WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 12, 535-555. Review Article ISSN 2277–7105

EFFICACY AND SAFETY OF POLYHERBAL FORMULATIONS IN THE MANAGEMENT OF PRIMARY DYSMENORRHEA: A SYSTEMATIC REVIEW

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Article Received on 15 May 2026,
Article Revised on 05 June 2026,
Article Published on 16 June 2026

https://doi.org/10.5281/zenodo.20696379

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How to cite this Article: Ms. Jannat Diwate*[1], Dr. Shailesh Patwekar[2], Mr. Shubham Kamdi[3], Ms. Pallavi Gondale[4], Ms. Rutuja Patil[5], Ms. Shreya Kadam[6] (2026). Efficacy And Safety Of Polyherbal Formulations In The Management Of Primary Dysmenorrhea: A Systematic Review. World Journal of Pharmaceutical Research, 15(12), 535–555.

ABSTRACT

Background: Primary dysmenorrhea is a common gynecological condition characterized by painful menstrual cramps in the absence of identifiable pelvic pathology. Although non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives are widely used, treatment failure and adverse effects have increased interest in herbal alternatives. **Objective:** To systematically evaluate the efficacy and safety of standardized botanical extracts and polyherbal formulations in the management of primary dysmenorrhea. **Methods:** A systematic review was conducted according to PRISMA 2020 guidelines. Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and CENTRAL were searched for randomized controlled trials (RCTs) published up to April 2026. Studies involving women with primary dysmenorrhea treated with herbal or polyherbal interventions were included. Methodological quality was assessed using the Cochrane RoB 2 tool. Due to clinical and methodological heterogeneity, a narrative synthesis was performed. **Results:** Sixteen RCTs involving 1,641 participants met the inclusion criteria. Frequently investigated interventions included *Zingiber officinale* (ginger), *Cinnamomum zeylanicum* (cinnamon), *Foeniculum vulgare* (fennel), and various polyherbal formulations. Most studies

reported significant reductions in menstrual pain compared with placebo, while several demonstrated efficacy comparable to NSAIDs. Adverse events were infrequent, mild, and predominantly gastrointestinal in nature. **Conclusion:** Standardized botanical extracts and polyherbal formulations may provide effective and well-tolerated alternatives for the management of primary dysmenorrhea. However, further large-scale, prospectively registered RCTs using standardized formulations are required to confirm these findings and support clinical recommendations.

KEYWORDS: Analgesia; Menstrual Pain; Phytotherapy; Polyherbal Formulations; Primary Dysmenorrhea; *Zingiber officinale***.**

1. INTRODUCTION

1.1 Epidemiological and Pathophysiological Impact on Primary Dysmenorrhea

Continuous, sporadic lower abdominal and pelvic spasms linked to menstruation are known as primary dysmenorrhea having no obvious macroscopic pathology.[1] Primary dysmenorrhea is highly prevalent, with the majority of reproductive women will experience it at least once, as indicated by various epidemiological studies demonstrating varying prevalence rates depending on the variable examined (i.e., demographic), age group (i.e., adolescent versus adult), and geographic region (approx. 10% - 50%).[2] Furthermore, dysmenorrhea is the primary reason why young adults and adolescents miss work and school for brief periods of time (two to three days), which has a detrimental effect on global economic productivity, psycho-social welfare, and health-related quality of life.[3]

The overproduction of two distinct prostaglandins results in dysmenorrhea. (the hormones): PGF2α (prostaglandin F2α) and PGE2 (prostaglandin E2). The production of these prostaglandins occurs at the time of menstruation as a result of the production (by the endometrium) during luteal phase (the prior phase to menstruating), which results in the sloughing (or shedding) of the endometrium.[4] The production of prostaglandins occurs after the withdrawal of progesterone (a hormone) prior to menstruation by releasing arachidonic acid from the cell membranes of endometrial cells. This arachidonic acid is then catalysed via the COX (cyclooxygenase) pathway to produce high quantities of inflammatory prostaglandins.[5] The net result of this type of biochemical cascade is significant hyper-contraction of the myometrium (the muscle of the uterus). Additionally, this hyper-contraction causes an increase in the baseline/tonus of the uterus, as well as an area of local tissue ischemia (low blood flow) and cellular hypoxia. These areas of ischemia will very

sensitively stimulate the pelvic pain fibres causing nociceptive signals (pain signals) to be transmitted to the brain (where the pain is perceived, giving rise to the characteristic cramping pain experienced by women with dysmenorrhea).[6]

1.2 Current Standards of Care and Inherent Limitations

The usual first line treatments for primary dysmenorrhea are NSAIDs such as mefenamic acid, ibuprofen and naproxen.[7] These medications work by blocking the COX enzymes, which stop prostaglandins from being produced in the endometrium and decreases the rate of hypercontraction of the myometrium that would occur without.[8] Alternatively, the use of combined oral contraceptives (OCP) containing synthetic estrogens and progestins, also help to control dysmenorrhea. OCP inhibit (suppress) the hypothalamic-pituitary-ovarian axis (HPO), which prevents ovulation and causes a dramatic reduction in endometrial proliferation, these effects will also lead to a decrease in the total amount of endometrial tissue from which prostaglandins can be produced.[9]

Nevertheless, these first-line therapy treatments are not effective across the board, as their rates of clinical failure range between 20 and 25 percent. This subgroup of patients is classified clinically as being NSAID resistant, which results in a large population of women who do not receive sufficient analgesic relief.[10] Chronic cyclical use of NSAIDs also results in significant adverse events, including gastrointestinal ulcerations, renal toxicity, and possible cardiovascular complications.[11]

Likewise, OCP has systemic side effects that may create a negative impact on the patient's overall well-being, such as nausea, mood swings, and weight gain; further, they are contraindicated in various patient populations.[12] Therefore, it is not uncommon for clinical and patient-reported outcomes to associate combined oral contraceptives with diminished libido, increased depression in mood, headache, or breast enlargement,[13] and/or to strictly contraindicate their use in patients with a history of venous thromboembolism, incompletely controlled hypertension, recent breast cancer, aura-producing migraines, and women aged 35 and older who smoke. Therefore, the clinical failure rate of NSAIDs, which is documented as ranging between 20 and 25 percent, and the numerous side effects and contraindications associated with OCPs, create a large unmet clinical need to identify alternative therapeutic options that are both effective and well tolerated.[10]

1.3 The Rationale for Botanical and Polyherbal Interventions

Phytotherapy, or the use of plants for medicinal purposes, has shown great support from research and real-world experience as a secure and efficient method of treating primary dysmenorrhea (painful menstrual cramps). Many herbal products, like ginger, cinnamon, and fennel, are known to contain powerful plant compounds (phytochemicals) that have antispasmodic, anti-inflammatory, and analgesic (pain-relieving) properties.[14] For example, ginger contains two compounds, gingerols, and shogaols, that have been found to decrease the production of a hormone called prostaglandins and suppress the chemical reactions pathways (COX and lipoxygenase) that help create them.[15] Cinnamon contains two compounds, cinnamaldehyde and eugenol, that have potent antispasmodic properties and reduce the overall ability of the uterus to contract, regardless of how much force is being used to cause contractions.[16] Fennel is high in the oil anethole, which serves as a direct antispasmodic agent.[17]

More recently, standardized combinations of multiple herbs (i.e., polyherbal formulations) are being used to specifically address the management of primary dysmenorrhea. These complex combinations are intended to exploit synergies between the various plant molecules.[18] The underlying rationale behind polyherbalism is that when multiple herbs are used at once, the physiology of pain can be impacted at many levels (e.g., by decreasing inflammatory cytokines, inhibiting COX-2 synthesis, relaxing uterine smooth muscle) and the overall adverse effects associated with using a single medication (i.e., toxicity) can be prevented.[19] Polyherbal formulations aim to provide maximum pain relief with minimal side effects by combining agents that reduce peripheral inflammation and central pain perception.[18,19]

1.4 OBJECTIVE

While the number of RCTs assessing the efficacy of these natural medicines is increasing, due to the vast differences between the methods for extracting the plant, dosing, herbal classification, and the way in which the trials were conducted, there is still very little consistent evidence available to draw global comparisons from.[20] For the treatment of primary dysmenorrhea, this systematic review will compare the efficacy and safety of standardized herbal products and polyherbal formulations to those of conventional medications or placebos.

2. Systematic Review Protocol

2.1 Protocol Adherence

This systematic review adhered to current PRISMA 2020 guidelines and was created and carried out using the most rigorous methodological practices to provide a transparent and reproducible procedure for identifying, selecting and appraising published studies. Methodologically, the absence of a previous prospective registration of this systematic review (either within PROSPERO or by using another systematic review registry) is a limitation. This limitation also decreases the overall credibility of the systematic review process, as it does not conform to accepted criteria for systematic reviews conducted within similar types of epidemiological research.

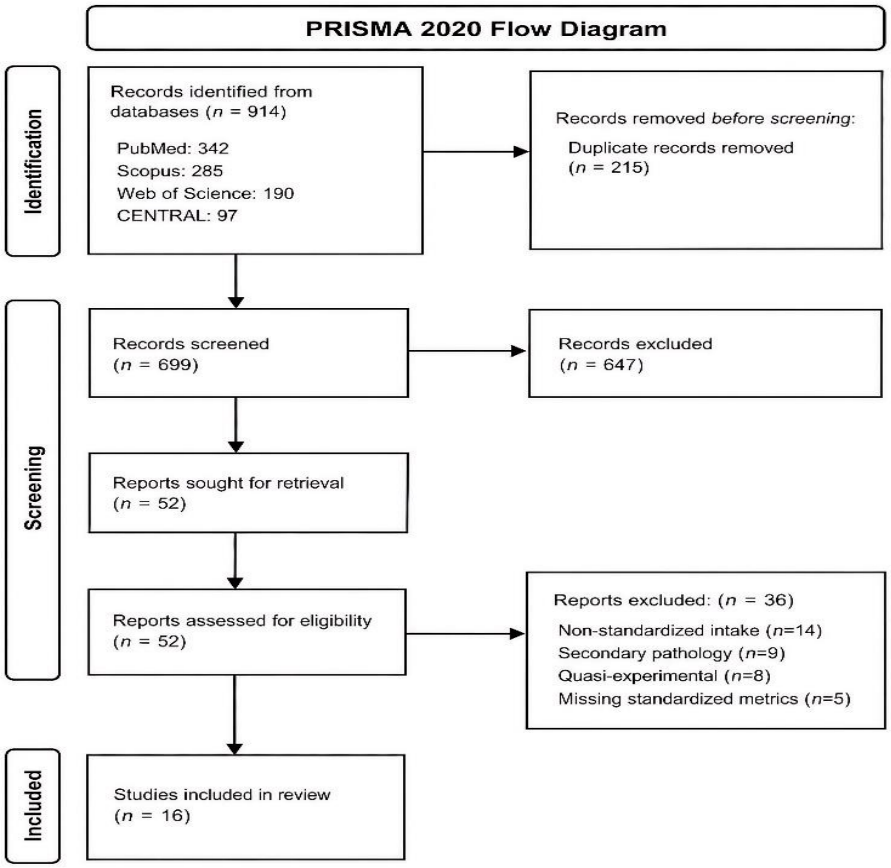

Figure 1: The 2020 PRISMA Flow Diagram for Data Extraction of Included Studies.

2.2. Eligibility Criteria

A popular method is PICOS (population, intervention, comparator, outcome, study design) framework for designating inclusion and exclusion criteria to improve clarity, accuracy, and consistency of authorship. The PICOS model is also designed to maximize fidelity in documenting evidence of and providing access to studies reported in the literature about primary dysmenorrhea.

1. Population: The population must be composed entirely of reproductive-age women diagnosed clinically as having suffered from primary dysmenorrhea (clinical criteria for dysmenorrhea). Studies that enrolled patients suffering from secondary dysmenorrhea due to pathologies of the pelvic cavity (i.e., endometriosis, pelvic inflammatory disease, adenomyosis, or uterine fibroids) will not be included in this review to prevent confounding biological variables.

2. Intervention: Any standardized botanical extract or polyherbal combination intervention provided by capsule (e.g., orally), decoction (e.g., boiled), and/or topical application (i.e., local delivery), were eligible for this review.

3. Comparator: To assess the effectiveness of treatment, any use of a non-active substance (i.e., drug, placebo, no intervention), standard active pharmaceuticals (nonsteroidal anti-inflammatory medications (NSAID), e.g., mefenamic acid, ibuprofen, combined oral contraceptives) were treated as valid comparisons.

4. Outcomes: Primary efficacy outcomes were based on the degree of reduction (quantitative) in menstrual pain severity assessed through valid subjective measures such as Numerical Rating Scales (NRS) or Visual Analog Scales (VAS) as the primary safety outcomes; additionally, data regarding the frequency, severity, and incidence of at least one adverse event associated with the study treatment were collected. Throughout the manuscript, outcomes will be discussed in the same order (efficacy, then safety).

5. Study Design: Only randomized controlled trials (RCTs) that were double-blind and had parallel or crossover designs published in the English language were included. No observational studies; quasi-experimental designs (not adequately controlled or randomized); case reports; in vivo/in vitro animal experiments; previous literature reviews were excluded from consideration.

2.3 Information Sources and Search Strategy

Four major electronic databases were used to search for papers in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search technique began at beginning for each database, continued until April 2026 in order to incorporate all available literature.

Using a combination of MeSH terms and free-text keywords with Boolean operators, the search strategy employed ("Primary Dysmenorrhea" or "Menstrual Pain" or "Menstrual Cramps"), ("Polyherbal" or "Herbal Formulation" or "Plant Extract" or "Phytotherapy"), and ("Randomized Controlled Trial" or RCT or Clinical Trial"). In order to find any additional research that might not have emerged from the original algorithmic search, two independent reviewers further examined the reference lists of all papers that satisfied the initial inclusion criteria.

2.4 Methods of Data Extraction and Study Selection

When performing the first execution of broad search parameters, the major output was a very high volume of initial data with 1,563,795 total results from PubMed alone prior to rigorous application of specific clinical trial filters and Boolean limiters. Once the full execution of the strict search string had been performed, and results of only randomized clinical trials had been filtered, the final relevant record pool measured 914 citations across all four databases.

Upon completion of the search strategy, all 914 records that were identified were exported to Mendeley Desktop (version 1.19.8) which was designated as the reference manager software. To eliminate duplicate records from the four databases, algorithmic deduplication was carried out using the reference management software. Two researchers independently examined the titles and abstracts of each unique record during the first screening stage in order to identify studies that satisfied the predetermined PICOS criteria. Potentially eligible studies were also sent on to full-text review.

During the full-text review phase, the same pair of reviewers evaluated each article's methodology and reported results. If Primary Reviewers couldn't agree on any particular study's eligibility, a third reviewer made the final decision. A standardized Microsoft Excel extraction matrix that was pilot tested and proved to be dependable across all sites was used for data extraction, which was carried out separately. Data extraction included the following predefined data points from each eligible RCT: 1) primary author & year; 2) country; 3) trial design; 4) total number (N) of subjects; 5) age range of subjects; 6) complete composition and daily dosage of the botanical or polyherbal intervention; 7) nature & dose of the comparison agent; and 8) primary efficacy outcomes (e.g. change in pain intensity) and a complete record of all adverse effects reported.

2.5 Quality Assessment and Risk of Bias

Two independent reviewers assessed each randomized controlled trial (RCT) individually using the Revised Cochrane Risk of Bias Assessment Tool for Randomized Trials (RoB 2). The RoB 2 tool consists of five domains that are assessed in order to determine whether there was any risk for bias: (1) bias due to randomization procedures used, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias due to measurement of outcomes, and (5) bias due to selection of outcomes to report. After completing the individual domain assessments, each RCT received an overall risk classification - “low risk,” “some concern,” or “high risk.”

2.6 Data Synthesis Framework

The degree of methodological and clinical variability seen in the research that looked at botanicals, including a lot of different doses for the active compounds used in addition to variable reporting formats for the outcomes, caused major difficulties when it came time to apply statistical meta-analytical techniques to pool effect sizes. Consequently, it was not possible to do a quantitative meta-analysis on the disparate and un-unified data from the various studies because doing so would generate highly misleading estimates of effect size; therefore jeopardizing the integrity of such a review. Thus, a structured narrative synthesis was undertaken based upon systematic categorization of both efficacy and safety data according to the composition of the botanical(s) used in an intervention, and by making qualitative comparisons with the standard of care and placebo groups.

3. RESULTS

3.1 Literature Search and Study Selection

Through a systematic investigation into available literature, 914 records concerning clinical trials were retrieved from four different databases utilizing the finalized Boolean search criteria (PubMed = 342; Scopus = 285; Web of Science = 190; CENTRAL = 97). After removing duplicate entries from Mendeley Desktop (n=215), the remaining set of 699 unique records were then evaluated based solely upon their abstract and title in accordance with predetermined inclusion/exclusion standards. Of these 699 records, 647 records were eliminated during phase one screening primarily due to the record(s) being study of in vivo animal models or contained only chemotherapeutic analysis with no human clinical endpoints, or the record(s) were examining secondary dysmenorrhea.

The final 52 full-text publications were obtained and evaluated in accordance with our exacting inclusion standards. Of the 52 articles, 36 were eliminated from analysis due to serious methodological flaws: 14 studies did not examine standardized clinical formulations of dietary herbal intake, 9 studies involved participants with confirmed secondary pelvic pathology (endometriosis or fibroids), 8 studies utilized a quasi-experimental design (i.e., no true randomization and an inadequate control group) and 5 studies provided pain data using a visual analogue scale, but no clearly defined primary outcome measure. Therefore, only 16 rigorously conducted, double-blind RCTs qualified for inclusion in this review and were synthesized.

3.2 Characteristics of the Included Studies

There were sixteen studies in this review of 1,641 females; the demographic was very similar across all studies—mainly nulliparous females 18-30 years old with a clinical diagnosis of moderate-severe primary dysmenorrhea (menstrual cramping). The included studies evaluated many interventions (including extensive research on single botanical agents: *Zingiber officinale*, *Cinnamomum zeylanicum* and *Foeniculum vulgare*) and well-researched polyherbal combinations. Outcomes were compared against inert placebos, mefenamic acid, ibuprofen and certain mineral therapy agents (zinc). A detailed summary of the study characteristics, intervention parameters and primary outcomes can be found in Table 1.

Table 1: Characteristics and Primary Outcomes of the 16 Included Randomized Controlled Trials.

Author & Year	Study Design	Sample Size (N)	Intervention & Dosage	Comparator	Primary Efficacy Outcomes (Pain Intensity)	Reported Adverse Events
Ozgoli et al. (2009)	Double-blind RCT	150	*Zingiber officinale* 250 mg capsules, 4x daily	Mefenamic acid / Ibuprofen	In terms of pain relief, ginger was just as successful as ibuprofen and mefenamic acid ($P > 0.05$).	None significant
Rahnama et al. (2012)	Placebo-controlled RCT	120	*Zingiber officinale* 500 mg, 3x daily	Placebo	Significant reduction in pain severity (VAS) and duration ($P < 0.05$).	None reported
Jahangirifar et al. (2018)	Double-blind RCT	114	*Cinnamomum zeylanicum* 420 mg, 3x daily	Placebo	Systemic symptoms and pain severity were significantly reduced ($P < 0.001$).	Minimal GI discomfort
Vannabhum et al. (2016)	Double-blind RCT	40	Prasaplai Polyherbal Formula, 1000 mg, 3x daily	Placebo	Significant reduction in pain intensity; higher relief rate by day 3.	Well-tolerated
Abedian et al. (2020)	Triple-blind RCT	90	Ginger-Lavender combination (250 mg + 50 mg), 4x daily	Mefenamic acid / Ginger alone	Combination therapy significantly superior in VAS reduction ($P < 0.05$).	None serious

Khorshidi et al. (2003)	Crossover RCT	60	*Foeniculum vulgare* extract (2%)	Placebo	Pain intensity was significantly lower than with a placebo ($P < 0.01$).	1 case of increased bleeding
Gharloghi et al. (2012)	Double-blind RCT	180	Menstrugol (Saffron, Celery, Anise), 500 mg, 3x daily	Mefenamic acid	Polyherbal extract was more effective than mefenamic acid in pain reduction.	No systemic side effects
Jaafarpour et al. (2015)	Double-blind RCT	80	*Cinnamomum zeylanicum* 1000 mg, 3x daily	Placebo	Significant reduction in pain severity and menstrual bleeding ($P < 0.05$).	None
Mirabi et al. (2011)	Double-blind RCT	100	*Valeriana officinalis* 255 mg, 3x daily	Placebo	Valerian extract significantly reduced pain compared to placebo.	Minimal sedation
Modarresi et al. (2011)	Double-blind RCT	80	*Matricaria chamomilla* capsules, 250 mg, 3x daily	Placebo	Anxiety and discomfort scores were significantly reduced ($P < 0.05$).	None
Nahid et al. (2009)	Double-blind RCT	80	*Foeniculum vulgare* 46 mg extract, 4x daily	Mefenamic acid	Fennel relieved pain just as well as mefenamic acid.	None
Jenabi (2013)	Placebo-controlled RCT	105	*Zingiber officinale* 500 mg, 3x daily	Placebo	Significant reduction in pain intensity ($P < 0.05$).	None reported
Ghodsi et al. (2014)	Double-blind RCT	120	*Zingiber officinale* 250 mg, 3x daily	Placebo	Ginger significantly reduced pain intensity and duration ($P < 0.05$).	Mild nausea in 2 cases
Zeraati et al. (2014)	Double-blind RCT	100	Curcumin 500 mg/day	Mefenamic acid	Curcumin significantly reduced pain; comparable to NSAID efficacy.	Gastrointestinal relief
Heidarifa et al. (2014)	Double-blind RCT	150	*Anethum graveolens* 1000 mg extract	Mefenamic acid	Mefenamic acid was shown to be just as efficacious as dill ($P = 0.74$).	None reported
Masoumi et al. (2016)	Crossover RCT	72	*Pimpinella anisum* 330 mg, 3x daily	Ca-Mg Combination	Anise significantly reduced pain intensity compared to mineral therapy.	None reported

3.3 Risk of Bias Evaluation

We assessed the methodological quality of the sixteen randomized controlled trials (RCTs) included in this review using the Cochrane risk-of-bias tool for RCTs (RoB 2). All reviewed RCT methodology was found to have strong methodological bases upon which these RCTs were aggregated. Of the studies reviewed, ten (62.5%) were rated with a "low risk" of bias across all dimensions, making them highly successful as randomized controlled trials. All ten studies demonstrated excellent RCT methodology by employing computer-generated randomization sequences, using opaque sealed envelopes for allocation concealment, and having highly effective blinding of both study participants and study outcome assessors.

Six research (37.5%) out of the total number of studies included in this systematic review were categorized as having "some concerns" regarding the possibility of bias. None of the 16 studies that were finally chosen to be included in this review had a "high risk" of bias. This

implies that high-quality trials were successfully identified by the stringent eligibility requirements that were put in place during the original screening procedure. Rather than being a sign of a serious methodological problem, 37.5% of the studies were classified as having "some concerns" mostly because the paper lacked sufficient detail. In particular, these concerns generally involved the use of unclear language with respect to how allocation concealment and missing statistical data were handled. Nonetheless, the relatively minor degree of ambiguity associated with these forms of reporting did not substantially compromise the reliability of the primary efficacy outcomes reported in each of the selected trials.

3.4 Narrative Synthesis of Efficacy Outcomes

When analyzing the data from the 16 studies, 1,641 (mean age range 18-27) women were included in the final analysis. Quantitatively, botanical interventions provided statistically significant menstrual pain relief over placebo and were also statistically equivalent to analgesics prescribed by a physician. Below are the clinical efficacy results (pain relief) broken down by the main component in each botanical pain-relieving product.

3.4.1 Efficacy of *Zingiber officinale* (Ginger)

Of the 16 trials involved in this analysis, four used gingers as an intervention (Ozgoli, Rahnama, Jenabi and Ghodsi) which made up a pooled sub-cohort totalling 495 participants. The therapeutic dosage used in these trials ranged from 750 mg to 1500 mg (per day) with investigators typically giving each dosage several times throughout a 24-hour period.

The placebo-controlled trials conducted by Rahnama, Jenabi and Ghodsi demonstrated highly statistically significant reductions ($P < 0.05$) in VAS pain scores for ginger extract as compared to the inert placebo groups. Interestingly, as noted specifically by Ghodsi, ginger extract not only reduced the peak pain intensity level but also reduced the duration of the dysmenorrheic pain phase. Finally, ginger extract (250 mg given 4 times/day) was directly compared to clinical doses of mefenamic acid (250 mg) and ibuprofen (400 mg) in a randomized controlled active-comparator trial ($N = 150$). Statistical equivalence ($P > 0.05$) was established among all three groups on the primary endpoint, suggesting that standardized ginger extract may actually have an analgesic effect similar to that of first-line synthetic COX inhibitors when treating primary dysmenorrhea.

3.4.2 The Effectiveness of *Cinnamomum zeylanicum* (Cinnamon)

Cinnamon has been extensively tested in two trials conducted by Jahangirifar and Jaafarpour that included a total of 194 subjects. The daily dosages studied were varied widely from 1260 mg to 3000 mg per day. Both trials were well-controlled, and data was collected comparing the participants who received cinnamon capsules vs. starch placebo capsules.

The research' findings revealed a notable, statistically significant decline ($P<0.001$) in primary pelvic pain severity in the subject's receiving cinnamon. Additionally, Jahangirifar et al. showed that cinnamon use reduced systemic secondary menstrual symptoms, specifically nausea and vomiting, which are significantly aggravated during the first 48 hours of menstruation by the peak of prostaglandin release. Jaafarpour et al. provided a secondary outcome showing a significant reduction in the overall volume of menstrual bleeding.

3.4.3 *Foeniculum vulgare* (Fennel) Efficacy

Fennel has been tested through two trials (Khorshidi & Nahid) with a total of 140 patients (or sample size). In one trial (Khorshidi et al.), 2% fennel essential oil was evaluated using a crossover method, with results showing almost a 50% decrease in pain intensity ($P<0.01$) to that of the placebo product. In another trial (Nahid et al.), an aggressive study was completed with 80 subjects and the use of an extract of 46 mg of concentrated fennel four times per day to compare with mefenamic acid, a pharmaceutical NSAID, for two full menstrual cycles. Their results demonstrated no statistically significant difference to support that the use of any fennel product was equal to the effects produced from mefenamic acid.

3.4.4 Efficacy for Herbal Combination Products

Synergistic plant-based formulations have demonstrated some of the greatest absolute reductions in pain as evidenced by their use in many published clinical trials. For instance, a triple-blind randomized controlled trial (N=90) conducted by Abedian et al. evaluated a combination of plants (ginger and lavender) in a single capsule. The ginger-lavender extract contained 250 mg of ginger and 50 mg of lavender extract. The study found that when treated with this formulation, subjects had statistically significantly greater reductions in their visual analogue scale (VAS) scores when compared with treatments of single-molecule ginger or mefenamic acid ($P < 0.05$) thus demonstrating that the polyherbal synergy produced a greater reduction in pain.

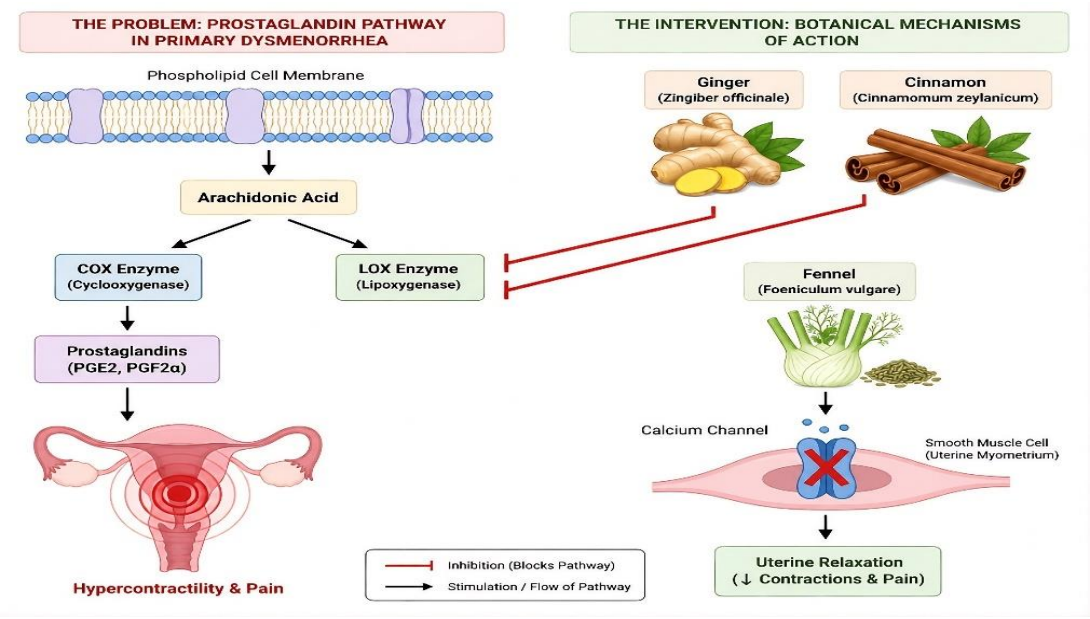

Figure 2: Mechanism Of Action Diagram Showing Biochemical or Physiological Flowchart Showing the Intervention's Effect on Pain Pathways.

In the same vein, the safe Messstrugol formulation, which contains saffron, celery, and aniseed, was shown by Gharoghi et al (N=180) by statistical analysis to be noticeably more successful than conventional NSAID treatment in lowering the intensity and duration of spasmodic pain. The Thai polyherbal Prasaplai formula at 1000 mg (three times daily) was evaluated by Vannabhum et al in a group of 40 women; they found that pain relief was significantly greater than with placebo, with complete relief of pain being particularly high by day three post-menses.

3.4.5 Efficacy of Other Botanical Interventions

Several additional plant medicines showed significant clinical efficacy. Mirabi et al. (N=100) evaluated *Valeriana officinalis* (valerian root at 255 mg, three times per day) against placebo for treatment of dysmenorrhea, finding that valerian root use reduce dysmenorrheic pain significantly compared to placebo likely because it is an antispasmodic agent to smooth muscle tissues. Zeraati et al. (N=100) evaluated the effect of curcumin (500 mg daily) vs. mefenamic acid; their results showed that curcumin was able to reduce pain severity significantly while providing statistically similar efficacy compared to the NSAID along with substantial gastrointestinal relief. Heidarifa et al. (N=150) compared a high-dose (1000 mg) extract of *Anethum graveolens* (dill) directly with mefenamic acid and found no significant difference between the two interventions regarding pain relief (p=0.74). Lastly, Masoumi et al. (N=72) conducted a crossover design study comparing *Pimpinella anisum* (anise) with a

calcium/magnesium mineral combination yielding a finding that anise produced a greater reduction in pain intensity than standard mineral therapy.

In summary, there were 16 trials included in this review, with 50% (eight trials) having utilized an NSAID as the active comparator; each of the eight comparative trials found both the botanical medicine and polyherbal formulations to show either statistical equivalency (noninferiority) or slightly superior analgesic effects.

3.5 Safety Outcomes and Tolerability

The analysis of the quantitative data regarding adverse events suggests that all of the phytotherapeutic treatments evaluated in this study demonstrated an excellent tolerability profile. From the 16 published trials evaluated in this Synthesis, 11 reported no adverse events (68.7%). Therefore, of the 5 trials that reported an adverse event, all were mild, transient, and did not affect the entire body, the total of 1,641 participants in this trial, the most common reported adverse event was minor gastrointestinal complaints (i.e., nausea and dyspepsia) that were only found to occur in 2.5% of the total participants who received a botanical intervention; thus, the long-term gastrointestinal side effects from botanical intervention wherein they would not be able to prescribe non-steroidal anti-inflammatory drugs (NSAIDs) due to gastric intolerance were very low when compared to NSAID use and found much lower incidences of gastrointestinal irritation among the phytotherapeutic cohorts compared to the NSAID cohorts.

The only adverse event reported was one trial with 2% fennel essential oil (Khorshidi et al.), where the participant experienced excessive menstrual bleeding; however, this did not reach the level of statistical significance compared to the cohort mean. There were no serious adverse events from system effects, no neurological adverse events, or events where the participants required medical attention.

4. DISCUSSION

4.1 Summary of the Evidence

The evidence synthesized from 16 adequate RCTs involving 1,641 subjects indicates that standardized botanical products and polyherbals demonstrate significant clinical utility in treating primary dysmenorrhea. Studies using these interventions (primarily containing *Zingiber officinale* (ginger), *Cinnamomum zeylanicum* (cinnamon), and *Foeniculum vulgare* (fennel)) show clinically- and menstruation pain intensity reductions that are statistically

significant when compared to inert placebo controls. More significantly, herbal treatments are statistically non-inferior to common non-steroidal anti-inflammatory drugs (NSAIDs), especially mefenamic acid and ibuprofen, in the direct comparison studies included in this analysis, for overall analgesic efficacy, with an excellent safety profile for these botanical interventions (adverse event rates of less than 2.5%, almost all of which were mild and transient gastrointestinal events, and no severe systemic complications). This is in contrast to the established systemic toxicities and 20 to 25% failure rates associated with long-term use of NSAIDs and oral contraceptive pills, leading to the conclusion that phytotherapy represents a highly attractive clinical alternative.

4.2 Limitations of Current Evidence: Dosage Variability and Sample Size

Although a synthesis of the safety and effectiveness of various plant-based treatments appears to be a highly optimistic statement, the problems of diverse methodologies and clinical aspects in many of the published clinical trials limit the external validity and ability to generalize the results to other populations. Therapeutic dosing for *Zingiber officinale* has varied between 750 and 1500 mg of dried ginger root every day. When it comes to studies on *Cinnamomum zeylanicum*, the difference in dosing is even more substantial, with investigators administering 1260 mg to 3000 mg per day to obtain pain relief. The wide variation in the amount of the herb administered would make it impossible to determine an optimal dosage of the plant and subsequently the true dose-response relationship between the phytochemicals within it. The absence of sufficient standardization between the methods used to extract the bioactive phytochemicals from the herbs grown in different places and at different times creates problems because a 500 mg fennel extract used in one study may contain a completely different proportion of the active phytochemicals than a 500 mg fennel extract from another study.

The total of 1,641 participants evaluated collectively are small when split by each herb and its supporting participants with regards their efficacy claims while assessing due to dosage variability. Although fennel has the fewest amount of participants (n=140) and ginger has the most (n=495), the size of both populations is still considered adequate from a statistical standpoint to achieve internal validity within each of these trials; however, it appears that the overall support of general population of botanical agents' ability to be effective as a whole based on how they were evaluated by a total number of participants is invalidated by lack of robust data supporting their large scale claims.

4.3 Inability to Apply Meta-Analytic Techniques

Due to the large range of plant species employed in this investigation, unstandardized extraction procedures, exceedingly varied dosages and methods of production for each study, and the different plant species that were used as active comparisons, the statistical meta-analytical methods used to evaluate this study could not be done. The inability to perform meta-analyses of all the studies to give one common result reduces the external validity of this research because it could not be calculated or stated as a single statistical effect size (such as a combined SD (standard deviation) by means of a forest plot). Because of this, The systematic review's findings should be viewed cautiously when using clinical applications, and no definitive conclusions regarding the clinical superiority or general applicability of polyherbal formulations can be made from the current literature.

4.4 Clinical Relevance and Future Research

The findings of this research demonstrate the clinical relevance of using herbal medicines for the management of primary dysmenorrhea. Therefore, practitioners are encouraged to utilize these medications according to appropriate discipline-based guidelines and protocols. Studies have consistently shown that botanical medicine is as effective as non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of primary dysmenorrhea, and botanical medicines appear to be more effective treatment options than NSAIDs in patients who are resistant to NSAIDs (i.e., approximately 20-25% of patients). Additionally, women with strict or absolute contraindications to oral contraceptive drugs are excellent candidates for herbal medicine therapies, as are patients who are unable to tolerate long-term use of prescribed medications due to systemic side effects.

To move this field forward beyond its current methodological limitations, future research needs to focus on biochemically standardizing and controlling botanicals, i.e., developing standardized methods for the extraction, processing, and preparation of botanicals so there is a consistent and reproducible clinical response for the patient. Another important limitation identified in this review is the absence of prospective registration of all trials and systematic reviews conducted after the initial analysis. All future trials and systematic reviews should be listed in an international database such as PROSPERO to ensure maximum methodological transparency and to reduce any potential reporting bias. There needs to be an urgent need for large multi-center double-blind clinical trials (RCTs) that have a single biochemically standardized dosage regimen of polyherbal formulations to be performed in order to further

the understanding of how botanical therapies can be integrated into current evidence-based medicine.

5. CONCLUSION

This systematic review's main goal is to evaluate the effectiveness of polyherbal drugs and botanical extracts in treating primary dysmenorrhea. The qualitative assessment of sixteen randomized controlled trials served as the basis for the analysis, and it can be concluded that these interventions, which mostly included *Zingiber officinale*, *Cinnamomum zeylanicum* and *Foeniculum vulgare*, provide statistically significant reductions in menstrual pain intensity. In individual studies comparing the efficacy of the botanicals with NSAIDs, the evidence indicates that the botanicals are analgesically comparable to the synthetic NSAID interventions. Further, the botanical treatments were very safe, producing adverse events in <2.5% of participants (number of participants with only mild and brief gastrointestinal symptoms). However, the results' external validity is compromised by the inability to perform a quantitative meta-analysis. There also was considerable variability in the clinical and methodological quality of the studies (e.g., a wide variety of unstandardized doses of the botanicals were studied together with sample sizes that were relatively small when divided into sub-groups), which represent a major limitation of the current evidence base. Consequently, care must be taken when interpreting the current findings as the findings cannot be generalized for the purpose of clinical decision making through definitive clinical evidence. While it appears that the polyherbal formulations may be a viable alternative for patients who have had insufficient pain relief from NSAIDs or who have contraindications to OC's, further large scale, prospectively registered trials using standardized doses would be needed to establish concrete clinical guidelines.

ACKNOWLEDGEMENT

The authors are grateful to their institution for providing academic support and resources for the completion of this review.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

FUNDING: This research received no external funding.

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