International Journal of Women's Health

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CLINICAL TRIAL REPORT

An Examination into the Safety and Efficacy of Khapregesic®, a Khaya Senegalensis Preparation, on Women Experiencing Menstrual Pain and Menstrual Distress: A Randomized, Double-Blind, Placebo-Controlled Trial

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Purpose: In traditional medicine, Khaya senegalensis has been used to treat menstrual pain, dysmenorrhea, and digestive pain and discomfort. However, there are no human clinical trials examining its safety and efficacy for the treatment of menstrual distress. Therefore, the purpose of this two-arm, parallel-group, randomized, double-blind, placebo-controlled trial was to examine the safety and efficacy of supplementation with a Khaya senegalensis preparation (Khapregesic®) on menstrual pain and menstrual distress in menstruating women.

Methods: Eighty-four women experiencing menstrual pain and distress were supplemented 3g daily with this Khaya senegalensis preparation or a placebo for one menstrual cycle. Changes in menstrual pain and other symptoms of menstrual distress were examined through daily ratings and validated self-report questionnaires. Moreover, changes in the use of rescue medications, C-reactive protein, and safety blood measures were examined.

Results: Compared to the placebo, this Khaya senegalensis preparation was associated with greater reductions in daily menstrual pain ratings (p=0.033) and reductions in overall menstrual distress (p=0.042). Improvements in emotional wellbeing were also identified, along with reductions in the use of rescue medications, although this latter finding requires confirmation in future trials. No changes in C-reactive protein were identified. This Khaya senegalensis preparation was well-tolerated and there were no significant changes in safety blood markers.

Conclusion: This study provides evidence supporting the safety and efficacy of a Khaya senegalensis preparation on menstrual pain and menstrual distress in women. Further investigations will be important to confirm and expand on the current findings and to help identify its potential mechanisms of action.

Trial Registration: ANZCTR, ACTRN12624000731594p. Registered 14 June 2024, https://www.anzctr.org.au/ACTRN12624000731594p.aspx.

Keywords: menstrual disturbances, dysmenorrhea, herbal medicine, clinical trial

Introduction

Menstrual distress refers collectively to all the negative symptoms that are associated with the menstrual cycle, such as abdominal pain and discomfort, nausea, breast tenderness, fatigue, headaches, and mood disturbances. These menstrual-related problems diminish quality of life and have a high rate of prevalence in menstruating women.[1,2] Based on a meta-analysis and large population-based surveys, approximately 50% of women report experiencing premenstrual syndrome

Received: 13 March 2025
Accepted: 5 July 2025
Published: 12 July 2025

(PMS)[3] and 70% dysmenorrhea (pain during the menstrual cycle).[4] Hot flushes in women of reproductive age are also a common occurrence, where at least one episode of chills and sweats was reported by 83.4% of women with PMS.[5]

In primary dysmenorrhea, increased intrauterine secretion of prostaglandins F2α and E2 are believed to be responsible for the pelvic pain associated with this disorder.[6] The etiology of PMS and premenstrual dysphoric disorder is complex, but is considered to be related to disturbances in ovarian reproductive steroid production, altered sensitivity in GABAergic neurons, and reduced serotonin availability.[7] Pharmacological agents such as nonsteroidal anti-inflammatory drugs and hormonal agents such as progestins or estrogen-progestin combinations are often used to treat dysmenorrhea.[6] In addition, non-pharmacological and non-invasive therapeutic options such as therapeutic exercise, biofeedback, thermotherapy, acupoint stimulation, electrotherapy, and manual therapies have also been used and investigated for the treatment of dysmenorrhea.[8,9] Manual therapy comprises the synergistic application of movement-oriented strategies, integrating exercise and manually applied mobilization and manipulation procedures such as massage, acupressure and spinal manipulation. Investigations into herbal medicines for PMS have also been undertaken with some positive, albeit inconsistent, findings on plant ingredients such as Crocus sativus Linn (saffron), Borage officinalis Linn (borage), Vitex agnus castus Linn (chaste berry), Matricaria chamomilla Linn (chamomile), and Zingiber officinale (ginger).[10] Phytoestrogens to treat hot flushes have also been investigated with some demonstrated efficacy; however, the overall quality of evidence is considered suboptimal.[11,12]

Khaya senegalensis (KS), with common names including African mahogany, dry zone mahogany, Gambia mahogany, khaya wood, and Senegal mahogany, is a tree species native to Africa. KS is on the International Union for Conservation Red List of threatened species; however, it is now cultivated and processed in Australia under strict agricultural certification using Australian Certified Organic and United States Department of Agriculture guidelines. KS has traditionally been used as an antimicrobial and anthelmintic agent for treating malaria, headaches, fever, rheumatism, jaundice, and epilepsy.[13–15] In traditional medicine, KS has also been used to treat menstruation pain, dysmenorrhea, ovulation disturbances, and digestive pain and discomfort. In animal and in vitro trials, the bark from KS has demonstrated antinociceptive (pain-blocking) and anti-inflammatory activity.[16] This may be due to its ability to stimulate opioid receptors, inhibit cyclooxygenase enzymes (enzymes associated with pain), and suppress prostaglandin E2 production.[16–18] KS also has significant antioxidant activity.[18,19] Moreover, KS is rich in limonoids, a phytochemical with anti-inflammatory effects.[14,20] In a recent animal trial, KS prevented seizures and reduced anxiety, likely through its effects on gamma-aminobutyric acid neurotransmission (a neurotransmitter implicated in anxiety), reductions in oxidative stress, and its neuroprotective effects.[13]

In an unpublished, open-label investigation, the therapeutic effects of a KS preparation were undertaken on 24 women presenting with abdominal pain and digestive complaints during menstruation. Positive symptomatic improvements in abdominal pain, stomach bloating, emotional symptoms, and sleep were reported by most participants after 7 to 10 days of treatment at doses ranging from 1 to 6 grams daily. However, there have been no controlled clinical trials investigating the efficacy and safety of KS in treating menstrual-related symptoms and pain in women. Therefore, the aims of this study were to examine the safety and efficacy of KS in reducing menstrual pain and menstrual distress in women. Based on traditional evidence and the anecdotal results from the preliminary open-label investigation, it was hypothesized that supplementation with KS in menstruating women experiencing menstrual pain and other symptoms of menstrual distress would be associated with reductions in pain, general menstrual symptoms, and an improvement in general wellbeing.

Materials and Methods

Study Design and Procedures

This study was conducted in accordance with the Declaration of Helsinki and received ethics approval from the National Institute of Integrative Medicine Human Research Ethics Committee (approval number 0142E_2024). Informed consent was obtained from all participants and the study was registered prospectively with the Australian and New Zealand Clinical Trials Registry (ACTRN12624000731594p).

This was a two-arm, parallel-group, randomized, double-blind, placebo-controlled trial (Figure 1). Interested volunteers completed an online screening survey where they provided background information and a summary of menstrual-

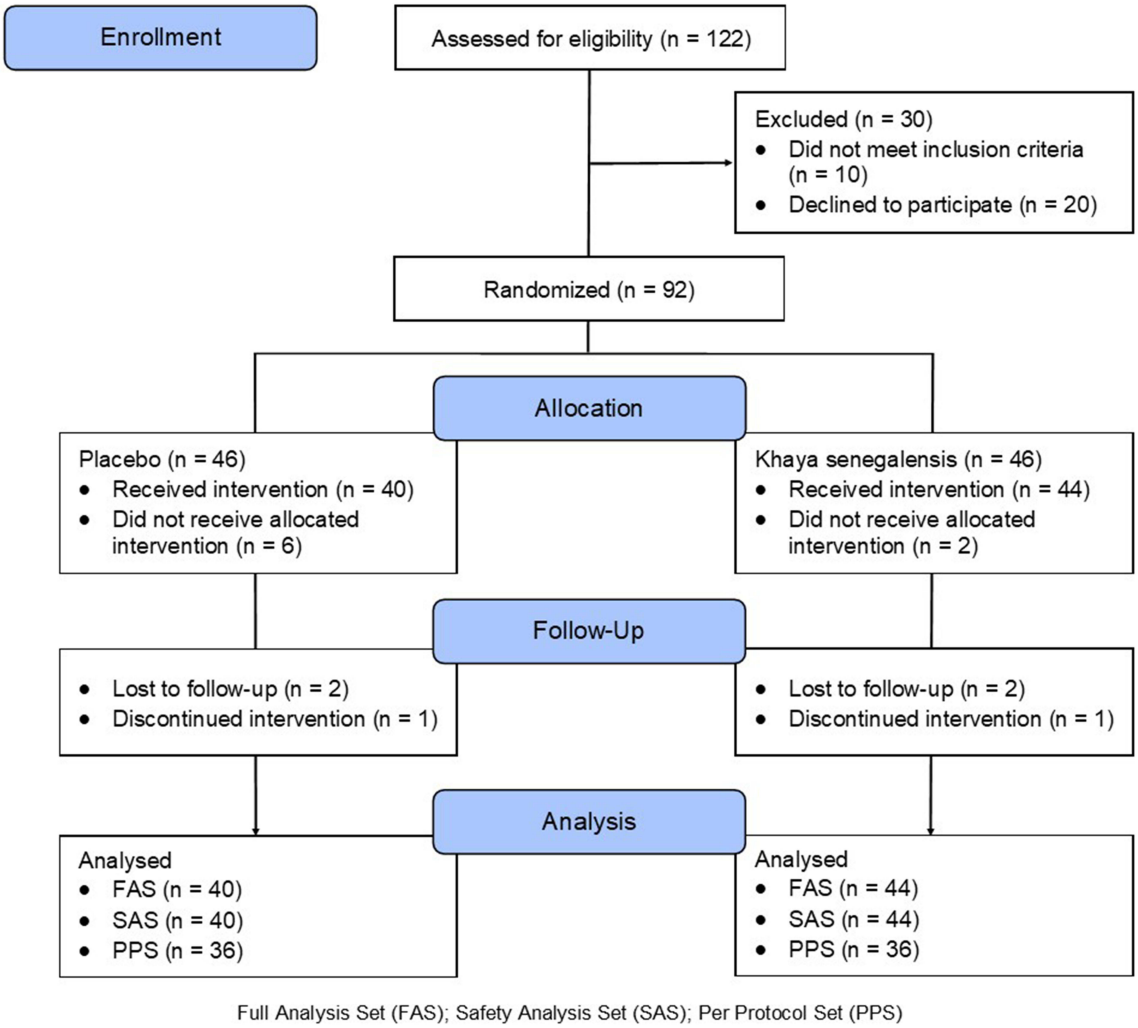

Figure 1 Systematic illustration of study design.

related symptoms. If deemed potentially eligible, they were contacted by telephone by a researcher and underwent a more comprehensive telephone interview. Further details were obtained about their menstrual pain, other symptoms experienced around menstruation, menstrual status, predicted next menstrual date and the typical length of their menstrual cycle. Moreover, other details were obtained pertaining to the eligibility criteria, such as current treatments, medications, and physical and mental health history. Participants were provided with a full explanation of the study, and if eligible and willing to participate in the study, were then required to sign an electronic version of the informed consent form. After completion of the consent form, participants were sent their study tablets by express freight. They were instructed to not start taking their tablets until the completion of their next menses/ bleeding. Details of the study procedures are included in Figure 2.

Recruitment and Randomization

Recruitment occurred from August 2024 to November 2024, using advertisements on social media and emails to a database of interested volunteers. Eligible participants were randomly assigned to one of two conditions (KS or placebo) on an equal ratio using a randomization calculator. The randomization structure, arranged by the study sponsor who was not involved in study recruitment and data collection, comprised 90 permuted blocks, with 10 participants per block. A participant number was designated based on the order of participant enrolment. All tablets were packed in

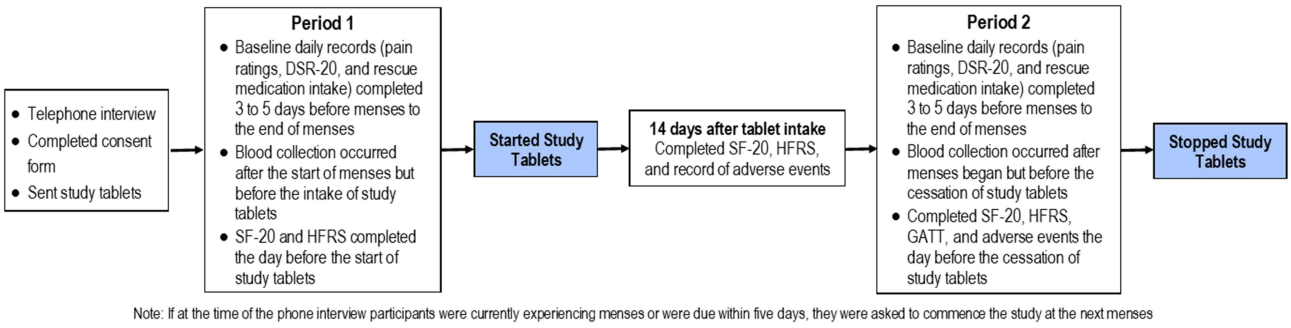

Figure 2 Study steps and procedures.

identical containers and bottle codes were held by the study sponsor. Researchers and the statistician were blind to the condition allocation until all outcomes were collected and a blind review was completed.

Participants

Inclusion Criteria

Inclusion criteria for the trial comprised the following: healthy menstruating females, aged 18 to 50 years; experience of mild-to-moderately-severe pain before and/or during menstruation, with a history of at least 3 months; experience of physical and/or emotional symptoms associated with menstruation, with a history of at least 3 months; having a regular menstrual cycle length of 21 to 35 days; non-smoker; body mass index between 18 and 30 kg/m^2; and no plan to commence new treatments over the study duration.

Exclusion Criteria

The exclusion criteria comprised the following: had a recent diagnosis of, or an unmanaged medical condition, including but not limited to, diabetes, hypertension, cardiovascular disease, gastrointestinal disease, biliary disease, autoimmune disease, cancer/malignancy, or endocrine disease; had a psychiatric (other than mild-to-moderate depression or anxiety) or neurological diagnosis (eg, Parkinson's disease, Alzheimer's disease, or head injury); the regular intake of medications, including but not limited to, opioids, corticosterone, hormone-replacement therapy, or gonadotropin-releasing hormone agonists; a change in medication in the last 2 months or an expectation to change during the study; the intake of vitamins or herbal supplements that were reasonably expected to influence study measures; in the last month, commenced or changed the dose of nutritional and/or herbal supplements that may impact treatment outcomes; planned a major lifestyle change in the next 2 months; alcohol consumption more than 14 standard drinks per week; current use or a 12-month history of illicit drug use; pregnant women, women who were breastfeeding, or women who intended to become pregnant during the study; in the last year, had significant surgeries (except exploratory surgery for endometriosis or other menstrual conditions); participated in any other clinical trial in the last month.

Interventions

The intervention comprised either KS or a placebo. The Khaya Senegalensis preparation (Khapregesic®) is derived from the dry stem bark. It is the only regulatory-approved form of KS developed to date, where it is listed with the Australian Federal Government Therapeutic Goods Administration. The Khaya Senegalensis preparation is cultivated and processed in Australia under strict agricultural certification using Australian Certified Organic and United States Department of Agriculture guidelines. Participants were instructed to take two tablets three times daily, with or without food. Each dose was taken 6 hours apart where it was recommended that the first dose be taken at approximately 8 am, the second at 2 pm, and the third at 8 pm or 1 hour before bedtime. Each KS tablet contained 500 mg, delivering a total daily dose of 3g. The active and placebo tablets were identical in appearance, matched for shape, color, and size, with both tablets containing similar excipients (calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, croscarmellose sodium, crospovidone, glyceryl monostearate, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, and

povidone). Adherence to tablet intake was assessed by asking participants to provide a count of remaining tablets at the end of the study. Treatment blinding was evaluated by asking participants to predict their condition allocation (placebo, KS, or unsure) at the end of the study, along with a reason for their prediction.

Outcome Measures

Details of the outcome measures collected in this study are included below and information on timing of collection are included in Figure 2.

Mean Daily Pain Ratings

Participants completed a daily pain rating (primary outcome measure) using a Likert scale ranging from 0 (no pain) to 10 (severe pain).

Daily Symptom Report (DSR-20) Total Score

The DSR-20 is a daily self-report measure used in trials to assess symptoms associated with menstruation and the menstrual cycle.[21] Ratings from 0 (not present at all) to 4 (severe, symptoms are overwhelming and/or unable to carry out daily activities) for 20 items are provided. A total score is calculated (primary outcome measure), plus a psychological and physical sub-scale score (secondary outcome measures).

Short-Form-20 (SF-20)

The SF-20 is a self-report, health-related quality-of-life questionnaire that assesses the impact of health on an individual's everyday life.[22] The SF-20 includes 20 questions where the following scores are calculated: total score, pain, physical functioning, physical role functioning, emotional wellbeing, social functioning, and general health.

Intake of Pain-Relieving Medication

A daily record of the intake of rescue medications (eg, paracetamol, ibuprofen, aspirin, naproxen sodium, and mefenamic acid) was recorded to assess changes over time.

High-Sensitivity C-Reactive Protein (hs-CRP)

Hs-CRP is a blood marker of general inflammation in the body. Having hs-CRP greater than 3 mg/L was as positively associated with premenstrual mood symptoms, abdominal cramps/back pain, appetite, cravings, weight gain, bloating, and breast pain.[23]

Hot Flush Rating Scale (HFRS)

The HFRS is a 5-item questionnaire assessing the frequency and problems associated with hot flushes over the past week.[24]

Safety Measures

The tolerability of tablet intake was assessed using an online question enquiring about the experience of any adverse events. Moreover, at the end of the study, participants completed the Global Assessment of Tolerability to Therapy (GATT), where they provided a response to their tolerability to tablet intake ranging from poor to excellent. Blood was collected at the beginning and end of the study to examine changes in safety blood markers comprising complete blood count, and liver and renal function.

Sample Size Calculations

No clinical trial examining the effects of KS on menstrual distress has been conducted. In previous trials investigating the effects of herbal ingredients and nutraceuticals in premenstrual syndrome, effect sizes have varied widely. In a meta-analysis on Vitex agnus-castus, effect sizes utilising a range of PMS-related self-report measures, an effect size of 2.57 [CI: 1.52, 4.35] was identified.[25] In a meta-analysis on several herbal and nutraceutical ingredients utilizing the DSR total score (primary outcome measure in this study), an effect size of 2.86 [CI: 1.02, 4.69] was identified.[10] However, the effects of KS were not investigated and treatment durations ranged from 2 to 4 menstrual cycles. As this study comprised administration for only one menstrual cycle and no clinical studies have been conducted on KS, a more conservative

effect size of 0.6 was predicted for changes in the primary outcome measure (DSR-20 total score). Assuming a power of 80% and a type one error rate (alpha) of 5%, the number of total participants required to find a treatment effect utilizing the DSR-20 total score was 72. Assuming a 10 to 15% dropout rate, it was planned to recruit 90 participants in total, which was hypothesised to give suitable power to find an effect compared to the placebo, even after dropouts.

Statistical Analysis

Outcome analyses were conducted on the full analysis set, per-protocol set, and safety analysis set. For the DSR-20 and mean daily pain ratings, mean ratings/scores were calculated for Phase 1 (2 days before the first menses to the end of the first menses) and Phase 2 (2 days before the second menses to the end of the second menses). For the SF-20 the time points comprised day 0 (the day before IP commencement), day 15 (14 days after tablets), and end of menses 2 (the day after the end of menses 2/ day before ceasing tablets). Generalized Linear Mixed Models (GLMM) assessed differences between intervention groups for treatment outcomes comprising the DSR-20, pain ratings, and SF-20, with intervention effects assessed via entry of the intervention group (placebo and KS) x time interaction. Random intercepts were utilized in each model, with the covariates of age and body mass index included. For all GLMMs, where applicable, gamma (with log link function) and normal (with identity link function) target distributions were used. Appropriate covariance structures were used to model correlation associated with repeated time measurements in gamma models. As there were slight differences (albeit not statistically significant) in some DSR-20, pain rating, and SF-20 outcome scores at baseline, GLMMs were completed on change in scores/ratings from period 1 to period 2. Random intercepts were utilized in each model, with covariates age, BMI, and corresponding baseline value included. Changes in the intake of pain-relieving medicines were examined using repeated-measures ANOVA (menses 1 and menses 2). Time x group interactions were used to examine group differences over time. Within-group changes in hs-CRP and safety blood markers were examined using repeated-measures ANOVA (menses 1 and menses 2). Time x group interactions were used to examine group differences over time. As the prevalence of reported hot flushes and night sweats using the HFRS was low, there was insufficient power to complete statistical analyses. A chi-square test was used to examine group differences in the frequency of GATT responses. All data were analyzed using SPSS (version 28; IBM, Armonk, NY) and the critical p-value was set at $p \leq 0.05$ for all analyses.

Results

Study Population

A total of 191 people underwent a telephone screening and 92 people were randomized. The most common reasons for exclusion were withdrawing consent after the telephone interview (n=22) and extensive travel during the study period (n=9).

Baseline Questionnaire and Demographic Information

Baseline demographic and clinical characteristics are detailed in Table 1. The two groups were similarly matched in age, BMI, marital status, and educational levels. Baseline scores on outcome measures were also similar between the two groups, although there was a slightly higher score on the SF-20 total score in the KS group, indicating a better overall quality of life/health.

Outcome Measures

Menstrual Distress

As demonstrated in Table 2 and Figure 3, based on the GLMM, there was a statistically significant group difference in the change in the mean DSR-20 total score (primary outcome measure 1) during period 1 and period 2 ($p = 0.042$). In the KS group, the mean total score decreased by 30.6% ($p < 0.001$) and in the placebo group, it decreased by 15.5% ($p = 0.017$), with a Cohen's D effect size of 0.43. An analysis of the per-protocol set revealed similar findings (Supplementary Table 1).

Table 1 Baseline Sociodemographic and Clinical Characteristics

		Placebo	KS
Age (years)	N	40	44
	Mean	32.38	35.62
	SE	1.34	1.21
Number of children	N	40	44
	Mean	0.68	1.18
	SE	0.22	0.22
BMI (kg/m^2)	N	40	44
	Mean	24.43	23.54
	SE	0.59	0.48
Marital Status (n)	Single	17	24
	Married/ defacto	29	22
Education (n)	Secondary	19	20
	Tertiary	13	15
	Post-graduate	8	9
Number of pain-relieving pills consumed during period 1	N	40	44
	Mean	6.23	4.41
	SE	7.61	6.22
International Physical Activity Questionnaire category (n)	Low	17	17
	Moderate	20	21
	High	3	6
Occupation (n)	Unemployed	1	7
	Services and sales worker	4	6
	Professional	4	9
	Plant and machine operators and assemblers	0	1
	Elementary occupation	2	2
	Clerical support worker	2	1
	Craft and related trades worker	2	1
	Manager	5	3
	Student	9	3
	Retired	0	1
	Technicians and associated trades	13	9

(*Continued*)

https://doi.org/10.2147/IJWH.S521349

Table 1 (Continued).

		Placebo	KS
DSR: Total Score	N	39	44
	Mean	16.87	16.88
	SE	1.54	1.48
DSR: Physical Score	N	39	44
	Mean	10.24	10.11
	SE	0.89	0.75
DSR: Psychological Score	N	39	44
	Mean	7.22	7.73
	SE	0.83	0.91
Pain Rating	N	39	44
	Mean	3.37	3.85
	SE	0.27	0.34
SF-20 Total Score	N	40	43
	Mean	75.49	81.24
	SE	2.36	1.72

An analysis of the DSR-20 Psychological Score revealed a statistically significant between-group difference in the change scores during period 1 and period 2 ($p = 0.016$). In the KS group, the mean score decreased by 35.5% ($p < 0.001$) and in the placebo group, it non-significantly decreased by 12.0% ($p = 0.156$), with a Cohen's D of 0.58. An analysis of the per-protocol set revealed similar findings (Supplementary Table 1).

Table 2 Change in Self-Ratings From Menstrual Period 1 to Period 2 (Estimated Marginal Means) (FAS)

		Placebo (n=40)				KS (n=44)				p-value[b]	Cohen's D Effect Size
		Period 1	Period 2	% Change	p-value[a]	Period 1	Period 2	% Change	p-value[a]		
DSR-20: Total Score	Mean	15.59	13.17	−15.5%	0.017	17.63	12.24	−30.6%	<0.001	0.042	0.43
	SE	1.44	1.26			1.60	1.14				
DSR-20: Physical Score	Mean	9.24	7.70	−16.7%	0.011	10.67	7.62	−28.6%	<0.001	0.107	0.38
	SE	0.78	0.67			0.88	0.65				
DSR-20: Psychological Score	Mean	7.04	6.20	−12.0%	0.156	7.96	5.14	−35.5%	<0.001	0.016	0.58
	SE	0.86	0.79			0.95	0.63				
Pain rating	Mean	3.23	2.60	−19.5%	0.041	3.94	2.13	−45.8%	<0.001	0.033	0.51
	SE	0.26	0.28			0.25	0.27				

Notes: Results (estimated means) are generated from generalized mixed-effects models adjusted for age and BMI. [a]P-values are generated from repeated measures generalized mixed-effects models adjusted for age and BMI (time effects period 1 and period 2). [b]P-values are generated from the change in mean rating from baseline using generalized mixed-effects models adjusted for age, BMI, and corresponding baseline score.

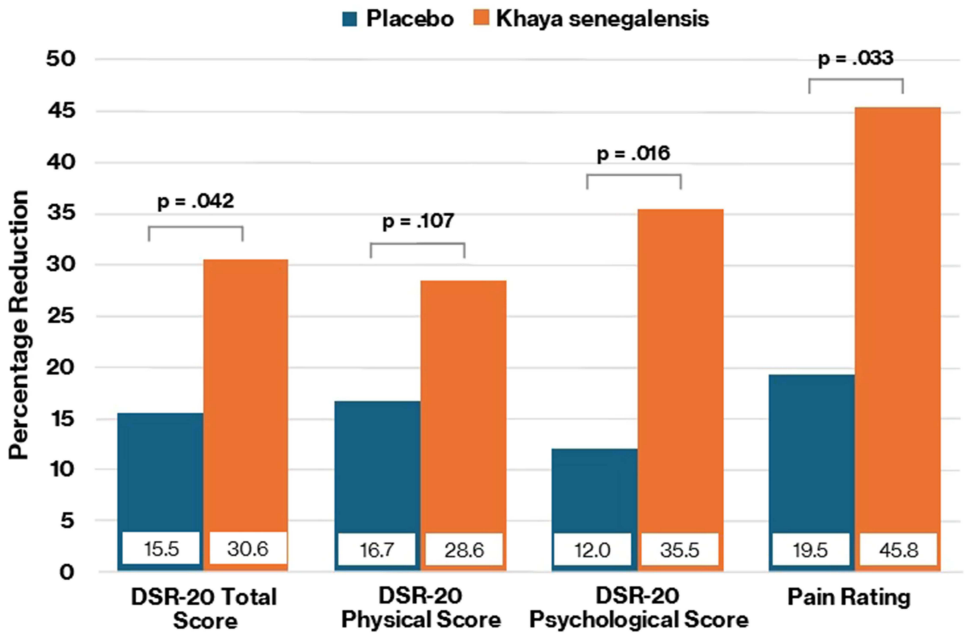

Figure 3 Percentage Change in Mean Self-Ratings from Menstrual Period 1 to Menstrual Period 2 (Full Analysis Set).

In relation to the DSR-20 Physical Score, there was no statistically significant between-group difference in the change in scores during period 1 and period 2 (p = 0.107). In the KS group, the mean score decreased by 28.6% (p < 0.001) and in the placebo group, it decreased by 16.7% (p = 0.011), with a Cohen's D of 0.38. An analysis of the per-protocol set revealed similar findings, although there was a trend of between-group differences (p = 0.088) (Supplementary Table 1).

Pain

As demonstrated in Table 2 and Figure 3, based on the GLMM, there was a statistically significant between-group difference in the change in the mean pain rating during period 1 and period 2 (p = 0.016). In the KS group, the mean rating decreased by 45.8% (p < 0.001) and in the placebo group, it decreased by 19.5% (p = 0.041), with a Cohen's D of 0.51. An analysis of the per-protocol set revealed similar findings (Supplementary Table 1).

Quality of Life and Wellbeing

As demonstrated in Table 3, based on the GLMM, there were no statistically significant time-by-group interactions for any SF-20 score. However, as there was a near-statistically significant group difference in the SF-20 baseline total score (p=0.05), an

Table 3 Change in SF-20 Scores (Estimated Marginal Means) (FAS)

		Placebo (n=40)					KS (n=44)					p-value[b]
		End of Period 1	14 Days After IP Intake	End of Period 2	% Change	p-value[a]	End of Period 1	14 Days After IP Intake	End of Period 2	% Change	p-value[a]	
SF-20 Total Score	Mean	76.05	80.08	80.52	5.88	<0.001	80.38	83.00	85.07	5.83	<0.001	0.463
	SE	1.78	1.88	1.90			1.83	1.90	1.95			
SF-20 Physical Functioning	Mean	92.13	95.75	96.23	4.46	0.001	94.50	96.70	97.31	2.98	0.020	0.660
	SE	1.61	1.63	1.65			1.57	1.59	1.59			
SF-20 Role Functioning	Mean	96.20	95.34	93.89	−2.40	0.348	96.26	99.22	98.37	2.19	0.374	0.376
	SE	1.92	1.91	1.91			1.84	1.96	1.90			

(*Continued*)

https://doi.org/10.2147/IJWH.S521349

Table 3 (Continued).

		Placebo (n=40)					KS (n=44)					p-value[b]
		End of Period 1	14 Days After IP Intake	End of Period 2	% Change	p-value[a]	End of Period 1	14 Days After IP Intake	End of Period 2	% Change	p-value[a]	
SF-20 Emotional Wellbeing	Mean	62.93	67.84	69.09	9.79	<0.001	68.67	73.71	77.57	12.96	<0.001	0.555
	SE	2.40	2.60	2.67			2.55	2.76	2.90			
SF-20 Social Functioning	Mean	82.42	90.36	85.44	3.66	0.260	86.58	89.84	92.78	7.16	0.025	0.134
	SE	2.45	2.73	2.64			2.51	2.65	2.74			
Pain	Mean	57.22	98.10	62.59	9.38	0.060	60.10	98.39	68.02	13.17	0.007	0.477
	SE	2.20	3.90	2.52			2.26	3.77	2.61			
SF-20 General Health	Mean	67.08	69.39	70.78	5.52	0.062	71.95	73.66	75.86	5.43	0.054	0.958
	SE	3.02	3.15	3.24			3.16	3.26	3.36			

Notes: Results (estimated means) are generated from generalized mixed-effects models adjusted for age and BMI. [a]P-values are generated from repeated measures generalized mixed-effects models adjusted for adjusted for age and BMI (time effects period 1 and period 2). [b]P-values are generated from repeated measures generalized mixed-effects models for age and BMI (time x group interaction).

exploratory analysis of change in SF-20 scores from menstrual period 1 to menstrual period 2 was undertaken, where corresponding baseline scores were entered as covariates. This revealed no statistically significant between-group differences in the change in SF-20 scores, except for the SF-20 emotional wellbeing score (p=0.026). After controlling for baseline scores, in the KS group, the emotional score increased by 14.7% and in the placebo group, it increased by 7.4%, with an increase indicating an improvement in emotional wellbeing.

Rescue Medication Intake

The mean total number of rescue medicines taken during menstrual period 1 and period 2 are detailed in Table 4. As the most common medicines comprised paracetamol and ibuprofen, only details of these medicines are included in the table, along with the total number of rescue pills taken during period 1 and period 2. Other pain-relieving medicines taken by participants included mefenamic acid, naproxen sodium, aspirin, ibudeine, tramadol, eletriptan, and diclofenac; however, the frequency of the intake of these medicines was low. There were no statistically significant between-group differences in the change in these medicines over time. However, in the KS group, the intake of ibuprofen significantly decreased from 2.29 pills to 1.12 pills (p=0.001). Moreover, the overall number of pain-relieving pills also significantly reduced from 4.34 to 2.29 in the KS group (p=0.007). There were

Table 4 Pain-Relieving Medicines Taken During Menstrual Period 1 and 2 (Completed Participants)

		Placebo (n=37)			KS (n=41)			p-value[b]
		Period 1	Period 2	p-value[a]	Period 1	Period 2	p-value[a]	
Paracetamol (500mg)	Mean	2.81	1.73	0.176	1.61	0.80	0.155	0.771
	SD	6.07	3.16		3.66	1.78		
Ibuprofen (200mg)	Mean	2.35	1.92	0.477	2.29	1.12	0.001	0.273
	SD	3.40	3.32		3.80	2.48		
Number of all pain-relieving pills taken	Mean	6.14	4.19	0.092	4.34	2.29	0.007	0.938
	SD	7.76	5.49		6.38	3.41		

Notes: [a] repeated-measures ANOVA within-group change from period 1 to period 2; [b] repeated-measures ANOVA time x group interaction.

non-significant decreases in the use of pain-relieving pills in the placebo group. An analysis of the per-protocol set revealed similar findings (Supplementary Table 2).

Inflammation

An ANOVA revealed no between-group difference in change in hs-CRP over time (p = 0.454). Moreover, within-group analyses revealed there was no statistically significant change in hs-CRP for both the placebo (p = 0.184) and KS (p=0.446) groups.

Intake of Investigational Products

Tablet bottles with remaining tablets were counted by participants at the end of the study. Based on these details, 97% (n=76) of participants who completed the study took over 80% of their tablets.

Efficacy of Participant Blinding

To assess the effectiveness of condition concealment during the trial, participants predicted their group allocation (ie, placebo, KS, or unsure) at the end of the study. Group concealment was maintained, as 57% of participants in the placebo group and 63% in the KS group were unsure or incorrectly guessed their group allocation. In total, only 5 participants correctly predicted treatment allocation, by citing taste, smell, or tablet appearance as reasons for their prediction.

Safety, Adverse Reactions and Treatment Discontinuation

Participants reported no serious adverse events, and there was a similar frequency of adverse events classified as possibly or probably related to the tablet intake (Table 5). In the KS group, 90.9% (n=40) of participants did not report experiencing any treatment-related adverse event, compared to 82.5% (n=33) in the placebo group. The GATT results demonstrated that in KS group, over 98% of participants reported good or excellent tolerability to tablets, compared to 97% in the placebo group. One person in the KS group reported moderate tolerability (see Supplementary Table 3).

In participants who commenced their tablets, 6 people discontinued the study (3 in each group). One participant in the KS group discontinued due to a believed treatment-related adverse event (head fogginess and nausea commencing

Table 5 Possibly or Probably Related Adverse Events by Class and Term

AE Class	Diagnosis or Symptom	Placebo (n=40)	KS (n=44)
Gastrointestinal	**Number of participants**	**4 (10.0%)**	**3 (6.8%)**
	Increased bowel movements/ loose stools	1 (2.5%)	0 (0.0%)
	Constipation	0 (0.0%)	2 (4.5%)
	Abdominal pain	1 (2.5%)	0 (0.0%)
	Stomach bloating	0 (0.0%)	1 (2.3%)
	Decreased appetite	1 (2.5%)	0 (0.0%)
	Nausea	2 (5.0%)	0 (0.0%)
Neurological	**Number of participants**	**2 (5.0%)**	**0 (0.0%)**
	Headaches	1 (2.5%)	0 (0.0%)
	Mood disturbance	2 (5.0%)	0 (0.0%)
Reproductive/ Hormonal	**Number of participants**	**2 (5.0%)**	**1 (2.3%)**
	Changes in menstrual cycle	1 (2.5%)	1 (2.3%)
	Pain in uterus	1 (2.5%)	0 (0.0%)
Number of participants experiencing no treatment-related adverse event		**33 (82.5%)**	**40 (90.9%)**

Note: Some participants experienced more than one treatment-related adverse event.

https://doi.org/10.2147/IJWH.S521349

immediately after the intake of the first tablet), and no participant in the placebo group discontinued due to a reported treatment-related adverse event.

An analysis of changes in blood measures of renal function, liver function and hematology revealed no statistically significant or clinically significant changes in blood measurements over time in the KS group (Supplementary Table 4).

Discussion

In this randomized, double-blind, placebo-controlled study, the effect of supplementation with a KS preparation in menstruating women aged 18 to 50 years on menstrual pain and other menstrual-related symptoms was examined. Participants took 3g daily for one menstrual cycle and changes in self-reported symptoms were investigated. Based on the results of the primary outcome measures, KS supplementation was associated with significant reductions in menstrual pain and general menstrual distress. In the KS group, there was a 30.6% reduction in the DSR-20 total score compared to a 15.5% reduction in the placebo group, which denotes a moderate effect size of 0.43. Pain ratings also reduced by 45.8% in the KS group compared to a 19.5% reduction in the placebo group, which represents a moderate effect size of 0.51. A further analysis of DSR-20 scores suggested KS had greater beneficial effects on psychological/ mood-related symptoms, as the DSR-20 psychological score decreased by 35.5% in the KS group compared to a 12.0% reduction in the placebo group (Cohen's D = 0.58). Changes in hot flashes and night sweats could not be adequately investigated due to the low prevalence of these symptoms in participants at baseline. An analysis of changes in the intake of rescue medications during period 1 and period 2 indicated that KS was associated with a significant reduction in total rescue medication use, and in particular, ibuprofen intake. This contrasts with non-statistically significant reductions in the placebo group. However, these findings should be considered preliminary as an extensive evaluation of changes in medication use was not undertaken. KS was well tolerated with no significant adverse effects or changes in safety blood parameters comprising liver function, renal function, and complete blood count. Moreover, 98% of participants in the KS group reported either good or excellent tolerability to the intake of 6 tablets per day for up to 35 days.

A comprehensive investigation into the mechanisms of action associated with the therapeutic effects of KS was not undertaken in this study and requires investigation in future trials. No changes in hs-CRP, a general measure of inflammation, were identified. This suggests KS may work through mechanisms other than anti-inflammatory actions. However, this finding should be viewed cautiously as hs-CRP is an acute phase protein and there remain other markers of inflammation that can provide a more comprehensive indication of inflammatory and immune-related activity. This includes the measurement of a range of cytokines with anti-inflammatory and pro-inflammatory actions. Preclinical studies suggest KS may stimulate opioid receptors, inhibit cyclooxygenase enzymes, and suppress prostaglandin E2 production.[16–18] KS also has significant antioxidant activity[18,19] and is rich in limonoids, a phytochemical with anti-inflammatory effects.[14,20] In an animal trial, KS also influenced gamma-aminobutyric acid neurotransmission, which may partly account for the mood-enhancing effects that were demonstrated in this study.[13]

Although there were several positive findings identified in the study, the following recommendations for further research are offered. The recruited population primarily comprised menstruating women who were not yet experiencing the menopausal transition. An investigation into the effects of KS supplementation in peri-menopausal and post-menopausal women is, therefore, recommended. This will also enable a better assessment of the effects of KS on hot flushes and night sweats. Along with improvements in pain, psychological improvements were identified in this study. Therefore, it seems KS may have specific mood-enhancing effects that will be worthy of investigation in future trials. The results of this study demonstrate its pain-relieving effects in menstruating women. However, the effects of KS on pain sensations in other pain conditions will be of interest. Moreover, an investigation into its acute and rapid pain-relieving effects will be of interest. A reduction in the use of rescue medications occurred in the KS group. However, to accurately identify changes in the use of rescue medications, more objective and controlled monitoring of medication intake is required. Although the results of this investigation demonstrate that KS taken at a dose of 1g, 3 times daily for 28 days has therapeutic effects, further investigations using different doses, timing and duration of intake will be helpful. In particular, the effects of KS over more than one menstrual cycle will be important to examine in future trials as this will provide evidence of safety and efficacy over a longer duration. Finally, in this study, KS was utilized as a stand-alone intervention for menstrual distress. However, non-pharmacological options with therapeutic efficacy are available. These

include therapeutic exercise, biofeedback, thermotherapy, acupoint stimulation, electrotherapy, and manual therapies.[8,9] In a recent systematic review, it was concluded that in comparison with placebo interventions, drug treatment, counseling, or no intervention, both manual therapy and electrotherapy were effective techniques for the treatment of women with primary dysmenorrhea.[9] An examination of the efficacy of KS compared to these non-pharmacological approaches will be worthwhile. Moreover, the effects of KS as an adjunct to these treatment options should be investigated to determine if greater therapeutic outcomes can be achieved.

In summary, this study has demonstrated positive support for the effects of a KS preparation on pain, menstrual distress, and emotional wellbeing in menstruating women supplementing for one menstrual cycle. To help further understand the therapeutic effects of KS, further trials will be important in examining its stand-alone or adjunctive efficacy effects in women with varying symptomatology, along with an investigation into its potential mechanistic actions.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Ethics Committee at the National Institute of Integrative Medicine (Approval No: 0142E_2024). Informed consent was obtained from all participants involved in the study.

Acknowledgments

The authors gratefully acknowledge Bioactive Natural Health Pty Ltd. for funding the project and supplying the investigational products and prior research used for this study.

Funding

Study funding and the investigational product used in the study was provided from Bioactive Natural Health Pty Ltd.

Disclosure

ALL is the managing director of Clinical Research Australia, a contract research organization that receives research funding from nutraceutical companies. ALL has also received presentation honoraria from nutraceutical companies. SJS is an employee of Clinical Research Australia. FRF is the head of research, co-founder, and CEO of Bioactive Natural Health Pty Ltd, the study funder and the manufacturer of the investigational product examined in this study. The authors report no other conflicts of interest in this work.

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