ORIGINAL ARTICLE

The Efficacy and Safety of Leard-Ngam Remedy Powder versus Mefenamic Acid for Relieving Primary Dysmenorrhea

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Background: Primary dysmenorrhea refers to uterine contractions and pain during menstruation. Leard-ngam remedy (LG) is listed as a Thai Herbal Medicine Product for the treatment of the menstrual period.

Objective: To study the efficacy and side effects of LG compared with mefenamic acid (MFA) for reducing menstrual pain in primary dysmenorrhea.

Materials and Methods: A randomized controlled trial was conducted at Thammasat University Hospital in women diagnosed with primary dysmenorrhea. The numerical rating scale (NRS) was used for the pain score assessment, which was scaled from 0 to 10. The LG group received two capsules of 1 g, three times a day before meals for three days. The MFA group received two capsules of 500 mg, three times a day after meals for three days. Matching placebo capsules before and after meals were to be taken the same way as the LG and MFA capsules. Both groups started from the first day of menstruation and were told to repeat the same treatment for the subsequent two menstrual cycles.

Results: Eighty-nine participants were enrolled, with 45 in the LG group and 44 in the MFA group. The groups had similar baseline demographic, clinical, and laboratory characteristics. Both drugs reduced menstrual pain when given for the first three days of the menstrual cycle. The mean pain scores in the first three months, as M1 to 3, were 5.22, 3.38, and 1.76 in the LG group versus 5.00, 4.16, and 2.24 in the MFA group on the first-, second-, and third-day period, respectively. They were not significantly different, and pain recurred when both drugs were stopped.

Conclusion: LG was effective and well tolerated in young women with primary dysmenorrhea.

Keywords: Primary dysmenorrhea; Thai Herbal Medicines

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Dysmenorrhea is defined as pain during the menstrual cycle and refers to uterine contractions during menstruation, resulting in pain in the lower abdomen and pelvic area. It falls under two main categories, primary and secondary. Primary dysmenorrhea is defined as menstrual pain that is not associated with macroscopic pelvic pathology, while secondary dysmenorrhea is defined as menstrual pain resulting from anatomic or macroscopic pelvic pathology. Of the two, primary dysmenorrhea is more common. Severe dysmenorrhea can have adverse effects on the quality of life in adolescent women, including a limitation in daily activities and an absence from school or work[1]. The main treatments are non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives. NSAIDs decrease menstrual pain by decreasing intrauterine pressure and lowering prostaglandin F2α (PGF2α) levels in menstrual fluid[2-4]. Supportive treatments include magnesium, calcium antagonists, vitamin B, vitamin E, and herb drugs, which can all reduce uterine contraction[5]. However, taking NSAIDs for a long time may have adverse effects, such as gastrointestinal disorders[6,7]. Thai traditional medicine is one of the pathways to natural healing and maintaining human health. Listed as a Thai traditional medicine in the Thai National List of Herbal Medicine Products, Leard-ngam (LG) remedy is known to be effective in primary dysmenorrhea[8]. A previous study reported that LG remedy reduced prostaglandins, the leading cause of uterine pain, with a mean IC_{50} of

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8.69±0.89 µg/mL[7]. The LG remedy consists of twenty herbs mixed in equal ratios, and the marker compounds of the ethanolic extract are eugenol and piperine[9]. Eugenol and piperine in previous studies showed anti-inflammatory activity, especially cyclo-oxygenase (COX)-2 inhibitory activity, one of the causes of primary dysmenorrhea[10-12]. LG remedy are *Allium sativum* Linn, *Amomum xanthioides* Wall, *Artemisia vulgaris* Linn, *Boesenbergia rotunda* (Linn) Mansf, *Citrus aurantifolia* (Christm et Panz) Swingle, *Citrus hystrix* DC, *Cymbopogon citratus* (DC) Stapf, *Glycyrrhiza glabra* Linn, *Mentha cordifolia* Opiz, *Myristica fragrans* Houtt, *Ocimum sanctum* Linn, *Oroxylum indicum* (Linn) Kurz, *Piper nigrum* Linn, *Piper retrofractum* Vahl, *Piper sarmentosum* Roxb, *Plumbago indica* Linn, *Syzygium aromaticum* (Linn) Merr et Perry, *Zingiber cassumunar* Roxb, *Zingiber officinale* Roscoe, and *Zingiber zerumbet* (Linn.) Smith[13]. Interestingly, various herbal medicines have anti-inflammatory and antioxidant properties[7]. Previous studies have reported that ethanolic extracts of three herbs, *Piper nigrum*, *Zingiber officinale*, *Citrus hystrix*, and 95% ethanolic extract of LG remedy showed potent anti-inflammatory activity by reducing the production of nitrous oxide (NO) with mean IC_{50} values of 1.31±0.42, 2.87±0.31, 3.03±3.27, and 28.18±4.63 µg/mL, respectively. Herbal antioxidant activity, assessed by DPPH radical scavenging assays, found that the 95% ethanolic extracts of *Syzygium aromaticum*, *Oroxylum indicum*, and *Zingiber officinale* showed high antioxidant activity, with mean EC_{50} values of 9.20±0.29, 9.94±0.91, and 14.34±0.28 µg/mL, respectively[7,9].

There are no reports on the treatment of primary dysmenorrhea using LG remedy. Therefore, the study set out to assess the efficacy and side effects of LG remedy compared with mefenamic acid (MFA) for reducing menstrual pain in women with primary dysmenorrhea.

Materials and Methods

Study design

The present study was a double-dummy, randomized, controlled safety, and efficacy trial conducted at Thammasat University Hospital from AA to BB, which use a program to randomly divide into two groups, code group AA and group BB, in women diagnosed with primary dysmenorrhea. The nursing team randomized the study participants, at a ratio of 1:1, to receive either standard-of-care MFA or LG remedy powder capsules for the intervention group. The required sample size is calculated based on results of previous possibility study[14].

A sample size of 98 women, with 49 in the control group and 49 in the experimental group, would provide 99% power to show a difference of 10 points on a numerical rating scale (NRS) of pain at a two-tailed 0.01 level of significance. The sample size allowed for a dropout rate of 20%.

Criteria

Inclusion criteria:

Study participants were females aged 18 to 25 years at Thammasat University Hospital suffering from primary dysmenorrhea diagnosed by a gynecologist, who had regular menstrual cycles that required analgesic drugs for pain relief, whose pain score was 3 or more, had no allergy to the study drugs, and who gave written informed consent.

Exclusion criteria

Study participants who were pregnant or breastfeeding, taking an oral or injectable contraceptive for six months before enrollment, had any severe gastrointestinal, gynecological, or autoimmune disease, had recently given birth or had an abortion, underwent gynecological surgery within one year before the trial were excluded.

Discontinuation criteria:

Participants were withdrawn from their allocated treatment for any one of the following reasons. The development of raised liver enzyme AST (SGOT), ALT (SGPT), and blood urea nitrogen (BUN) by more than 2.5 times the upper limit of normal (ULN), raised creatinine by more than 1.5 times the ULN, have MFA and LG remedy sensitivities, decision by the principal investigator, or voluntary withdrawal by the participant.

Termination criteria:

Volunteers have severe complications exceeding 10%.

Data collection

The study duration was seven months with three months, as M1 to M3, before randomization to collect pain scores for the first three months, three months of treatment, and follow-up, as M4 to M6, to monitor pain scores, followed by stopping the treatment with pain score monitoring for one month as M7. Participants were followed up by the research team every month.

Instruments

Questionnaires were used for the systematic collection.

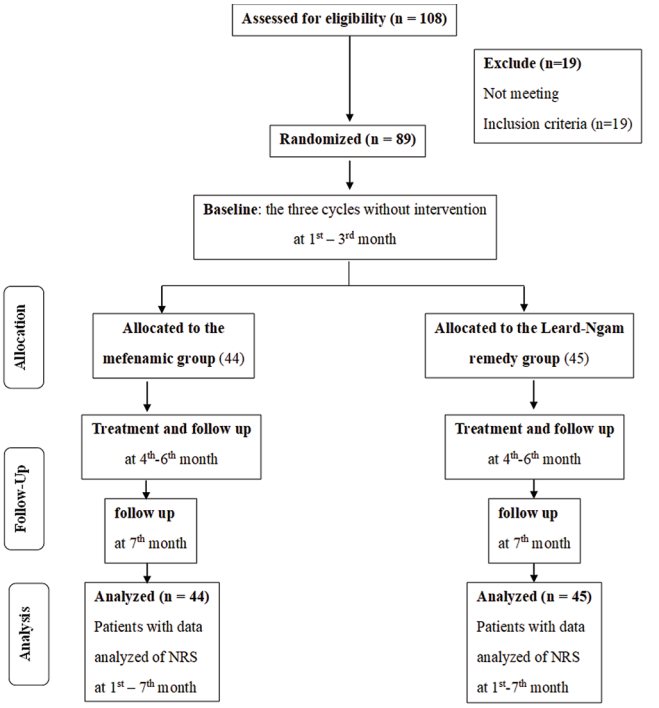

Figure 1. CONSORT flow diagram of participants throughout the study.

Medication administration

Leard-ngam remedy and mefenamic acid:

The present study was a double-dummy, randomized controlled trial. According to the National List of Essential Medicines, 2013[8], the LG remedy must be given before meals, as the MFA must be given after meals. Therefore, a placebo was administered before meals in the MFA group, and a placebo was provided after meals to the LG remedy group.

Leard-ngam remedy:

Twenty herbs in this remedy were pulverized and mixed using the ratios specified in the National List of Essential Medicines, 2013[8]. The LG remedy with red and black capsules was encapsulated in 500 mg according to the National List of Essential Medicines, 2013[8]. The volunteers received two capsules, thus 1 g, three times a day before the meal for three days starting from the first day of menstruation and were told to repeat the same treatment for the subsequent two menstrual cycles, thus, three months in total. Matching placebo capsules containing cornstarch were also prepared to be taken like the MFA capsules.

Mefenamic acid:

MFA 250 mg was encapsulated in 500 mg blue and white capsules. The dose was two capsules of 500 mg, three times a day after a meal for three days starting from the first day of menstruation, as above. Matching placebos containing corn starch were prepared and given with the LG remedy capsules.

Statistical analysis

The statistical analysis was performed using SPSS Statistics for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). It included descriptive statistics, an independent t-test to compare continuous data between the two groups, chi-squared for between-group proportional data, and a repeated measures ANOVA test to compare continuous data before and after mean within and between groups, such as pain scores. A p-value less than 0.05 was considered to be statistically significant.

Ethical approval

The present study was approved by the Human Research Ethics Committee of Thammasat University No.1, Faculty of Medicine (Project no MTU-EC-TM-6-190/59).

Results

Of the 108 screened, 89 adolescent women with primary dysmenorrhea met the inclusion criteria were enrolled and randomized: 45 in the remedy group and 44 volunteers in the MFA group, who all completed

Table 1. Comparison of the demographic and menstrual characteristics in LG remedy and MFA groups

Characteristic	LG remedy (n=45); mean±SD	MFA (n=44); mean±SD	p-value
Age (year)	21.00±1.71	20.50±1.72	0.172
Menarche (year)	12.33±1.24	12.45±1.19	0.640
Period of menstruation (day)	5.9±1.19	5.7±1.15	0.336
Pain score (NRS)	6.49±1.60	6.49±1.51	0.759
Mild; n (%)	-	-	
Moderate; n (%)	26 (57.8)	21 (47.7)	
Severe; n (%)	19 (42.2)	23 (52.3)	
Weight (kg)	53.76±7.88	54.73±8.78	0.585
Height (m)	1.61±054	1.61±0.46	0.597
BMI (kg/m^2)	20.66±2.86	21.19±3.18	0.418
Renal function			
BUN (mg/dL)	11.74±3.36	11.57±2.84	0.433
Creatinine (mg/dL)	0.65±0.82	0.65±0.90	0.718
Total protein (g/dL)	7.89±0.53	7.99±0.46	0.174
Liver function			
AST (U/L)	18.87±5.64	19.75±5.16	0.531
ALT (U/L)	22.82±8.88	20.68±8.18	0.674
Alkaline phosphate (U/L)	60.89±15.84	64.07±16.76	0.419
White blood cell (K/cumm)	6.17±1.50	6.23±1.68	0.361
Hemoglobin (gm/dL)	12.46±0.94	12.34±1.13	0.945
Hematocrit (%)	36.91±2.55	36.24±3.10	0.640
Platelet count (K/cumm)	268.96±58.38	273.27±50.78	0.426

SD=standard deviation; LG=Leard-ngam; MFA=mefenamic acid; NRS=numerical rating scale; BMI=body mass index; BUN=blood urea nitrogen; AST=aspartate transaminase; ALT=alanine transaminase

the study, as shown in Figure 1.

Baseline characteristics before receiving LG remedy and MFA

The volunteers in the LG remedy and MFA groups had similar baseline demographics, such as mean ages of 21.0 and 20.5 and menstrual periods of 5.9 and 5.7 days. Menstrual pain before treatment showed moderate and severe pain scores, with mean scores of 6.49 in both groups. The clinical and laboratory characteristics were not significantly different, as shown in Table 1.

Menstrual pain score

The mean pain scores in the first three months, M1 to M3, were 5.22, 3.38, and 1.76 in the LG group versus 5.00, 4.16, and 2.24 in the MFA group on the period's first, second, and third day, respectively. They were not significantly different (Table 2, 3).

Post-treatment, the MFA group's mean pain score in M4 was significantly lower on days 1 and 2 and showed a strong trend on day 3 (Table 2). For all other time points, the mean pain scores were similar.

Menstrual symptoms

Table 3 showed menstrual-associated symptoms over time. The most frequently reported areas of pain in both groups were lower abdominal, back, and body pain. Common symptoms during menstruation in both groups were weakness, myalgia, irritability, diarrhea, dizziness, and headache, respectively.

Adverse events

Belching was significantly more common in the LG group by about 3-fold. There were no significant differences between the groups for all other reported adverse events. Dyspepsia was widespread, and a hot feeling in the abdomen was 2-fold higher in the LG group (Table 4).

Clinical laboratory evaluation

Checks of the laboratory parameters, such as renal functions, liver function test, and CBC, to assess the toxicity, were done. The results found that mean laboratory parameters were normal at all-time points in both groups (Table 5). Only the mean total protein and total white cell counts fell significantly over time.

Table 2. Comparison each time of menstrual pain score when receiving LG remedy and MFA groups using NRS

Treatment	Baseline (M1-3) mean±SD	Follow 1 (M4) mean±SD	Follow 2 (M5) mean±SD	Follow 3 (M6) mean±SD	Stop treatment (M7) mean±SD	p-value[a] (within group)	Effect size
Day 1							
LG remedy (n=45)	5.22±1.92	4.29±2.39[b]	3.13±2.37[a]	2.78±2.33[a]	4.03±2.76[a]	<0.001	5.35
MFA (n=44)	5.00±1.59	2.77±2.29[a,b]	3.21±2.31[a]	3.05±2.31[a]	4.48±2.72	<0.001	0.81
p-value[b] (between group)	0.554	0.003[b]	0.886	0.588	0.447		
Day 2							
LG remedy (n=45)	3.38±1.87	3.03±2.35[b]	2.23±2.23[a]	1.78±1.99[a]	2.73±2.25	<0.001	2.38
MFA (n=44)	4.16±2.39	1.59±1.88[a,b]	1.89±2.09[a]	1.84±2.13[a]	2.75±2.32[a]	<0.001	2.15
p-value[b] (between group)	0.089	0.002[b]	0.451	0.885	0.973		
Day 3							
LG remedy (n=45)	1.76±1.67	1.47±1.95	1.33±1.98	1.11±1.87	1.51±1.96	0.071	0.80
MFA (n=44)	2.24±2.07	0.80±1.27[a]	1.07±1.81[a]	0.84±1.58[a]	1.32±1.81[a]	<0.001	0.81
p-value[b] (between group)	0.224	0.058	0.511	0.465	0.631		

SD=standard deviation; LG=Leard-ngam; MFA=mefenamic acid

(a) p-value within group compared with baseline, p<0.01, Repeated measure ANOVA; (b) p-value compared between group; p<0.01, Independent t-test

Table 3. Menstrual symptoms of LG remedy and MFA

	LG remedy (n=45, 100%); n (%)			MFA (n=44, 100%); n (%)		
	Before treatment (M1-M3)	Treatment (M4-M6)	After treatment (M7)	Before treatment (M1-M3)	Treatment (M4-M6)	After treatment (M7)
Areas of pain						
Lower abdomen	45 (100)	45 (100)	37 (82.2)	43 (97.7)	44 (100)	38 (86.4)
Back	29 (64.4)	26 (57.8)	13 (28.9)	31 (70.5)	24 (54.5)	19 (43.2)
Body	14 (31.1)	16 (35.6)	5 (11.1)	20 (45.5)	15 (34.1)	11 (25.0)
Thighs	9 (20.0)	7 (15.6)	3 (6.7)	12 (27.3)	8 (18.2)	5 (11.4)
Pubis	11 (24.4)	6 (13.3)	5 (11.1)	25 (34.1)	7 (15.9)	4 (9.1)
Common symptoms during menstruation						
Weakness	37 (82.2)	31 (68.9)	27 (60)	37 (84.1)	34 (77.3)	23 (52.3)
Irritability	32 (71.1)	31 (68.9)	18 (40)	36 (81.8)	33 (75.0)	22 (50)
Myalgia	33 (73.3)	30 (66.7)	18 (40)	30 (68.2)	31 (70.5)	20 (45)
Diarrhea	25 (55.6)	21 (46.7)	8 (17.8)	25 (56.8)	22 (50.0)	12 (27.3)
Dizziness	13 (28.9)	8 (17.8)	3 (6.7)	23 (52.3)	16 (36.4)	8 (18.2)
Insomnia	13 (28.9)	11 (24.4)	7 (15.6)	15 (34.1)	13 (29.5)	4 (9.1)
Headache	13 (28.9)	9 (20.0)	5 (11.1)	15 (34.1)	12 (27.3)	4 (9.1)
Flatulence	11 (24.4)	12 (26.7)	1 (2.2)	18 (40.9)	18 (40.9)	10 (22.7)
Nausea	11 (24.4)	8 (17.8)	-	6 (13.6)	7 (15.9)	1 (2.3)
Arthralgia	10 (22.2)	7 (15.6)	6 (13.3)	13 (29.5)	12 (27.3)	9 (20.5)
Rash	5 (11.1)	-	1 (2.2)	3 (6.8)	3 (6.8)	1 (2.3)
Fever	5 (11.1)	4 (8.9)	4 (8.9)	12 (27.3)	3 (6.8)	1 (2.3)
Vagina	3 (6.7)	2 (4.4)	-	3 (6.8)	2 (4.5)	-
Swelling	3 (6.7)	2 (4.4)	1 (2.2)	3 (6.8)	-	1 (2.3)
Faint	2 (4.4)	1 (2.2)	-	3 (6.8)	2 (4.5)	-

LG=Leard-ngam; MFA=mefenamic acid

Discussion

MFA and LG remedies were effective in relieving menstrual pain. In the present double-dummy trial, the authors compared LG remedy, a Thai traditional medicine, with MFA, a well-established anti-inflammatory drug. Both drugs reduced menstrual pain when given for the first three days of the menstrual cycle. The study duration was seven months counting the first three months and non-intervention before randomization to collect

Table 4. Comparison of side effects between both groups during treatment

Side effect	LG remedy (n=45, 100%); n (%)	MFA (n=44, 100%); n (%)	p-value
Nausea/vomiting	2 (4.4)	3 (6.8)	0.629
Warm/hot feeling in abdomen	6 (13.3)	3 (6.8)	0.311
Heartburn	-	2 (4.5)	0.150
Urticaria	-	-	-
Angioedema	-	-	-
Dyspepsia	12 (26.7)	8 (18.2)	0.340
Dizziness	2 (4.4)	3 (6.8)	0.629
Palpitation	-	-	-
Rash	-	-	-
Dyspnea	1 (2.2)	1 (2.3)	0.987
Other			
Belch	10 (22.2)	3 (6.8)	0.041
Body heat	1 (2.2)	-	0.323
Acne	1 (2.2)	-	0.323
Hiccup	1 (2.2)	-	0.323
Flatus	1 (2.2)	-	0.323

LG=Leard-ngam; MFA=mefenamic acid

* p<0.01 compared between group, chi-square test

Table 5. Comparisons each time of blood chemistry when receiving LG remedy and MFA groups

Treatment	Baseline (M1-3); mean±SD	Follow 2 (M5); mean±SD	Follow 3 (M6); mean±SD	Stop treatment (M7); mean±SD	p-value
BUN (7.0-18.0 mg/dL)					
LG remedy (n=45)	11.72±3.23	11.79±2.90	11.01±2.70	11.47±3.57	0.524
MFA (n=44)	11.60±3.00	11.23±2.90	11.06±2.50	10.80±2.15	0.420
Creatinine (0.51 to 0.95 mg/dL)					
LG remedy (n=45)	0.65±0.09	0.68±0.09	0.67±0.10	0.68±0.09	0.152
MFA (n=44)	0.65±0.08	0.67±0.01	0.66±0.10	0.66±0.09	0.577
Total protein (6.4 to 8.2 g/dL)					
LG remedy (n=45)	7.89±0.53	7.77±0.46	7.73±0.49	7.65±0.50	0.027
MFA (n=44)	7.98±0.46	7.94±0.43	7.85±0.44	7.74±0.47	0.023
AST or SGOT (15 to 37 U/L)					
LG remedy (n=45)	19.22±5.15	13.18±3.41*	13.18±4.93*	12.18±2.89*	<0.001
MFA (n=44)	19.38±5.70	14.61±5.96*	13.91±4.20*	13.21±5.15*	<0.001
ALT or SGPT (14 to 57 U/L)					
LG remedy (n=45)	21.09±7.17	22.33±9.37	20.56±6.45	20.93±4.64	0.587
MFA acid (n=44)	22.45±9.82	20.43±9.20	20.86±6.92	21.64±11.43	0.601
Alkaline (46 to 116 U/L)					
LG remedy (n=45)	61.42±16.84	60.24±17.61	57.33±13.61	57.02±13.18	0.203
MFA (n=44)	63.52±15.82	64.09±16.56	64.95±20.55	61.25±20.36	0.501
WBC (4 to 11 U/L)					
LG remedy (n=45)	6.04±1.41	6.25±1.55	6.14±1.61	6.36±1.49	0.452
MFA (n=44)	6.35±1.75	6.20±1.79	5.79±1.34	5.95±1.44	0.037
Hb (12 to 16 U/L)					
LG remedy (n=45)	12.38±0.86	12.49±0.95	12.51±0.75	12.50±0.89	0.619
MFA (n=44)	12.41±1.19	12.59±1.07	12.51±1.07	12.53±1.19	0.143
Hct (35 to 45 U/L)					
LG remedy (n=45)	36.51±2.48	36.68±2.88	36.91±2.20	36.92±2.71	0.613
MFA (n=44)	36.64±3.19	36.90±2.64	36.68±2.64	37.17±3.41	0.240
Platelet count (10^3/μL)					
LG remedy (n=45)	273.16±52.54	280.40±60.11	267.62±67.36	276.87±56.73	0.245
MFA (n=44)	268.98±56.93	276.16±67.88	275.05±75.04	272.18±67.57	0.556

SD=standard deviation; LG=Leard-ngam; MFA=mefenamic acid; BUN=blood urea nitrogen; AST=aspartate transaminase; ALT=alanine transaminase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamate-pyruvate transaminase; WBC=white blood cell; Hb=hemoglobin; Hct=hematocrit

* p<0.01, Repeated measure ANOVA

pain scores, three months of treatment and follow-up, which are three months with interventions, to monitor pain scores, followed by stopping the treatment with pain score monitoring for one month on the seventh month.

On the first day of the fourth month, or the first intervention monthly, MFA would better relieve menstrual pain than LG remedy. However, the LG remedy is more effective than MFA on the first day of the fifth and sixth months, or the second and third intervention month. MFA can relieve menstrual pain better than LG remedy on the second day of the fourth and fifth months. However, when it is the second day of the sixth month, the LG remedy is more effective than MFA in reducing pain. MFA can alleviate menstrual pain better than LG remedy on the third day of the fourth, fifth and sixth months. In the seventh month, which is one month after stopping the medicine, volunteers who received the LG remedy had lower pain scores than volunteers who received MFA, especially in the first two days of their menstrual periods.

It can be concluded that MFA and LG remedies effectively relieved menstrual pain, and there were no significant differences between the two groups. LG remedy can gradually relieve menstrual pain because it takes time to balance women's physical health.

The effectiveness of the LG remedy for menstrual pain relief can be described as the underlying pathophysiology of primary dysmenorrhoea is prostaglandin and NO-related inflammation[8], which would be expected to respond to anti-inflammatory drugs. The LG remedy comprises twenty herbs and is known to reduce Prostaglandin E2 (PGE2) and NO production. MFA is a non-selective inhibitor of COX-1 and 2. The COX-2 pathway leads to the production of PGE2, which is associated with pain and fever. Clinical studies have reported that herbs used in the LG remedy, such as *Zingiber officinale*, relieve menstrual pain when given two days before the onset of the menstrual period and continue through the first three days of the menstrual period[15]. *Zingiber cassumunar*, another LG component, is combined with other herbal extracts in a Thai remedy called "Prasaplai", which was as effective as MFA in primary dysmenorrhea[16]. *Glycyrrhiza glabra* is another component of LG that significantly decreases intracellular Ca2+ levels in the uterus compared to controls. One mechanism by which herbal medicines may be effective in primary dysmenorrhea is blocking Ca2+ channels to decrease intracellular Ca2+ levels[17].

Concomitant symptoms most often reported included weakness, irritability, and myalgia, which tended to decrease over time after receiving MFA and LG remedies. Both drugs were well tolerated, but LG remedy was associated with symptoms of a heated feeling in the abdomen, dyspepsia, and belch, which may have been caused by spicy herbs in the LG remedy. All measured laboratory parameters were unremarkable. The present study had limitations as the age group was restricted and the findings may not apply to older women. The present study follow-up was short; therefore, longer-term studies are needed to assess the long-term safety of LG remedy in women.

To conclude, the present study showed that LG remedy was effective and well-tolerated in young women with primary dysmenorrhea. More research is needed to define an optimal dose and ascertain its underlying action mechanism.

What is already known on this topic?

In Thai traditional scripture for women's health, LG remedy is used for abdominal pain occurring during menses. It consists of twenty herbs. A previous study reported that LG remedy reduced prostaglandins, the main cause of uterine pain, with a mean IC_{50} of 8.69±0.89 µg/mL. Interestingly, various herbal plants in the remedy exhibited anti-inflammatory and antioxidant properties. LG remedy shows the potential for the development of a traditional Thai drug for the treatment of primary dysmenorrhea. For these reasons, the authors assessed the efficacy of LG remedy.

What does this study add?

Eighty-nine volunteers were enrolled with 45 in the LG group and 44 in the MFA group. The two groups had similar baseline demographic, clinical, and laboratory characteristics. Both drugs reduced menstrual pain when given for the first three days of the menstrual cycle. The mean pain scores in the first three months, which were M1 to M3, were 5.22, 3.38, and 1.76 for the LG group and 5.00, 4.16, and 2.24 for the MFA group on the first-, second-, and third-day period, respectively. They were not significantly different, and pain recurred when both drugs were stopped. In conclusion, the LG remedy was effective and well tolerated in young women with primary dysmenorrhea and had no adverse reactions.

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Conflict of interest

The authors have no conflict of interest.

References

1. Crompton S. Women in Canada: A gender-based statistical report. Ottawa: Minister of Industry; 2011.
2. Milsom I, Sundell G, Andersch B. The influence of different combined oral contraceptives on the prevalence and severity of dysmenorrhea. Contraception 1990;42:497-506.
3. Chen FP, Soong YK. The efficacy and complications of laparoscopic presacral neurectomy in pelvic pain. Obstet Gynecol 1997;90:974-7.
4. Dawood MY, Khan-Dawood FS. Clinical efficacy and differential inhibition of menstrual fluid prostaglandin F2alpha in a randomized, double-blind, crossover treatment with placebo, acetaminophen, and ibuprofen in primary dysmenorrhea. Am J Obstet Gynecol 2007;196:35.e1-5.
5. Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. BMJ 2006;332:749-5.
6. Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. Obstet Gynecol 2006;108:428-41.
7. Threrapanithan C, Jaiaree N, Itharat A, Makchuchit S, Thongdeeying P, Panthong S. Anti-inflammatory and antioxidant activities of the Thai traditional remedy called "Leard-ngam" and its plant ingredients. Thammasat Med J 2015;15:376-83.
8. The Institute of Thai Traditional Medicine. List of herbal medicinal products A.D. 2011. Nonthaburi, Thailand: Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health of Thailand; 2011. p. 56.
9. Poomirat S, Jaiarree N, Itharat A, Threrapanithan C. Phytochemical analysis of Lead-Ngam remedy and its composition. Thammasat Med J 2020;20:60-73
10. Poomirat S, Jaiarree N, Itharat A, Ruangnoo S. Cytotoxicity against cervical and breast cancer cells of Leard-Ngam remedy and its plant compositions. Sci Technol Asia 2020;25:38-50.
11. Leem HH, Kim EO, Seo MJ, Choi SW. Antioxidant and anti-inflammatory activities of eugenol and its derivatives from clove (Eugenia caryophyllata Thunb.). Journal of the Korean Society of Food Science and Nutrition 2011;40:1361-70.
12. Kim HG, Han EH, Jang WS, Choi JH, Khanal T, Park BH, et al. Piperine inhibits PMA-induced cyclooxygenase-2 expression through downregulating NF-κB, C/EBP and AP-1 signaling pathways in murine macrophages. Food Chem Toxicol 2012;50:2342-8.
13. Thailand Development Research Institute (TDRI). National list of essential medicines. Bangkok: Royal Thai Government Gazette; 2018.
14. Kamalashiran C, Lekskulchai O. The comparative study of the efficacy and side effect of prasaplai extract versus mefenamic acid on relieving primary dysmenorrhea: A clinical phase II trials. Thammasat Medical Journal 2012;12:749-56.
15. Rahnama P, Montazeri A, Huseini HF, Kianbakht S, Naseri M. Effect of Zingiber officinale R. rhizomes (ginger) on pain relief in primary dysmenorrhea: a placebo randomized trial. BMC Complement Altern Med 2012;12:92. doi: 10.1186/1472-6882-12-92.
16. Sriyakul K, Kietinun S, Pattaraarchachai J, Ruangrungsi N. A comparative double-blinded randomized study: The efficacy of prasaplai herbal extract versus mefenamic acid in relieving pain among primary dysmenorrhea patients. Open Complement Med J 2012;4:16-21.
17. Park KS, Park KI, Hwang DS, Lee JM, Jang JB, Lee CH. A review of in vitro and in vivo studies on the efficacy of herbal medicines for primary dysmenorrhea. Evid Based Complement Alternat Med 2014;2014:296860.