Original Article

The evaluation of Thai herbal Leard-Ngam formula for relieving pain in primary dysmenorrhea: Randomized controlled trial

Sunisa Leemud[1], Kusuma Sriyakul[1*], Chuntida Kamalashiran[1], Sucharat Tungsukruthai[2], Somboon Kietinun[1], and Parunkul Tungsukruthai[1]

[1] *Integrative Medicine, Chulabhorn International College of Medicine, Thammasat University, Khlong Luang, Pathum Thani, 12120 Thailand*

[2] *Division of Health and Applied Sciences, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

Abstract

Leard-Ngam (LG) is a traditional Thai herbal remedy for treating primary dysmenorrhea (PD). However, the effectiveness of this regimen based on experimental studies is still unknown. Consequently, this study aimed to compare the efficacy of pain relief and side effects between Leard-Ngam (LG) formula and Mefenamic acid (MA) in women with PD. Seventy-four participants were randomly assigned into two groups: LG and MA. In LG group, participants were received 2 LG capsules (500 mg/cap) orally three times per day for three days starting from the first day of menstruation. The MA group received 2 MA capsules (250 mg/cap) as the same time. The main outcome variables included the visual analogue scale (VAS), verbal multidimensional scoring system (VMS), and signs of potential adverse effects during a four-month period (M1-M4). The VAS pain score of LG group was significantly decreased from 5.51 ± 1.46 to 3.23 ± 1.89 at M3 and 3.03 ± 1.77 at follow-up M4 ($p < 0.05$). In MA group, VAS pain score was significantly decreased from 4.43 ± 1.64 to 3.03 ± 1.70 at M3 and 3.08 ± 1.63 at follow-up M4 ($p < 0.05$). The VMS score of LG group significantly decreased from 1.71 ± 0.46 to 1.03 ± 0.70 at M3 and to 1.03 ± 0.70 at follow-up M4 ($p < 0.05$), while the MA group had significantly decreased from 1.46 ± 0.50 to 0.97 ± 0.79 at M3 and to 0.97 ± 0.68 at follow-up M4 ($p < 0.05$). However, there were no statistically significant differences between the two groups ($p = 0.637$ for VAS and $p = 0.756$ for VMS). In addition, blood chemistry, hematology, liver, and renal function were all within normal ranges. Moreover, there were six incidences of side effects in the MA group, but only one in the LG group. The findings suggested that LG is as effective as MA for alleviating pain in primary dysmenorrhea while having less adverse effects. As a result, LG could be an alternative treatment for primary dysmenorrhea.

Keywords: Thai herbal Leard-Ngam formula, dysmenorrhea, mefenamic acid

1. Introduction

Primary dysmenorrhea (PD) is one of the most common gynecologic diseases, affecting around 50% of all reproductive age women (Itani *et al.*, 2022). In the absence of a recognizable pathologic lesion, PD is characterized by pelvic pain during menstruation (De Sanctis *et al.*, 2015; Sharghi *et al.*, 2019). The underlying cause of PD is not completely understood. The symptoms are usually associated with high prostaglandin (PG) production during menstruation. The rise in prostaglandins is linked with the intensity of the pain and promotes uterine contractions (Barcikowska, Rajkowska-Labon, Grzybowska, Hansdorfer-Korzon, & Zorena, 2020; Fajrin, Alam, & Usman, 2020).

First-line treatment for women with PD frequently involves the use of non-steroidal anti-inflammatory medicines (NSAIDs), such as ibuprofen and mefenamic acid to alleviate

---

*Corresponding author
Email address: kusuma-s@tu.ac.th

pain. However, these medications do have side effects, the most prevalent of which are gastrointestinal issues such as nausea, stomach ache, and vomiting. Therefore, researchers have investigated alternative treatments such as herbal and dietary therapies for PD patients. In Thailand, LG, a Thai herbal formula, has long been used for treating PD, and is listed on the National Drug List of Herbal Medicinal Products (DTAM, 2012). It consists of 20 herbs such as *Piper nigrum* Linn, *Zingiber officinale* Roscoe (Ginger)*,* and *Zingiber zerumbet* (Linn.) Smith. Previous studies have found that the extract of *Z. officinale* and *Z. zerumbet* has potential to inhibit prostaglandin E2 (PGE2) (Dugasani *et al.*, 2010; Zakaria *et al.*, 2010).

Due to traditional knowledge and beliefs, these herbal recipes' components and methods of use vary, and there have not been enough experimental studies to conclusively demonstrate the effectiveness of this regimen. As a result, this regimen needs to be proven to be truly effective at relieving pain. The primary objective of this study was to compare the efficacies of LG and MA against pain in women with PD. The secondary objective was to determine side effects of LG treatment.

2. Materials and Methods

2.1 Study design and participants

This study was conducted in October 2022 to March 2023 at Thammasat University Hospital, Pathum Thani, Thailand. This research was a single-blind randomized controlled trial, in which the investigator was blinded to MA group and LG group. The gynecologist examined all participants who met the inclusion criteria.

The inclusion criteria were women aged 18-25 years old, with regular menstrual cycles, who had been diagnosed with PD of mild and moderate pain, and who required analgesic drug for relieving pain. Each participant completed the questionnaires, which included scales from well-established instruments including visual analog scale (VAS) and verbal multidimensional scoring system (VMS) (Atallahi, Amir Ali Akbari, Mojab, & Alavi Majd, 2014; Pakniat, Chegini, Ranjkesh, & Hosseini, 2019). Each participant in the research was chosen based on their VAS menstrual pain score, which ranged from 1 to 7, and their VMS Grade (grades 1-2), which indicated mild to moderate discomfort. The exclusion criteria included patients with severe gastrointestinal, gynecological, or autoimmune diseases, receiving gynecological surgery within 1 year, having medicinal and herbal sensitivities, taking dietary supplements such as evening primrose oil, or having blood diseases with disorders of the blood coagulation system.

2.2 Ethical considerations

All participants signed informed consent to participate in this study. This research was approved by The Human Research Ethics Committee of the Faculty of Medicine, Thammasat University Number of COA 098/2022. This trial was registered in the Thai Clinical Trials Registry (TCTR) with code TCTR20230516010 on 16 May 2023.

2.3 Sample size

The estimate of sample size was calculated by using a formula for estimation of two groups, G-Power program with statistical error threshold 0.05 (α-error), power 0.8, and effect size is 0.72 which was calculated based on a previous study (Sriyakul, Kietinun, Pattaraarchachai, & Ruangrungsi, 2012). The mean$\pm$SD of VAS was 0.77$\pm$0.37 for experimental group, whereas the control group had 1.16$\pm$0.67. The 32 participants in each group were recruited, plus an additional 15% for participation loss, for a total of 74 (37 in each group). A random number table was used to randomize the treatment groups; one group received LG and the other received MA.

2.4 Study instruments

Menstrual pain was measured using the visual analog scale (VAS) and verbal multidimensional scoring system (VMS) methods. For VAS, there was a 10-point scale: painless (score 0), mild (score 1–3), moderate (score 4–7), and severe (score 8–10 (Yong Ik *et al.*, 2001). The VMS considered the impacts of pain on daily activities, systemic symptoms, and analgesic requirements, using a four-point Likert scale ranging from no symptoms to severe symptoms: none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3) (Atallahi *et al.*, 2014; Pakniat *et al.*, 2019).

Laboratory tests, including CBC (WBC, Neutrophil, Lymphocyte, RBC, Hemoglobin, Hematocrit), liver function (Aspartate aminotransferase, Alanine aminotransferase, Alkaline Phosphatase), and renal function (Urea Nitrogen, Creatinine), were recorded and collected by specialist staff according to the experimental operation manual and kept confidential to ensure the privacy of the participants. Subsequently, the laboratory data were investigated at BANGKOK R.I.A. LAB Co., Ltd. (Bangkok, Thailand). The original data were entered, sorted, checked, and maintained by specialized data management personnel to ensure the accuracy and safety of the data.

Regarding adverse drug reactions (ADRs), the respondents answered questions concerning the details in reporting ADRs such as symptoms found after taking drug and the appearance of adverse reactions in their body. Then, the researcher used Naranjo's algorithm to evaluate adverse reactions, the severity, and the symptom relationship (Naranjo's algorithm scores: > 9 = certain, 5-8 = probable, 1-4 possible, and < 1 = unlikely) (Termwiset, Sriyakul, Srikaew, & Tungsukruthai, 2021). If severe adverse reactions occurred the medication was immediately stopped, and the patient was advised to visit a doctor.

2.5 Intervention

Both LG and MA were produced at Herbal Medicines and Products Manufacturing Unit, manufactured under GMP by Arjaro Hospital, Sakon Nakhon, Thailand (GMP certified since 2018 and re-accredited 2020, 2022). LG capsule contained 500 mg of LG and MA capsule contained 250 mg of MA. Either LG or MA was filled in white opaque capsules. All bottles were labelled with the code which was known only by the manufacturers.

Following a meal, all groups were instructed to take orally two capsules three times per day, starting on the first day of menstruation and continuing for three days. The VAS score, VMS grade and ADRs were recorded at the end of their first menstrual day. Additionally, evaluations of laboratory results and systemic symptoms were conducted at baseline and 3rd month (M3). Moreover, the participants were instructed to stop from the medicine for 1 month. Then, the researcher made a follow-up appointment for 4th month (M4). All participants were scheduled for monthly follow-up and assessment by a gynecologist, which included VAS, VMS, and ADRs.

2.6 Outcome and data collection

The outcomes were recorded in a self-diary during four menstrual cycles. Primary dysmenorrhea, presenting with cyclic pain, begins within 48 hours of the first day of the menstrual cycle and resolves by menstrual cycle days 2 or 3 (Torkan *et al.*, 2021). Therefore, VAS, VMS and ADRs were measured at the end of first day after taking LG or MA. VAS had a 10-point scale, with 0 indicating no pain and 10 denoting severe suffering. Furthermore, VMS had a four-point scale ranging from no symptoms to severe symptoms (Grade 0-3). All data were obtained from participants during the follow-up day.

2.7 Statistical analysis

All analyses were performed using SPSS version 25 (Armonk, NY: IBM Corp). Descriptive statistics were used for demographic data, with menstruation results which were presented as means and standard deviations. The paired *t*-test was used to compare the differences of mean reduction within treatment groups. The independent *t*-test was used to compare the differences of mean reductions between treatment groups. Statistical differences of VAS and VMS within a group were determined by repeated measures ANOVA test, and calculated by independent-samples *t*-test for between groups comparison. The statistical significance required $p < 0.05$.

3. Results

Seventy- two participants completed the study presented in Figure 1.

No significant differences were observed between the two groups for the participant characteristics such as age, BMI, age at menarche, or duration of menstruation. However, the dysmenorrhea duration was significantly different. The characteristics of the study samples are presented in Table 1.

Participants in both groups were administered the prescribed medication beginning on the first day of menstruation for M1-M3. It was found that VAS pain score of LG group significantly decreased from 5.51±1.46 to 3.23±1.89 at M3 and to 3.03±1.77 at M4 of follow-up ($p < 0.05$). In addition, VAS pain score of MA group significantly decreased from 4.43±1.64 to 3.03±1.70 at M3 and to 3.08±1.63 at M4 of follow-up ($p < 0.05$) (Figure 2). Although there was a significant difference in initial VAS scores between the groups, the impact of LG was shown to be comparable to MA at M2-M4 following the treatment.

Participants in both groups were administered the drug during M1-M3. The results showed that the VMS in the LG group significantly decreased from 1.71±0.46 to 1.03±0.70 at the follow-up (M4) when compared to the baseline ($p < 0.05$). Similarly, the VMS in the MA group
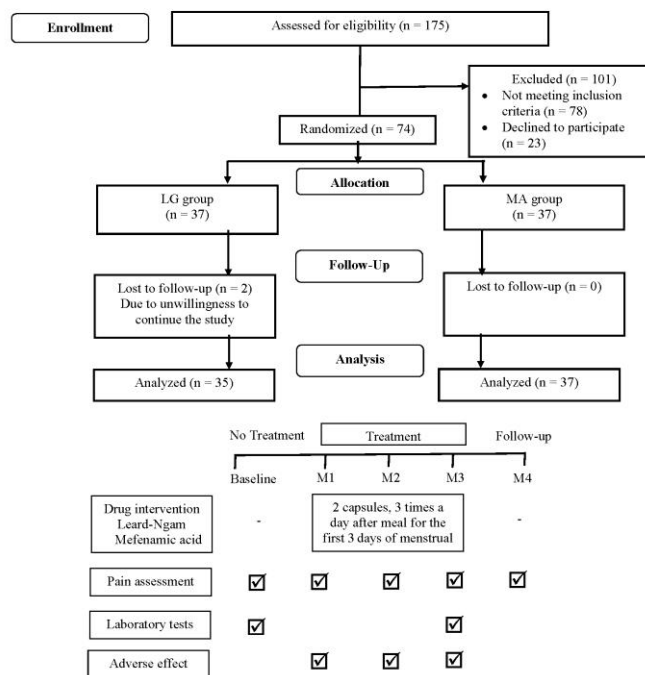

Figure 1.   Flowchart of the study
(M1: 1st month of treatment, M2: 2nd month of treatment, M3: 3rd month of treatment, M4: Follow-up period after discontinuation treatment)

Table 1.   Characteristics in both groups

Variable	LG (N=35)	MA (N=37)	P
Age (year) (mean±S.D.)	19.91±1.147	19.97±1.280	0.839
BMI: body mass index (kg/m^2) (mean±S.D.)	20.33±1.245	20.44±1.381	0.721
Menarche age (year) (mean±S.D.)	12.54±1.314	12.11±0.737	0.092
Duration of menstruation (day) (mean±S.D.)	5.66±1.211	5.54±1.070	0.666
Dysmenorrhea duration (day) (mean±S.D.)	2.49±0.887	2.08±0.829	0.049*
Amount of menstruation (PAD/Day) (mean±S.D.)	3.14±0.810	3.30±1.051	0.489

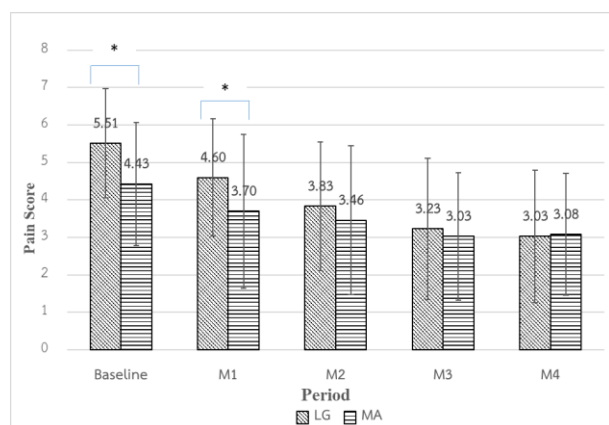*$p < 0.05$ in independent samples *t*-test between the groups, S.D. = standard deviation

Figure 2.   Average pain scores from baseline to M4 during the study in the treatment groups (VAS score)
M1: 1st month of treatment
M2: 2nd month of treatment
M3: 3rd month of treatment
M4: Follow-up period after discontinuation treatment
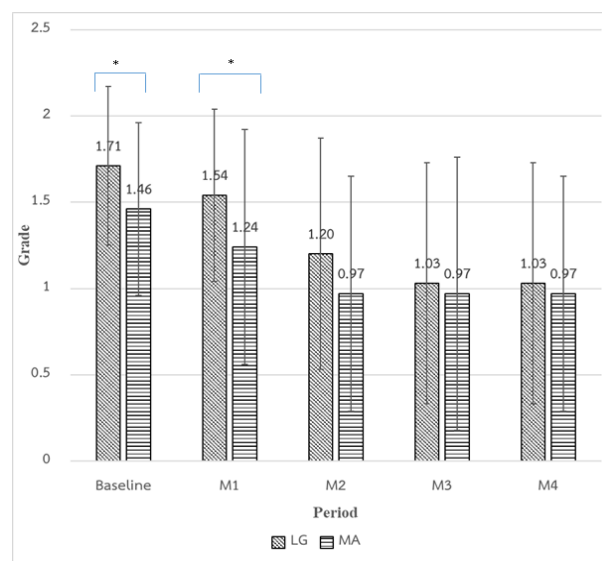*$p < 0.05$ in independent samples *t*-test between treatment groups

Figure 3.   Average pain scores from baseline to M4 during the study in the treatment groups (VMS score)
M1: 1st month of treatment
M2: 2nd month of treatment
M3: 3rd month of treatment
M4: Follow-up period after discontinuation treatment
*$p < 0.05$ in independent samples *t*-test between treatment groups

significantly decreased from 1.46±0.50 to 0.97±0.68 at the follow-up (M4) ($p < 0.05$) as well. However, when comparing between the groups, no significant difference was found, as shown in Figure 3.

Systemic symptoms, such as headaches and nausea, improved in both the LG and MA groups following the intervention. In the LG group, 71.43% of participants (N=25) had VMS grade 2 at baseline, which interfered with daily activities and necessitated the use of analgesics. Three months after the intervention period, only 25.71% (N=9) of the participants had VMS grade 2, and this percentage remained constant during the extension period. In the MA group, after using MA for three months, VMS grade had decreased from baseline 45.95% (N=17) to 29.73% (N=11) (Table 2). Furthermore, following the intervention, the VMS grade 0 increased in both groups. Consequently, LG showed improvement on the VMS score of symptoms, including daily functioning and quality of life, which were comparable to MA in treating PD.

In the results of laboratory tests, there was no significant difference between the groups. Nevertheless, the outcomes showed that the levels of hemoglobin, lymphocytes, and neutrophils were significantly affected using LG or MA (Table 3). For example, Hemoglobin in LG group was 12.48±0.99 at baseline while at M3 it was 13.00±0.96 (p-value < 0.05). Hemoglobin in MA group was 12.43±0.92 at baseline while at M3 it was 12.62±0.76 (p-value < 0.05). Besides, the results of the ADRs assessment revealed that only one participant in the LG group (2.86%) experienced symptoms of dizziness, nausea, and vomiting in the first month. On the other hand, 3 participants (8.11%) in the MA group experienced adverse effects including nausea and vomiting, severe abdominal pain, and a decrease in bleeding in M1. Furthermore, in M2, three participants (8.11%) in MA group had undesirable symptoms: one had unusually heavy periods, while the other two had less bleeding. As a result, LG has less side effects than MA in primary dysmenorrhea.

4. Discussion

PD was characterized by painful menstrual contractions caused by endometrial laceration (Azagew, Kassie, & Walle, 2020; Sharghi *et al.*, 2019). Dysmenorrhea had historically been treated with drugs such as non-steroidal anti-inflammatory medications (NSAIDs). However, this could result in adverse effects as well as NSAID resistance (Oladosu, Tu, & Hellman, 2018). Consequently, it became

Table 2.   Percentages of participants by VMS grades during the study in the treatment groups

	Baseline		M1		M2		M3		M4	
	LG	MA	LG	MA	LG	MA	LG	MA	LG	MA
G0	0 (0%)	0 (0%)	0 (0%)	5 (13.51%)	5 (14.26%)	9 (24.32%)	8 (22.86%)	12 (32.43%)	8 (22.86%)	9 (24.32%)
G1	10 (28.57%)	20 (54.05%)	16 (45.71%)	18 (48.65%)	18 (51.43%)	20 (54.05%)	18 (51.43%)	14 (37.84%)	18 (51.43%)	20 (54.05%)
G2	25 (71.43%)	17 (45.95%)	19 (54.28%)	14 (37.84%)	12 (34.29%)	8 (21.62%)	9 (25.71%)	11 (29.73%)	9 (25.71%)	8 (21.62%)

Grade 0 = Menstruation was not painful and daily activity is unaffected
Grade 1 = Menstruation was painful but seldom inhibits the women's normal activity
Grade 2 = Pain affecting daily activity which required analgesics
Grade 3 = Pain which clearly inhibits activity and is poorly controlled by analgesics

Table 3.   Averages of laboratory tests at baseline and M3 during the study in the treatment groups

	Mean±S.D.							
Variable	LG		p^a	MA		p^a	p^b	p^c
	Baseline	M3		Baseline	M3			
Complete blood count, CBC								
WBC (K/cumm.) (4.0-11.0)	6.44±1.25	7.06±1.47	0.005*	6.81±2.45	6.57±1.75	0.351	0.425	0.206
Neutrophil (%) (45-75)	55.24±7.30	51.95±7.86	0.012*	61.42±8.27	55.29±7.46	0.001*	0.001*	0.069
Lymphocyte (%) (20-45)	38.11±6.68	41.06±7.63	0.010*	32.24±7.24	37.88±6.73	0.001*	0.001*	0.064
RBC (x10^6/cumm.) (4.00-5.50)	4.73±0.54	4.83±0.46	0.037*	4.78±0.44	4.78±0.47	0.888	0.618	0.628
Hemoglobin (gm/dL) (12.0-16.0)	12.48±0.99	13.00±0.96	0.001*	12.43±0.92	12.62±0.76	0.040*	0.834	0.066
Hematocrit (%) (35.0-45.0)	37.79±3.00	39.29±2.70	0.008*	38.06±2.31	38.32±2.18	0.347	0.678	0.096
Liver results								
Aspartate aminotranferase (U/L) (15-37)	19.42±3.68	18.51±4.81	0.196	21.11±6.66	19.14±4.47	0.111	0.188	0.572
Alanine aminotranferase (U/L) (14-59)	26.80±8.06	24.69±10.99	0.186	26.08±10.01	24.05±7.47	0.274	0.739	0.775
Alkaline Phosphatase (U/L)(46-116)	69.29±15.30	69.37±14.88	0.953	68.84±14.36	65.43±13.12	0.023*	0.898	0.237
Renal results								
Urea Nitrogen (mg/dL) (801-1,666)	986.54±346.35	846.11±417.88	0.129	916.54±455.03	799.05±416.09	0.127	0.464	0.634
Creatinine (mg/dL) (29-226)	155.94±61.22	140.60±77.97	0.339	157.16±100.05	142.43±80.52	0.381	0.950	0.922

*$p < 0.05$, S.D. = standard deviation
[a] Paired *t*-test for before and after within group
[b] Independent samples *t*-test (at baseline) between groups
[c] Independent samples *t*-test (at M3) between groups

necessary to research novel therapies to lessen pain in women with PD. A significant finding of this study was that LG therapy had reduced side effects while having an efficacy comparable to MA in treating PD pain.

Our findings revealed that even though the baseline and M1 pain scores were significantly different, the average pain score between the LG and MA groups did not differ significantly after 2 months of treatment (M2) (Table 2-3).

Our research is corroborated by earlier research, which discovered that another Thai herbal formulation called Prasaplai had the ability to reduce pain from PD. Ingredients in Prasaplai that are similar to LG treatment are *Zingiber officinale* Roscoe*, Zingiber cassumunar* Roxb*, Allium sativum* L.*,* and *Piper retrofractum* Vahl. (Sriyakul *et al.*, 2012; Vannabhum *et al.*, 2016). The results indicate that Prasaplai reduced VAS pain score from 7.36±0.66 at baseline to

3.70±0.22 at M3 while LG decreased VAS pain score from 5.51±1.46 (baseline) to 3.03±1.77 (M3).

The question is, why LG treatment could alleviate pain in PD patients. We hypothesized that the major component in LG therapy had anti-inflammatory and analgesic characteristics similar to MA. MA reduces pain by blocking the formation of intracellular prostaglandins and COX-2, which are generally up-regulated in PD patients (Guzman-Esquivel *et al.*, 2022). In a search of the literature, we found that the primary phytochemicals present in LG formulation are eugenol, austrobailignan, aceteugenol, and piperine (Poomirat, Itharat, & Threrapanithan, 2020). Eugenol significantly inhibits PGE (2) synthesis, with an IC_{50} of 0.37 μM. Furthermore, eugenol reduces COX-2 expression in LPS-stimulated mouse macrophage cells (Kim *et al.*, 2003). Additionally, it was shown that eugenol found in *Cinnamomum zeylanicum* reduced the severity of dysmenorrhea more than placebo (Mirabi, Alamolhoda, Esmaeilzadeh, & Mojab, 2014). Likewise, Piperine, which was identified in *P. nigrum,* could suppress IL-6 expression, decrease PGE2 synthesis, and reduce nociceptive responses in a dose-dependent manner (10-100 μg/ml) (Bang *et al.*, 2009). Moreover, in LPS-induced murine peritoneal macrophages, gingerol (100 ng/ml) from *Zingiber officinale* Roscoe reduced levels of COX-2 and proinflammatory cytokines IL-1β, IL-12, and TNF-α (Tripathi, Maier, Bruch, & Kittur, 2007). Altogether, these findings suggest that key compounds in LG formula possess anti-inflammatory and analgesic properties comparable to MA. Interestingly, in our comparison of LG extract and MA, we observed that the LG group experienced just one case of nausea and vomiting, whereas the MA group experienced six cases of vomiting, abnormally heavy menstrual periods, and abnormally painful abdominal cramps. When considering the aforementioned information, it appears that LG treatment had effectiveness comparable to the standard treatment but with less side effects. However, this study had some limitations.

Regarding those limitations, data on dysmenorrhea might not have been accurately reported because the VAS and VMS, from self-administered questionnaire, were employed. Furthermore, this was a single-blind study because LG therapy included several herbs such as ginger and pepper, which are examples of pungent spices. These herbs had a strong smell and could leave a taste in the mouth, as well as possibly caused burping. Participants would be conscious of receiving herbal therapy. Accordingly, additional research incorporating a larger sample size, improved randomization, and comparison with other medications should be pursued in future studies.

5. Conclusions

The findings of this study indicate that the Leard-Ngam Formula was as safe and effective as mefenamic acid, but with less side effects. Taken together, Leard-Ngam Formula could be used as alternative treatment for relieving pain caused by primary dysmenorrhea.

Acknowledgements

References

Atallahi, M., Amir Ali Akbari, S., Mojab, F., & Alavi Majd, H. (2014). Effects of wheat germ extract on the severity and systemic symptoms of primary dysmenorrhea: A randomized controlled clinical trial. *Iranian Red Crescent Medical Journal, 16*(8), e19503. doi:10.5812/ircmj.19503

Azagew, A. W., Kassie, D. G., & Walle, T. A. (2020). Prevalence of primary dysmenorrhea, its intensity, impact and associated factors among female students' at Gondar town preparatory school, Northwest Ethiopia. *BMC Women's Health, 20*(1), 5. doi:10.1186/s12905-019-0873-4

Bang, J. S., Oh, D. H., Choi, H. M., Sur, B. J., Lim, S. J., Kim, J. Y., & Kim, K. S. (2009). Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models. *Arthritis Research and Therapy, 11*(2), R49. doi:10.1186/ar2662

Barcikowska, Z., Rajkowska-Labon, E., Grzybowska, M. E., Hansdorfer-Korzon, R., & Zorena, K. (2020). Inflammatory markers in dysmenorrhea and therapeutic options. *International Journal of Environmental Research and Public Health, 17*(4). doi:10.3390/ijerph17041191

De Sanctis, V., Soliman, A., Bernasconi, S., Bianchin, L., Bona, G., Bozzola, M., & Perissinotto, E. (2015). Primary dysmenorrhea in adolescents: prevalence, impact and recent knowledge. *Pediatric Endocrinology Reviews, 13*(2), 512-520.

DTAM. (2012). *Leard-ngam, Thai traditional herbal medicine formula bangkok: Agricultural co-operative federation of Thailand printing house.* Bangkok, Thailand: Department for Development of Thai Traditional and Alternative Medicine Ministry of Public Healh.

Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., & Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *Journal of Ethnopharmacology, 127*(2), 515-520. doi:10.1016/j.jep.2009.10.004

Fajrin, I., Alam, G., & Usman, A. (2020). Prostaglandin level of primary dysmenorrhea pain sufferers. *Enfermería Clínica, 30*, 5-9. doi:10.1016/j.enfcli.2019.07.016

Guzman-Esquivel, J., Galvan-Salazar, H. R., Guzman-Solorzano, H. P., Cuevas-Velazquez, A. C., Guzman-Solorzano, J. A., Mokay-Ramirez, K. A., & Delgado-Enciso, I. (2022). Efficacy of the use of mefenamic acid combined with standard medical care vs. standard medical care alone for the treatment of COVID-19: A randomized double-blind placebo-controlled trial. *International Journal of Molecular Medicine, 49*(3). doi:10.3892/ijmm.2022.5084

Itani, R., Soubra, L., Karout, S., Rahme, D., Karout, L., & Khojah, H. M. J. (2022). Primary dysmenorrhea: Pathophysiology, diagnosis, and treatment updates. *Korean Journal of Family Medicine, 43*(2), 101-108.

Kim, S. S., Oh, O. J., Min, H. Y., Park, E. J., Kim, Y., Park, H. J., & Lee, S. K. (2003). Eugenol suppresses cyclooxygenase-2 expression in lipopoly saccharide-stimulated mouse macrophage RAW 264.7 cells. *Life Sciences, 73*(3), 337-348. doi:10. 1016/s0024-3205(03)00288-1

Mirabi, P., Alamolhoda, S. H., Esmaeilzadeh, S., & Mojab, F. (2014). Effect of medicinal herbs on primary dysmenorrhoea- A systematic review. *Iranian Journal of Pharmaceutical Research, 13*(3), 757-767.

Oladosu, F. A., Tu, F. F., & Hellman, K. M. (2018). Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: Epidemiology, causes, and treatment. *American Journal of Obstetrics and Gynecology, 218*(4), 390-400. doi:10.1016/j.ajog. 2017.08.108

Pakniat, H., Chegini, V., Ranjkesh, F., & Hosseini, M. A. (2019). Comparison of the effect of vitamin E, vitamin D and ginger on the severity of primary dysmenorrhea: A single-blind clinical trial. *Obstetrics and Gynecology Science, 62*(6), 462-468. doi:10.5468/ogs.2019.62.6.462

Poomirat, S. J. N., Itharat, A., & Threrapanithan, C. (2020). Phytochemical analysis of Leard-ngam remedy and its composition. *Thammasat Medical Journal*, *20*(1), 60-73.

Sharghi, M., Mansurkhani, S. M., Larky, D. A., Kooti, W., Niksefat, M., Firoozbakht, M., & Jouybari, L. (2019). An update and systematic review on the treatment of primary dysmenorrhea. *JBRA Assisted Reproduction, 23*(1), 51-57. doi:10.5935/1518-0557.20180083

Sriyakul, K., Kietinun, S., Pattaraarchachai, J., & Ruangrungsi, N. (2012). A comparative double-blinded randomized study: The efficacy of Prasaplai herbal extract versus mefenamic acid in relieving pain among primary dysmenorrhea patients. *Open Complementary Medicine Journal, 4*, 16-21. doi:10.2174/1876391X01204010016

Termwiset, P., Sriyakul, K., Srikaew, N., & Tungsukruthai, P. (2021). Monitoring adverse drug reactions to Thai herbal remedies (Ya Satree) in Thailand: Observational study. *Songklanakarin Journal of Science and Technology*, *43*(5), 1329-1334.

Torkan, B., Mousavi, M., Dehghani, S., Hajipour, L., Sadeghi, N., Ziaei Rad, M., & Montazeri, A. (2021). The role of water intake in the severity of pain and menstrual distress among females suffering from primary dysmenorrhea: A semi-experimental study. *BMC Women's Health, 21*(1), 40. doi:10.1186/s12905-021-01184-w

Tripathi, S., Maier, K. G., Bruch, D., & Kittur, D. S. (2007). Effect of 6-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. *The Journal of Surgical Research, 138*(2), 209-213. doi:10.1016/j.jss.2006.07.051

Vannabhum, M., Poopong, S., Wongwananuruk, T., Nimmannit, A., Suwannatrai, U., Dangrat, C., & Akaraserenont, P. (2016). The efficacy of Thai herbal Prasaplai formula for treatment of primary dysmenorrhea: A short-term randomized controlled trial. *Evidence-Based Complementary and Alternative Medicine, 2016*, 2096797. doi:10.1155/2016/2096797

Yong Ik, K., M. D, Sang Goo, N., M. D, & Seung Taek, H., M.D. (2001). Comparison of visual analogue scale, categorical scale and satisfaction for postoperative pain. *The Korean Journal of Pain, 14*(2), 156-163.

Zakaria, Z. A., Mohamad, A. S., Chear, C. T., Wong, Y. Y., Israf, D. A., & Sulaiman, M. R. (2010). Antiinflammatory and antinociceptive activities of *Zingiber zerumbet* methanol extract in experimental model systems. *Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre, 19*(4), 287-294. doi:10. 1159/000312715