome reporting.

### 3.3. Outcome measurements

#### 3.3.1. DSS vs. analgesics

Three RCTs tested the effects of DSS compared to analgesics in women with dysmenorrhea [31–33]. Three RCTs showed a favourable effect of DSS in response rate. A meta-analysis also showed favourable effects ( $n = 395$ , RR: 1.31, 95% CI: 1.06 to 1.63,  $P = 0.01$ ) with high heterogeneity ( $I^2 = 73%$ ) (Fig. 3).

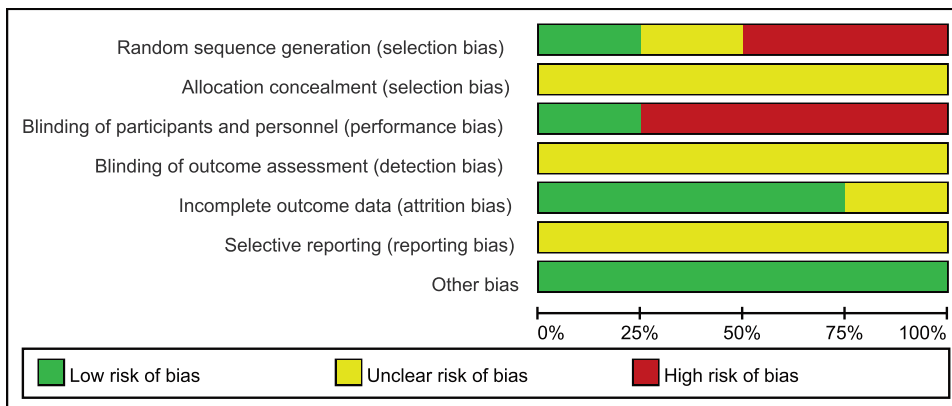
#### 3.3.2. DSS vs. placebo

One study compared the effects of DSS with placebo treatment on pain on VAS and total consumption of diclofenac sodium [34]. The results showed favourable effects of DSS on both outcome measures.

#### 3.3.3. Adverse events (AEs)

Only one trial assessed AEs [32], reporting abdominal pain and nausea as AEs that occurred in the conventional medicine group. The other three trials did not assess AEs. No trials assessed QoL as an outcome.

(A) Risk of bias graph



(B) Risk of bias summary

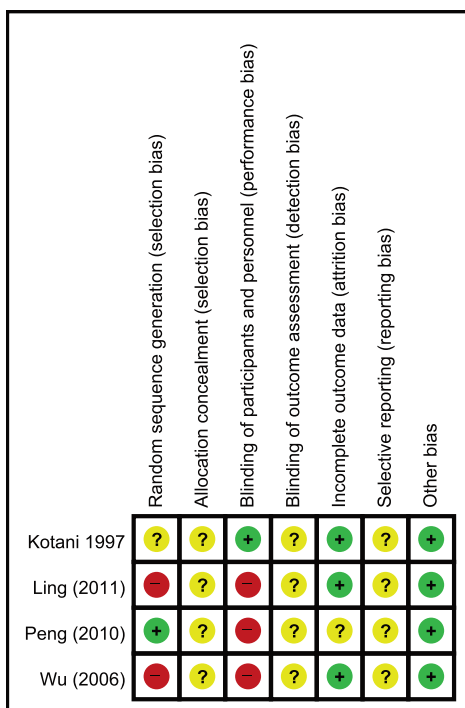


Fig. 2. (A) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies; (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

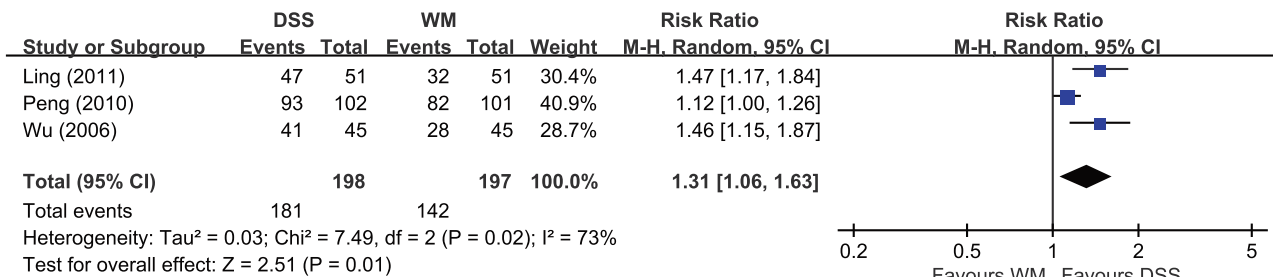


Fig. 3. Forest plot of the effects of DSS for response rate. DSS: Danggui Shaoyao San; WM: western medicine (analgesics).

4. Discussion

Few rigorous trials testing the effects of DSS for dysmenorrhoea are currently available. Our systematic review and meta-analysis

provide suggestive evidence of the superiority of DSS over analgesics and placebo treatment (Table 3). The quality of evidence for this finding was low to moderate because of a high risk of bias. The quality of reporting was generally poor in the included RCTs.

**Table 3**  
Summary of Findings table.

Danggui Shaoyao San compared to western medicine for dysmenorrhea						
Outcomes	Illustrative comparative risks <sup>a</sup> (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		Western medicine	Danggui Shaoyao San			
Response rate	Study population 721 per 1000 Moderate		RR 1.31 (1.06 to 1.63)	395 (3 studies)	⊕⊕⊖⊖ low <sup>b,c</sup>	
		944 per 1000 (764 to 1000)				
Danggui Shaoyao San compared to placebo for dysmenorrhea						
Outcomes	Illustrative comparative risks <sup>a</sup> (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		Placebo	Danggui Shaoyao San			
Pain	VAS		The mean pain in the intervention groups was 2.31 lower (3.21 to 1.42 lower)	40 (1 study)	⊕⊕⊕⊖ moderate <sup>b</sup>	
Total consumption of diclofenac sodium			The mean total consumption of diclofenac sodium in the intervention groups was 4.47 lower (6.20 to 2.73 lower)	40 (1 study)	⊕⊕⊕⊖ moderate <sup>b</sup>	

CI: Confidence interval.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

<sup>a</sup> The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).<sup>b</sup> Risk of bias are high or uncertain in several domain of most of studies.<sup>c</sup> Statistical heterogeneity is high.

Furthermore, the total number of RCTs and the total sample size included in our analysis were not sufficient to draw firm conclusions.

Our review aimed to update and complete the evidence by adding recent RCTs of DSS for dysmenorrhea. Compared to previous reviews [18], we identified two new RCTs of DSS [31,32] and successfully updated the evidence. The results of our review were similar to the results of the existing review. The previous review provided limited evidence for all types of CHM for primary dysmenorrhea and failed to consider different types of CHM or traditional East Asian medicines. Furthermore, the previous review did not use systematic approaches or register the title in PROSPERO for transparency.

Only one of the included trials reported random sequence generation methods [32], while the other two used inappropriate sequence generation [31,33]. Concealment of treatment allocation was not reported in any of the studies. Only one of the included trials blinded patients and practitioner [34]. Trials with inadequate blinding and inadequate allocation concealment are likely to show exaggerated treatment effects [35–38]. Most of the trials had small sample sizes, which undermines the possibility of drawing a meaningful conclusion [36]. No power analysis was included. None of the included trials used an intention-to-treat analysis. One trial has unclear risk of bias on incomplete outcome, reporting 203 enrolled patients but only 75 patients with response percentages [32]. We pooled the results with response percentages, so even if the number of 75 patients is accurate, it would not influence our conclusion.

Four of the reviewed trials reported no AEs related to DSS, while AEs have been reported in conventional medicine [32]. However, AEs were not the focus of this review and would require further research.

This systematic review had several limitations. First, most of the included trials used the response rate as outcome variable, which lacks reliability and validity and poses the risk of possible bias from the practitioner. Future trials should use international standards in the evaluation of treatment effects. Second, all of the RCTs were conducted in East Asian countries and the generalization of these results may be limited [39,40]. Third, failure to follow CONSORT reporting guidelines increases the risk of bias even though rigorous trials were performed.

In conclusion, the existing trials showed favourable effects of DSS for the management of primary dysmenorrhea. However, owing to the small number of studies and the high risk of bias, the evidence is limited. Further rigorous RCTs are needed to overcome the many limitations of the current evidence.

### Conflict of interest

None declared.

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## Provenance and peer review

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