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Review article

Efficacy of Prasaplai for Treatment of Primary Dysmenorrhea: a Meta-Analysis

Wiraphol Phimarn[1*], Bunleu Sungthong[2], Kritsanee Saramunee[1]

[1]Social Pharmacy Research Unit, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham, Thailand.
[2]Pharmaceutical Chemistry and Natural Products Research Unit, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham, Thailand.

Abstract

Prasaplai is used in Thai traditional medicine for treatment of primary dysmenorrhea; however, clinical evidence is limited regarding the efficacy of Prasaplai for primary dysmenorrheal outcomes. This study has constituted a systematic review and meta-analysis to evaluate Prasaplai as an effective treatment for primary dysmenorrhea. Randomized controlled trials were retrieved and identified through electronic searches (PubMed, CINAHL, Cochrane Central Register of Controlled Trials, SCOPUS, Science Direct, and ThaiLis publications until May 2017). A hand search for relevant trials was also conducted. Quality of the selected trials was assessed using Jadad's scoring and A Cochrane Risk of Bias Assessment Tool. Studies were recruited for the meta-analysis if 1) they were randomized controlled trials, 2) participants were diagnosed with primary dysmenorrhea, and 3) a pain score was included. Related outcomes and adverse events were also evaluated for all groups. Four randomized controlled trials met the criteria, totaling 460 participants. Results revealed that Prasaplai significantly improved pain scores. The pooled mean difference was -1.24 (95% CI -1.90 to -0.59; p = 0.0002). The results did not indicate significant effects of Prasaplai on menstrual characteristics and associated symptoms, compared with NSAIDs; however, participants receiving Prasaplai reported a low frequency of adverse effects compared to the NSAID group. Current evidence suggests that Prasaplai improved pain associated with primary dysmenorrhea. Prasaplai had no effect on menstrual characteristics and associated symptoms. Additional rigorously-designed trials with larger sample sizes are warranted to confirm the effects of Prasaplai on primary dysmenorrhea and related outcomes.

Keywords: meta-analysis; pain; Prasaplai; primary dysmenorrhea

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Introduction

Dysmenorrhea is a common condition experienced by post-pubescent menstruating women. Over 50% of women experience mild pain during their menstrual cycle while approximately 15% require complete rest and are unable to continue with normal activities [1,2]. Primary dysmenorrhea refers to common menstrual cramps that are caused by painful uterine contractions following a significant increase in prostaglandin levels during the menstrual cycle [2].

Prasaplai is a medicinal plant preparation used in Thailand, described as a Thai herbal preparation in the Herbal medicine product of the National List of Essential Medicines for treatment of primary dysmenorrhea and adjusting the menstrual cycle [3-6]. The Prasaplai preparation consists of ten herbs (*Acorus calamus* L., *Allium sativum* L., *Citrus hystrix* DC, *Curcuma zedoaria* Roscoe, *Eleutherine palmifolia* (L.) Merr, *Nigella*

*Corresponding author: wiraphol.p@msu.ac.th

sativa L., *Piper chaba* Hunter, *Piper nigrum* L., *Zingiber cassumunar* Roxb., *Zingiber officinale* Roscoe) and two chemical compounds (sodium chloride and camphor) [6]. The major components of standardized Prasaplai preparations (100 g) were reported to be (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-ol (0.176 g) and cis-3-(2',4',5'-trimethoxyphenyl)-4-[9(E)-2''',4''', 5'''-trimethoxystyryl]cyclohex-1-ene (0.075 g), both obtained from the major plant component *Z. cassumunar*; 6'-7'-dihydroxybergamotin (0.012 g) from *Citrus hystrix*; thymoquinone (0.005 g) from *Nigella sativa*, and piperine (0.211 g) from *Piper retrofractum* and *Piper nigrum* [7]. Storage alters the chemical composition of the herbal remedy, leading to the generation of new compounds, namely, (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl palmitate, (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl oleate, and (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl linoleate [6].

The major pharmacological activity of Prasaplai is anti-inflammatory effect. Chemical constituents in the traditional remedy are known to inhibit the activity of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and other inflammatory mediators [8]. Moreover, Prasaplai inhibits smooth muscle contraction and promotes uterine relaxation [4].

A recent clinical trial concluded that Prasaplai improved pain symptoms in primary dysmenorrhea; however, there was no meta-analysis to quantitatively summarize the evidence. Therefore we have undertaken a meta-analysis which aimed to examine the efficacy of Prasaplai as a treatment for primary dysmenorrhea.

Methods

Data sources and search strategies

To identify studies that investigated the effects of Prasaplai on dysmenorrhea, we conducted electronic searches in PubMed, CINAHL, Cochrane Central Register of Controlled Trials, SCOPUS, Science Direct, and ThaiLIS together with hand searching of the reference lists. Inclusive dates of publications ranged from the inception date of each database to May 2017. Relevant studies were identified using the combination of the following search terms: Prasaplai and primary dysmenorrhea OR dysmenorrhea OR pain relief, improvement, and adverse. To ensure thoroughness of the search, our study reviewed the reference lists from the retrieved articles and where possible, searched these lists for relevant unpublished works. No language restrictions were imposed. Finally, authors were contacted to obtain additional or missing information regarding the trials they had conducted.

Study selection

Studies on the clinical efficacy of Prasaplai for primary dysmenorrhea were selected for inclusion using the following criteria: (1) the study was a randomized controlled trial; (2) the study investigated the effects of Prasaplai on primary dysmenorrhea; (3) subjects received a standardized oral dose of Prasaplai extract in which the chemical composition or bioactive marker was identified or traceable compared with NSAIDs; (4) the study reported pain score as an outcome, with the duration of the study being at least one month of intervention.

Data extraction and study quality assessment

Two reviewers (Wiraphol Phimarn and Bunleu Sungthong) independently assessed the eligibility of trials. Data extracted by two reviewers (Wiraphol Phimarn and Bunleu Sungthong) using the CONSORT statement for reporting herbal medicine interventions [9] included participants' characteristics, duration of study, intervention, comparators, and outcomes measurement. A third opinion was sought from the other author (Kritsanee Saramunee) if any disagreement between Wiraphol Phimarn and Bunleu Sungthong arose. In cases where the original publication was missed data, we attempted to obtain the information by contacting the authors.

The quality of included studies were assessed according to a Cochrane Risk of Bias Tool (ACROBAT) and A Jadad's scale [10,11]. The Jadad scoring system provided guidelines for preliminarily evaluation of the methodological approach of the randomized controlled trial (RCT). Five items of a RCT were taken into account: (1) statement of randomization, (2) appropriateness of generating a randomized sequence, (3) use of double-blinding, (4) description of double-blinding method, and (5) details of withdrawals and dropouts. Studies that met at least three out of the five criteria were classified as high quality. Articles with a score of less than three indicated a low quality study, or a study with a high risk of bias [10]. Thereafter, selected studies were individually assessed for

risk of bias using ACROBAT. Each study was evaluated by considering the domains of sequence generation, allocation concealment, blinding of participants/personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Studies were classified as possessing low, uncertain, or high risk of bias according to the criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions [11]. Two authors (Wiraphol Phimarn and Bunleu Sungthong) independently performed the data extraction and quality assessment. A third opinion (Kritsanee Saramunee) was sought if a disagreement arose between two primary researchers.

Data analysis

The primary outcome measurement was pain score. Mean differences in measurements were calculated as follows: 1) pain score at the end of follow-up in the Prasaplai group minus pain score at baseline in the Prasaplai group, 2) pain score at the end of follow-up in the comparator group minus pain score at baseline in the comparator group, 3) SDs of the mean difference were calculated using the formula SD = square root $(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})$, assuming a correlation coefficient (R) = 0.5 [12]. The efficacy and laboratory results of the HS-treated group compared with the comparison group were statistically tested using the mean difference (MD) and 95% confidence interval (CI). The results of individual studies using random effect model was combined when the heterogeneity using Q-statistic was observed at significant level of 0.1; otherwise, the fixed effects model was applied. The statistical analysis was undertaken with Review Manager (Revman®) version 5.3 (Cochrane Collaboration). Outcome assessment with regard to the menstrual characteristics, associated symptoms, and safety of Prasaplai was also considered and reported as relative risk (RR) with 95% CI in this meta-analysis. To identify undue influence of individual effect estimation, sensitivity analysis was performed by systematically removing each individual study from the meta-analysis and recalculating and estimating the effect from the remaining studies. Finally, a funnel plot was performed to assess publication bias.

Results and Discussion

Description of studies

Figure 1 delineates the screening procedure and indicates the number of trials identified and selected for inclusion. The rigorous search paradigm identified 52 articles as meeting inclusion criteria. Seven of these 52 were duplicates resulting in 45 trials being eligible for this analysis. Thirty-nine studies conducting in animals (6) and in vitro experiments (33) were excluded from the meta-analysis. Therefore, four RCTs totaling 460 participants were included in the review. The primary features of the RCTs have been summarized in table 1. Information was extracted from each study following the CONSORT statement for reporting herbal medicine interventions. All studies [13-16] were conducted in Thailand. Three studies were conducted as randomized controlled trial (RCT) design describing a full statement of the blinding and allocation concealment in the methods.

Therefore, only two studies [15,16] earned a Jadad score of 5/5. All of the included articles reported the Latin binomial of individual ingredient herbs. Only one study did not explain the allocation concealment or the blinding between two groups. The method for authentication of raw materials was reported in all trials.

The majority of Prasaplai RCTs used 3,4-dimethoxyphenylbutadiene as their marker, with 70% ethanol as solvent. Only two trials reported 4% 3,4-dimethoxyphenylbutadiene as the bioactive marker of Prasaplai (table 2). Study length ranged from two to ten months. All studies used NSAIDs as comparators. Three studies used mefenamic acid [14-16] and one study used ibuprofen [13]. Most subjects had received NSAIDs prior to the study. For the outcomes measurement, all trials used pain scores where the maximum score was 10. However, only Chakchai [13] and Sasum [15] reported the number of participants with normal or abnormal menstrual characteristics such as whether the color of menstrual bleeding was dark red or bright red and whether blood clots were observed during menstrual periods. Three studies [13,15,16] reported associated symptoms during the menstrual period. In all four studies all of the outcomes assessments were based on the patient's judgment and self-reporting [13-16].

The methods used for monitoring clinical outcomes and adverse effects were also examined.

All included studies used a checklist to generate a pain score. The Chakchai [13] and Sasum [15] studies regularly monitored menstrual characteristics during the menstrual periods by utilizing a checklist with four categories that included (1) bright red, (2) dark red, (3) dark red with few blood clots, and (4) dark red with a moderate to high number of blood clots. In four trials the adverse effects were regularly monitored and reported, but only Chakchai [13] and Sasum [15] indicated the use of a checklist and self-reporting by participants. Kamalashiran et al. [14] and Sriyakul et al. [16] did not state the methods for reporting adverse effects.

Table 1. Characteristics of included studies

Authors	Design	Duration of study	Sample size (drop-outs)	Treatments (N)	Comparators (N)	Outcomes	Method of monitoring	Jadad score	Side-effects
Kritsada, 2008 [13]	RCT	2 months	60 (0)	Prasaplai extract capsule (30)	Ibuprofen (30)	Pain Menstrual characteristic Adverse effects	Pain score Checklist Spontaneous report	2	Nausea
Sasum, 2010 [15]	DRCT	5 months	150 (16)	Prasaplai extract capsule 250 mg x3 (67)	Mefenamic acid 250 mg x3 (67)	Pain Menstrual characteristic Adverse effects	Pain score Checklist Checklist	5	Nausea, epigastric pain
Sriyakul, 2012 [16]	DRCT	10 months	207 (0)	Prasaplai extract capsule 250 mg x3 (103)	Mefenamic acid 500 mg x3 (104)	Pain Adverse effects	Pain score Not stated	4	Nausea, epigastric pain, dizziness, Tremble
Kamalashiran, 2012 [14]	DRCT	7 months	64 (5)	Prasaplai extract capsule 200 mg 2 capsules x3 (32)	Mefenamic acid 500 mg x3 (27)	Pain Adverse effects	Pain score Not stated	5	Nausea

Remark: RCT : randomized controlled trial; DCRT : double blind randomized controlled trial; x3 : three times a day

Table 2. The standardization of Prasaplai preparation

Authors	Solvent extraction	Standard compound
Kritsada, 2008 [13]	70% ethanol	(E)-4-(3,4-dimethoxyphenyl)but-3-en-1ol (E)-1(3,4-dimethoxyphenyl)butadiene
Sasum, 2010 [15]	70% ethanol	(E)-4-(3,4-dimethoxyphenyl)but-3-en-1ol
Sriyakul, 2012 [16]	70% ethanol	3,4 dimethoxyphenylbutadiene
Kamalashiran, 2012 [14]	70% ethanol	3,4-dimethoxyphenylbutadiene

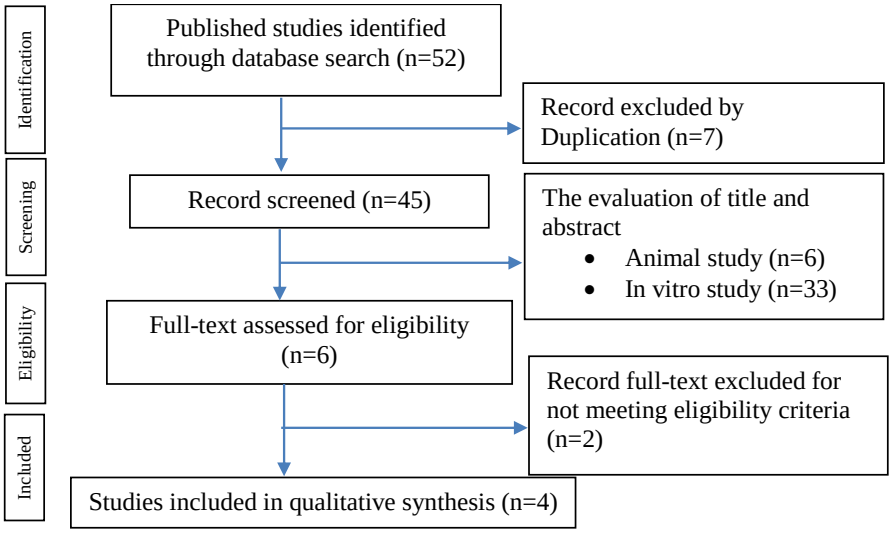

Figure 1. Trial flow depicting the process for selection of studies included in this analysis

Risk of bias

Based on their randomization and reporting methods, only one of the included trials was found to have a high risk of bias [13]. Risk of bias of the selected studies was assessed according to the following criteria: 1) random sequence generation, 2) allocation concealment, and 3) blinding of participants, personnel, and outcomes evaluator. Three studies were considered to be high quality based on the Cochrane Handbook for Systematic Reviews of Interventions [17] (figure 2).

Study, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kritsada, 2008 [13]	U	H	H	H	L	L	U
Sasum, 2010 [15]	L	L	L	L	L	L	U
Sriyakul, 2012 [16]	L	U	L	L	L	L	U
Kamalashiran, 2012 [14]	L	L	L	L	L	L	U

Figure 2. Risk of bias diagram derived from individual studies (L = low risk, H = high risk, and U = unclear)

Effect on pain score

The four Prasaplai studies involved a total of 460 primary dysmenorrheal participants [13-16]. The effects of Prasaplai on pain relieve was reported as being greater than the effect of NSAIDs on pain. The pooled mean difference was -1.24 (95% CI -1.90 to 0-0.59; p = 0.0002). Heterogeneity was detected in this sensitivity analysis (I^2 = 94%, p < 0.00001) (figure 3).

Effect on menstrual characteristics

The number of participants involved in the assessment of menstrual characteristics was reported in two trials [13,15]. Most participants reported their menstrual characteristics during the periods of menstruation as being dark red and dark red with a few blood clots. There were no significant differences in the number of participants when comparing the Prasaplai group with the NSAIDs group. The pooled relative risk was 0.99 (95% CI 0.81, 1.21; p = 0.91). Heterogeneity was detected in this sensitivity analysis (I^2 = 63%, P=0.10) (figure 4).

Effects on associated symptoms

A pooled meta-analysis indicated that the associated symptoms in participants treated with Prasaplai were not significant from those in the NSAIDs group: weakness (RR = 0.97; 95% CI: 0.89, 1.06; p = 0.55), fatigue (RR = 0.83; 95% CI: 0.43, 1.60; p = 0.58), mood alteration (RR = 0.96; 95% CI: 0.81, 1.15; p = 0.69), diarrhea (RR = 0.88; 95% CI: 0.62, 1.25; p = 0.48), and headache (RR = 0.82; 95% CI: 0.59, 1.14; p = 0.40). A statistically significant heterogeneity was detected in accordance with mood change outcomes (figure 5).

Adverse events

Adverse events were reported in four trials [13-16]. The pooled analyses indicated that the relative risk (RR) of adverse events among participants treated with Prasaplai were not different from the NSAIDs group (table 2). No severe adverse effects were reported in any of the included studies. The most frequently reported adverse events were related to gastrointestinal (GI) and central nervous system (CNS) side effects**.** Only one study [16] monitored some vital laboratory tests including liver function tests (AST, ALT, and ALP), blood urea nitrogen (BUN), serum creatinine, and complete blood count. However, all tests reported normal levels with no differences between individuals in the Prasaplai group and NSAIDs group.

Sensitivity analysis

The sensitivity analysis for all parameters illustrated a lack of difference regarding the one study removal approach and removal of one low quality study [13]. The pooled effect size did not differ with respect to the main outcomes.

Publication bias

We also generated funnel plots for all of the outcomes analyzed, using visual inspection of the plots to detect publication bias. Calculated effect sizes were found to be asymmetrical around the pooled effect size for pain score, associated symptoms, and adverse effects (figure 6).

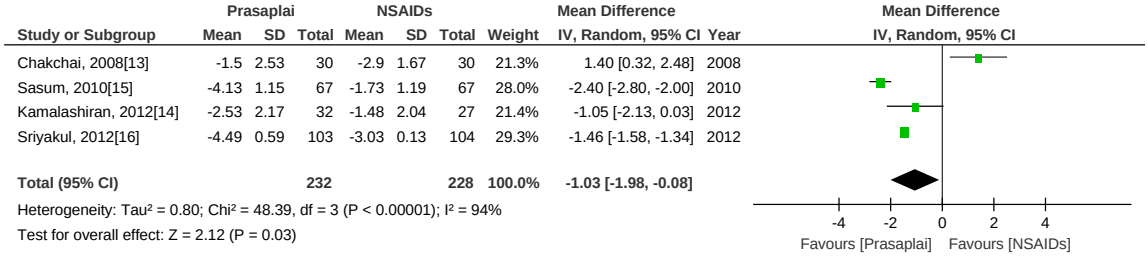

Figure 3. Forest plot showing comparison of Prasaplai vs NSAIDs with respect to pain score

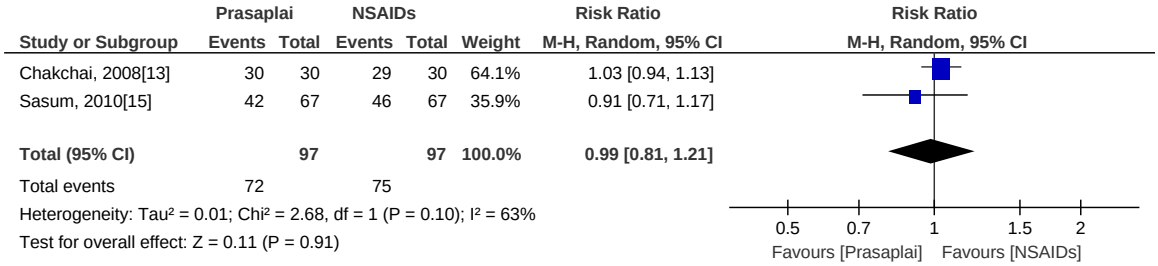

Figure 4. Forest plot showing comparison of Prasaplai vs NSAIDs with respect to menstrual characteristics

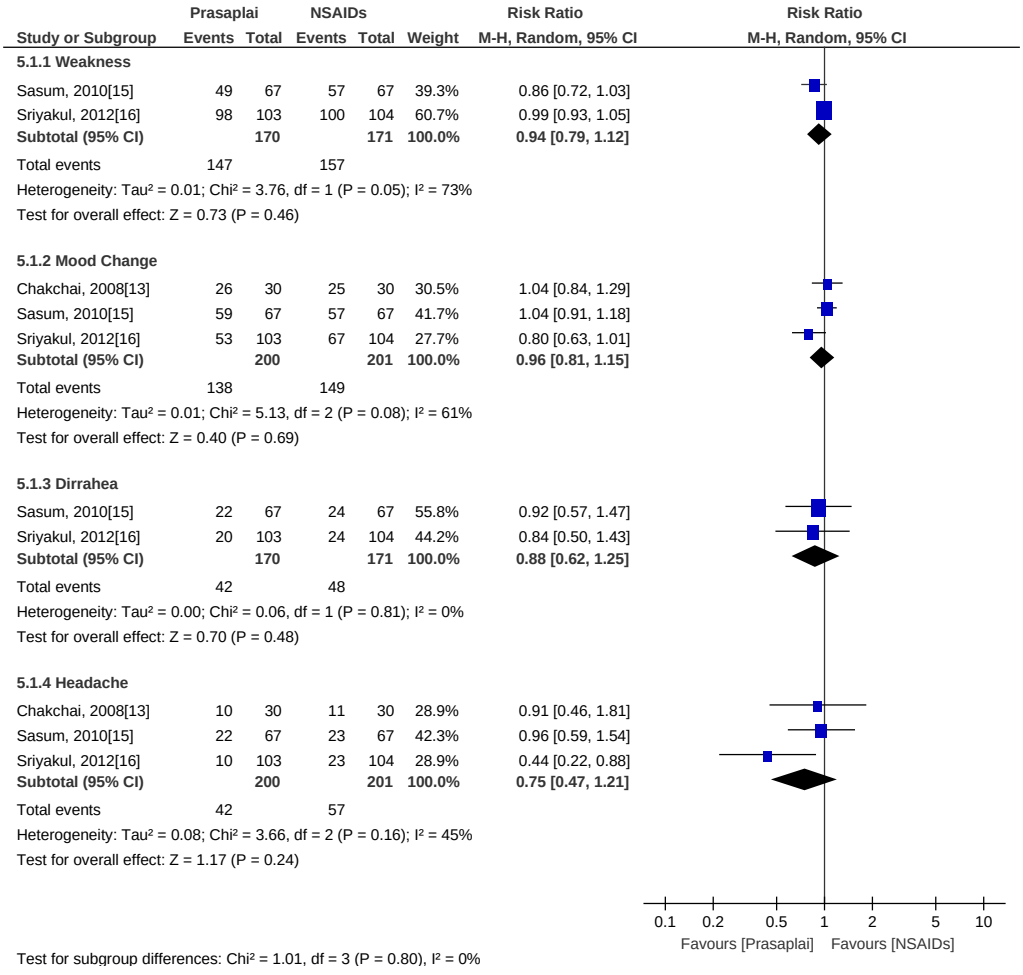

Figure 5. Forest plot comparing Prasaplai vs NSAIDs with respect to associated symptoms

Table 3. Adverse effects of Prasaplai vs NSAIDS

Adverse events	Risk ratio	95% CI	p^a	p^b
Nausea [13-16]	0.68	0.32 to 1.48	0.330	0.381
Gastrointestinal pain [15,16]	0.48	0.21 to 1.11	0.091	0.334
Epigastric burn [16]	8.08	1.03 to 63.44	0.051	N/A
Dizziness [16]	0.40	0.08 to 2.03	0.272	N/A
Tremble [16]	0.34	0.01 to 8.17	0.503	N/A

Remark: p^a: p-value of effect size; p^b : p-value of heterogeneity; N/A : Not applicable

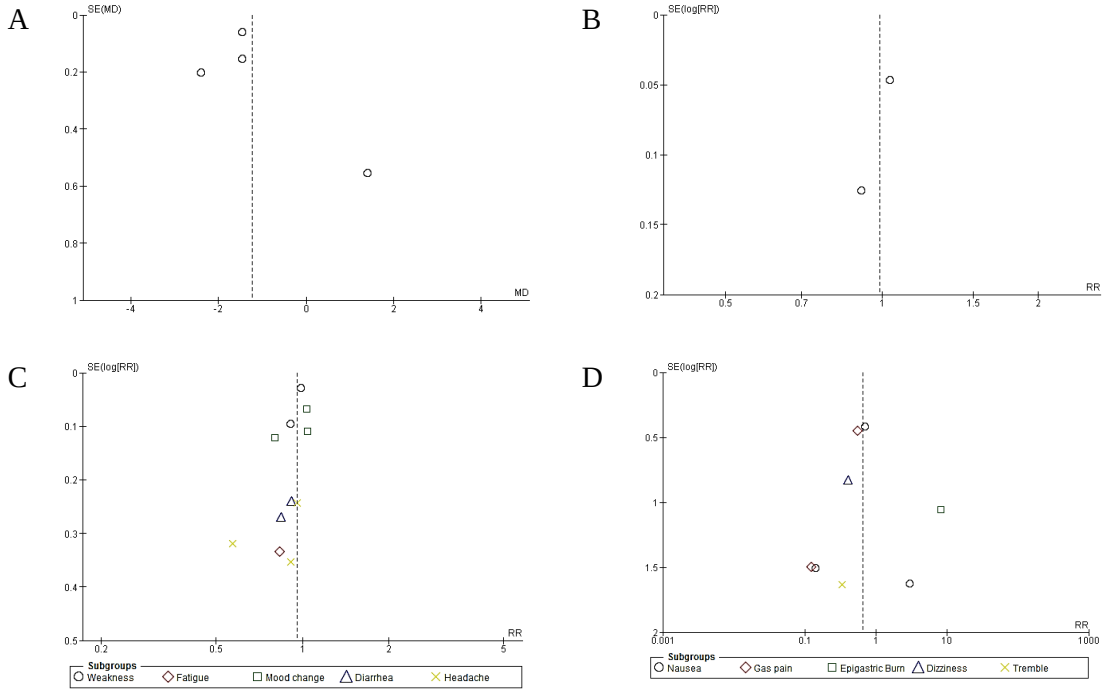

Figure 6. Funnel plots detailing publication bias in studies included in the meta-analysis of the effect of Prasaplai on (A) pain score, (B) menstrual characteristics, (C) associated symptoms, and (D) adverse effects.

To the best of our knowledge, this is the first meta-analysis examining data on Prasaplai efficacy derived from human studies. In this meta-analysis, Prasaplai significantly improved pain scores compared to NSAIDs. However, Prasaplai did not yield significant differences in menstrual characteristics and associated symptoms. Most of the previously published studies claimed that the mechanism of action underlying amelioration of primary dysmenorrhea by Prasaplai was a reduction of PG production by the endometrium. PGs derived from arachidonic acid and the cyclooxygenase pathway promote myometrial contractions. The mechanism of action of NSAIDs is to reduce cyclooxygenase activity and prevent PG production [4,18]. Another possible explanation for the positive finding reported for pain relief was inhibition of uterine motility mediated by acetylcholine, oxytocin, and PGE2 [6]. Experiments conducted in animals revealed that some components of Prasaplai exerted effects on smooth muscle. One example of this was decreased uterine motility in pregnant and non-pregnant rats and guinea pigs following administration of the water extract of *Allium sativum*. The *Nigella sativa* seed, which is enriched in a volatile oil, was found to inhibit rat uterine contractions; an extract of *Zingiber cassumunar* also promoted uterine relaxation. The inhibition of smooth muscle contraction by *Curcuma zedoaria* and *Acorus calamus* has also been reported [4,19]. Support for this notion was provided in a study by Rangsimantuchat et al. [20], in which it was confirmed that Prasaplai exhibited spasmolytic activity on rat uterine muscle. In addition, three artificial fatty acid esters found during storage were charactrized as

(E)-4-(3,4-dimethoxy-phenyl) but-3-en-1-yl linoleate, (E)-4-(3,4-dimethoxy-phenyl)but-3-en-1-yl oleate, and (E)-4-(3,4-dimethoxy-phenyl)but-3-en-1-yl palmitate, which had contributed to adjust the menstrual cycle [21].

Two trials [13,15] involving 194 participants reported menstrual characteristics, but there were no differences between the Prasaplai group and the NSAIDs group. While previous studies [3,4] reported that Prasaplai improved menstrual characteristics by regulating menstrual blood flow, the mechanism of this phenomenon was unclear. Published results failed to show that menstrual characteristics and associated symptoms improved in the Prasaplai-treated group. We also carried out a sensitivity analysis, in which the sources of heterogeneity were eliminated. The results of the sensitivity analysis did not change the significance of the calculated effect size.

This review found Prasaplai preparations to be tolerated. Adverse events reported in the included studies were often mild. Most of the reported adverse events affected the GI and CNS systems, but were not significantly different from adverse events reported after administration of NSAIDs. In addition, there were no reported changes in laboratory parameters such as those derived from renal and liver function tests.

Several limitations of this meta-analysis included 1) the relatively small number of trials that met the inclusion criteria, 2) the existence of heterogeneity among the included trials, and that 3) all of the studies included were self- reported by themselves in the pain, menstrual characteristic outcomes, and adverse effects. Self-reporting of pain, menstrual characteristics, and adverse effects is very subjective, which increases the chance of measurement bias. However, the strength of our study lies within a comprehensive review of herbal preparation that employed a systematic review and meta-analysis. Most of the studies included in this meta-analysis utilized high-quality methodological approaches. Our analysis was strengthened by the use of two guidelines (the Jadad scale and ACROBAT) to screen studies and ensure adherence to the study selection criteria. Our analysis revealed that all of the included studies had standardized the amount of active ingredients derived from Prasaplai. It is therefore, very important that the active ingredient be quantified in order to standardize dosing with herbal products [22].

Conclusion

The current meta-analysis suggests that the use of Prasaplai improved pain in primary dysmenorrhea. Supplementation with this herbal preparation with other medications may offer an alternative for pain relief in primary dysmenorrheal. The adverse effects are mild and infrequent. However, because of the small number of participants, the high risk of bias of the available evidence, and the high degree of heterogeneity of results for menstrual characteristics and associated symptoms, additional high quality and large randomized controlled trials are warranted to better elucidate the effects of Prasaplai for treatment of primary dysmenorrheal.

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Author contributions

All authors contributed to the design and concept of the study, statistical analysis, collection and interpretation of the data. Wiraphol Phimarn and Bunleu Sungthong drafted the manuscripts. All authors critically revised the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

COX-1: cyclooxygenase-1; NSAIDs: nonsteroidal anti-inflammatory drugs; RCT: randomized controlled trial; ACROBAT: A

Cochrane Risk of Bias Assessment Tool; CI: confidence interval; RR: relative risk; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen; GI: gastrointestinal tract; CNS: central nervous system; PGs: prostaglandins