

Study to evaluate the efficacy of Elix's Cycle Balance and its impact on PMS and menstrual symptoms

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1. Background and Purpose

The menstrual cycle is a process characterized by changes in hormone levels, specifically, fluctuating levels of estrogen and progesterone [1]. The menstrual cycle starts with the first day of the period and ends with the start of the next period. Usually, a menstrual cycle lasts between 24 and 38 days but the actual length may vary from cycle to cycle [2]. While 28 days seems to be the conventional length of a menstrual cycle, only 10-15% of women have cycles of exactly 28 days [3]. In the days following ovulation, both estrogen and progesterone levels are falling, which results in the transition from the luteal to follicular phase of the cycle, and eventually, menstruation [1]. PMS (premenstrual symptoms) and discomfort during menstruation are two of the most common health concerns women are facing [10]. And, the most common symptoms can impose significant economic and personal consequences to women, as social events and even school or work can be missed [11]. In fact, dysmenorrhea is the leading cause of absenteeism in school-aged girls, and reports show that 13%-51% of women have been absent at least once and 5%-14% are often absent due to the severity of period pain [33]. However, according to a recent study conducted with 43,000 women, more than half of these women did not tell their family, friends, or medical care provider about their menstrual problems [4]. During menstruation, dysmenorrhea or pelvic cramps, and feeling tired are commonly reported issues [4, 10], while prior to menstruation, the most common complaints and symptoms of premenstrual syndrome (PMS) are mood swings, bloating, and breast tenderness [5, 12]. Typically, PMS symptoms occur up to 1-2 weeks before menstruation and stop when menstruation begins, or shortly thereafter. Menstruation starts at puberty (menarche) and stops permanently at menopause.

The test product (Elix Cycle Balance) is specifically targeting dysmenorrhea, which is a debilitating gynecological condition that impacts women around the world. Dysmenorrhea is the term for describing pain during menstrual bleeding. It indicates a cramp-like, dull, throbbing, or colicky pain that usually emanates from the lower abdomen, and that occurs just before and/or during menstruation[30]. The pain usually lasts 8-72 hours. Back and thigh pain, headache, diarrhea, nausea, and vomiting may also be present [31]. Other symptoms often associated with menstruation are mood swings, changes in bowel movements, and dizziness, or even fainting [32]. One study found that menstrual pain was reported by 84.1% of women, with 43.1% reporting that pain occurred during every period, and 41% reporting that pain occurred during some periods [30]. Dysmenorrhea is associated with significant decrease in quality of life [35]. Women with primary dysmenorrhea have a significantly reduced quality of life, poorer mood, and poorer sleep quality during menstruation compared with their pain-free follicular phase and compared with the menstruation phase of pain-free control women [36, 37].

Options for mild to moderate discomfort as a result of menstruation are primarily either hormonal contraception [6] or non-steroidal anti-inflammatory drugs (NSAIDs) [7, 8]. Increasingly, however, consumers are interested in non-hormonal treatment options as well as the potential for more plant-based, herbal or dietary options, due to potential side effects of the above options. Dietary supplements capable of supporting the body as it responds to the natural fluctuations in hormone levels associated with menstruation are thus of significant interest for consumer wellbeing [9]. Numerous studies using dietary supplements have been conducted and shown to assist with menstruation-related symptoms.

The test product assessed in this study is based on Chinese herbal medicine (CHM). CHM has been used for centuries in China and it is currently used in public hospitals in China for the treatment of primary dysmenorrhea. For example, a 2008 Cochrane review found promising evidence for the use of Chinese herbal medicine in reducing menstrual pain in the treatment of primary dysmenorrhea, compared to conventional medicine such as NSAIDs and the oral contraceptive pill, or even acupuncture and heat compression. No significant adverse effects were identified in this review, however, the findings should be interpreted with caution due to the generally low methodological quality of the included studies [34].

This exploratory observational trial provides the opportunity to gather information on a multi-supplement intervention that is aiming to reduce inflammation and balance hormone levels through a customized all-natural blend of herbs based on individual menstrual symptoms. This study will provide evidence for marketing claims.

There is a well-understood connection between the menstrual cycle and the immune system where the immune system is suppressed following ovulation, and immune activity increases during menstruation [13]. The increased immune activity leading to menstruation results in increased inflammatory markers [14, 15, 16, 17], which are also linked with higher self-reported discomfort prior to and during menstruation [12, 18, 19].

Many dietary supplements have been extensively studied both in-vitro and in-vivo and shown to help mitigate inflammatory responses [26] and investigated the role that they might play in helping ease

menstrual discomfort [20, 8, 9]. Specifically, many of the dietary supplements that have been studied have a long history in traditional medicine as treatment options for PMS, and these include extracts from plants such as Vitex agnus-castus or dong quai (21, 22, 23). The biological effects of herbs have been shown to include affecting the central nervous system, endocrine system, the activity of sympathetic nerves, basal metabolic rate, the function of organs and tissues, and secretion of cytokines out of the body [38].

In addition to the diagnosis of a western-defined disease (such as dysmenorrhea), traditional Chinese medicine (TCM) doctors use a technique called pattern diagnosis to focus treatments on the subcategories of said disease; for example, blood stasis and cold accumulation of the uterus or blood and qi deficiency syndrome for dysmenorrhea [40]. The TCM pattern is determined by a TCM doctor on the basis of signs and symptoms displayed by the patient, their physical condition, disease status, and constitution, after which CHM prescriptions for treatment are given [39]. This individualization is a key primary requirement of traditional treatment with CHM [34]. Personalized medicine refers to the right treatment for the right individual at the right time and has the potential to diminish the incidence of drug adverse reactions, eliminate invalid therapy, improve the efficacy of treatments, ultimately, achieve optimal health outcomes [38].

Chinese herbal medicines (CHM) have been used to treat menstrual symptoms for centuries. There is strong evidence that CHM may be a suitable alternative to treat PMS and menstrual symptoms and that CHM is most effective when tailored to an individual's symptoms. In a 2008 Cochrane review, thirty-nine randomized controlled trials studying CHM for dysmenorrhea were analyzed, involving a total of 3,475 women in the review. Chinese herbal medicine resulted in significant improvements in pain relief, overall symptoms, and the use of additional medication when compared to the use of pharmaceutical drugs. Individualized CHM prescriptions resulted in significant improvements in pain relief, overall symptoms, and use of additional medication after up to three months of follow-up when compared to commonly used Chinese herbal health products. Chinese herbal medicine also resulted in better pain relief than acupuncture and heat compression. Of the 39 studies, all had an effectiveness range of 87-100% for herbal medicine interventions. Generally, the reviewed trials reported that CHM for primary dysmenorrhea was safe when compared with conventional medicines [34].

Lastly, most of the dietary supplements studied have followed a “one size fits all” approach. Given the wide array of symptoms women experience before and during their menstruation, this approach is inadequate and may treat symptoms that are irrelevant. The development of dietary supplements that provide a customized scenario to menstrual concerns and are taken immediately prior to menstruation would be of significant benefit.

2. Study Objectives

- The primary objective of this study is to assess if Elix provides relief from menstrual symptoms and to see if it improves accompanying symptoms such as fatigue and mood swings.
- The secondary objective is to examine if participants experience a reduction of the usage of OTC NSAIDS in the treatment of primary dysmenorrhea symptoms.

3. Study Design

This is an open-label observational single-group clinical trial to study the efficacy of a commercially available dietary supplement and its effect on common PMS and menstrual symptoms.

It is hypothesized that the dietary supplement marketed as “Elix Cycle Balance” will improve subjective wellbeing in trial participants by alleviating common symptoms of PMS and menstrual symptoms, such as cramps, bloating, and mood swings.

A total of 65 participants will be recruited for the trial following screening, with the expectation that at least 50 participants will complete the trial. The trial will be fully remote, a technology platform will be utilized to screen, enroll and capture study data of the participants. The total intervention study period will be 3 months. Participants will be taking their customized blend of “Elix Cycle Balance” - based on the study intake form for the study period.

The sequence of events for the participant is as follows:

- Eligibility pre-screening (inclusion/exclusion criteria including relevant demographic and medical information)
- Informed consent
- Study intake survey
- Test product distribution
- Onboarding participants on a technology platform that captures data
- Participants to complete the baseline survey
- Participants start their customized Elix Cycle Balance blend for 3 months
- Participants to write down any adverse or ill effects, as well as any positive effects any time after taking the test product
- Participants to take a monthly survey about their symptoms
- Participants to complete an exit survey and note any final adverse and positive events
- Participants receive \$75 compensation, as well as 3 additional months of Elix Cycle Balance after completion of the study

3.1. Study Procedures & Product information - intervention/treatment

As an investigatory trial studying a commercially available consumer product, an open-label design is most appropriate to gauge real-world perceived behavior. Focusing on 3 months minimizes the strain on the participants while providing a significant data-gathering opportunity. Furthermore, the survey results acquired from participants during baseline, and then the intervention will provide insights to guide further trials that are placebo-controlled.

Although discomfort during and prior to menstruation is extremely common and can have a moderate to severe impact on social and economic activities, there are few research-backed commercially available products to alleviate this discomfort. Many consumers are increasingly interested in dietary supplements to help support their bodies, and the opportunity to determine whether a commercially available product improves consumer wellbeing is a significant benefit to society.

3.2. Study Procedures

Individuals aged 18+ with regular menstrual cycles and moderate to severe menstrual discomfort, but otherwise healthy will be chosen to participate in the study (see “4. Participant Definition”). Participants will be advised to discontinue any other oral supplement or prescription targeting their menstruation prior to beginning with the study.

Participants will be asked to take a study intake questionnaire before the study begins to create a customized blend of the test product which is used for the study.

Before participants start the study, they will be asked to complete a baseline menstrual wellbeing survey.

Each day in the morning and at night in the week prior to the menstruation, the participants will take 6 drops of Elix Cycle Balance. Elix Cycle Balance can be taken alone or in combination with tea, water, or smoothies. Especially if this is the first time taking a traditional Chinese medicine product/herbs, it is recommended to mix the herbal formula in another beverage. Should participants present themselves with a sensitive stomach, it is recommended to take the drops with a meal to avoid an upset stomach. Participants will repeat this process for 3 months (study period) until the study is complete.

After the first month (approximately 30 days) and the subsequent months thereafter, the participants will take a menstrual wellbeing survey to track progress. In total there will be 3 wellbeing surveys.

After 3 months, participants will take their last menstrual wellbeing survey - marking the end of the 3 months study period.

Once they completed the study and last wellbeing survey, they will also complete an exit form.

3.3. Product information - intervention/treatment

The dietary supplement is designed and marketed commercially to be taken in servings of 6 drops. By focusing the clinical trial on this use case, we will obtain the best insight into physiological responses and perceived wellbeing for typical consumer behavior.

Elix is a customized blend of 21 herbs that target several symptoms for PMS and menstrual issues so that users find relief after a time of a maximum of 3 months. The ingredients are sourced from the most potent part of every plant. The blends include

- Angelica Sinensis, a powerful anti-inflammatory that's proven to reduce uterine spasms (or cramps), regenerate blood cells, stimulate circulation, as well as immune response;
- Atractylodes, an acute and chronic anti-inflammatory agent, as well as a powerful hormone balancer, proven to ease a wide range of menstrual symptoms and boost immune health;
- Bugleweed, a thyroid-regulating plant that assists in alleviating menstrual symptoms, as well as providing relief from pain and anxiety;
- Bupleurum, a powerful herb with immunoregulatory actions that supports pain, depression, and stress relief associated with premenstrual syndrome (PMS) and menopause;
- Corydalis, a potent pain reliever that is proven to ease uterine and upper abdomen cramping, and relieves insomnia due to pain;
- Cyperus, for regulating menstruation and reducing symptoms such as cramps, breast tenderness, and mood changes;
- Gardenia, which is proven to reduce cramping, minimize headaches, combat acne, and moderate mood swings;
- Ginger, which is clinically proven to ease menstrual cramps as well as reduce nausea & bloating, and has anti-inflammatory & antimicrobial properties which support immune and respiratory function;
- Licorice, great for abdominal discomfort, and ideal for treating menstrual cramping. It has been shown to relieve digestive discomfort and regulate bowel movement. It is also an antiviral and antimicrobial harmonizer, supporting how immune-boosting herbs work together in formulas;
- Mint, an effective, natural pain reliever that's been shown to reduce stress and even help with PCOS. Mint is also a potent antioxidant and antibacterial
- Motherwort, used for thousands of years in China, relieves menstrual pain by enhancing blood flow to the uterus and regulating stress hormones;
- Moutan Cortex, has a powerful ability to reduce inflammation and promote blood flow, making it an excellent treatment for severe menstrual cramps;
- Poria, an edible mushroom that suppresses inflammation (reducing menstrual cramps) and protects nerve cells (alleviating depression and boosting mood);
- Rehmannia, sometimes referred to as Chinese foxglove, is a flowering plant and adaptogen, known to support the circulatory system, to regulate blood production, and fight fatigue. It's a proven antioxidant, anti-inflammatory, and antidepressant, all of which aid with PMS symptoms.
- Red Ginseng Root, known for tonifying qi and regulating the central nervous system. A popular adaptogen, it's great for balancing stress and improving mental function.

- Safflower, which reduces inflammation, promotes blood circulation, and is especially great for regulating an irregular menstrual cycle;
- Skullcap, which reduces the inflammation and spasms that cause menstrual cramps, while cooling and calming the body and mind. With antiviral and anti-inflammatory properties, this herb is widely used in China to treat influenza and pneumonia, amongst other ailments;
- Szechuan Lovage Root is widely used for its ability to boost blood circulation and reduce inflammation, which is how it effectively minimizes menstrual cramping;
- Toosendan Fruit, a wonderful antioxidant and adaptogen, which helps your body adapt to a variety of stresses, which is especially useful during menstruation;
- Vitex Berry, an ideal hormone balancer—especially in cases of estrogen dominance—and helps keep the menstrual cycle regular;
- Water Plantain Root, commonly used to aid the body of heat by clearing dampness and promoting detox through urination;
- White Peony is proven to reduce pain and cramping while promoting peaceful sleep during menstruation;
- Magnesium is used to relax the smooth muscle of the uterus and reduce inflammation, specifically the prostaglandins that cause painful cramps (dysmenorrhea).

4. Participant Definition

A total of 65 individuals will be recruited through Citruslabs for this study. Patients who meet the following eligibility requirements will be introduced to the study by online pre-selection. All potential study participants (who are pre-selected) will be screened for eligibility by an online pre-screener prior to joining the study. Additionally, all participants will receive a study onboarding onto the technology platform that is used to capture the data for this study.

4.1. Inclusion Criteria

Individuals will be included in the study if all of the following criteria are met:

- Female aged 18-36
- Self-reported moderate to severe discomfort during menstruation, related to pelvic cramps, bloating, mood swings, or fatigue
- May experience regular or irregular menstrual cycle
- May be on birth control
- Must know or can estimate the date of the next cycle/period
- May find blood clots in menstrual blood
- Must be in good health (doesn't report any medical conditions asked in the screening questionnaire)
- Following a stable, consistent diet regimen

- Follow a stable, consistent exercise regimen and are willing, for the duration of the study, to not decrease or increase the amount of exercise in their regimen
- Agree to refrain from any lifestyle changes that may affect their menstrual cycle for the duration of the study (for example, getting on or off hormonal birth control, reducing the amount of exercise)
- Follow a stable consistent regimen when using any other interventions, such as massage, chiropractic medicine, or acupuncture; agree not to increase or decrease the number of their other interventions
- Willingness to adhere to the dietary supplement regimen
- Willingness to refrain from any other dietary supplements targeting the menstrual cycle during the study period
- Is able to communicate in English
- Is willing and able to share feedback via the used technology portal
- Must provide written informed consent (ICF)

4.2. Exclusion Criteria

Individuals will be excluded from the study if any of the following criteria are met:

- Don't experience a menstrual cycle
- Can't estimate the onset of their next menstrual cycle
- Don't experience menstrual cramping
- Follow an extreme diet intervention
- Experienced severe weight loss in the past 3 months prior to study participation
- Usage of any medication or herbal remedies/supplements which can affect the menstrual cycle
- If currently taking allowed supplements, the dosage needs to remain the same throughout the entirety of the study
- Food intolerances/allergies that require an EpiPen
- Known allergic reaction to any of the test product ingredients
- Currently pregnant, want to become pregnant for the duration of the study, or who are breastfeeding
- Previous users of Elix Cycle Balance
- Having more than 3 alcoholic drinks a day
- Have been diagnosed with the following conditions: PCOS, Endometriosis, PMDD, Adenomyosis, Hashimoto's, anorexia, bulimia, orthorexia, binge eating, any other eating disorder
- Smokers
- Not been on a stable dose of birth control for the past 6 months

5. Patient Enrollment

5.1. Informed Consent

In compliance with CFR 50.25, and the Declaration of Helsinki, no patient shall be enrolled in an investigation without the provision of adequate informed consent. Citruslabs and the Principal Investigator are responsible for ensuring that no patient is included in the study without adequate informed consent being provided.

All ICFs must have a favorable opinion of the ethics committee. Consent of a patient needs to be obtained from the patients themselves and documented on an ICF.

The Investigator or trained designee preliminarily screens to determine if a patient generally meets the eligibility criteria for the study. If so, the Investigator or trained designee shall offer study participation to those patients. If the patient agrees to participate, s/he will sign the informed consent document.

5.2. Patient Screening

After signing the informed consent documents, the patient will be screened for eligibility and will be listed on the Screening and Enrollment Log. The date of screening, the results of screening (included or not) and the primary reason for not including the patient (e.g., does not satisfy eligibility criteria,) will be recorded on this log. The original log is to be retained at the Citruslabs office and a summary of recruitment (de-identified) sent to Elix regularly during enrollment.

5.3. Patient Identification Numbering

The patient ID numbers will be assigned after consent is obtained. The patient number will become the unique identifier of the patient and will be recorded on each page of the completed surveys. For example, the first three (3) participants enrolled will be identified as 00-001, 00-002, 00-003. Once a patient identification number is assigned, it may not be reused.

5.4. Process for Discontinuation of Patient Participation

Patient participation may discontinue through major protocol deviation, withdrawal, or death. The participant is free to withdraw from the study at any time. In all instances of patient discontinuation after obtaining Informed Consent, an End of Study/Withdrawal form is required to be submitted by the patient to Citruslabs, and this will ultimately be reported to Elix.

5.5. Payment for Participants

Upon completion of the study, patients will be compensated for their time with \$75 in the form of an Amazon gift card, plus receive 3 additional months of Elix Cycle Balance after the study is complete (total value \$200+).

6. Data Management

All documents relevant to the study, including completed ICFs, will be hosted on a secure online portal. The ICFs will be completed via HelloSign, and will be transferred to the online portal, using a secured data transfer system on the online portal. Survey records will be stored within the online portal and Elix has access to the de-identified data set. After completion of the study, all data will be saved to a secured internal network at Elix. User access to the directory is controlled through user-level role-based security. All data will be anonymized during analysis.

6.1. Privacy/Confidentiality

Data will be stored encrypted on a secured online portal that uses the HIPAA compliant AWS servers. All patients will be de-identified and labeled using a coding system (00-01, 00-02, 00-03, etc.)

7. Data Analysis

To better document and elicit the key concepts, all recorded open-text responses to surveys will be analyzed using qualitative analysis software.

Responses to clinical outcome measures will be normalized and analyzed using the appropriate statistical test. This will allow for estimation of an effect size for future studies, and initial indicative directional evidence of differences between groups. However, as a feasibility study, it is not anticipated that these tests would be powered to detect (at a statistically significant level) anything other than a large clinically significant effect.

Any adverse events will be listed and reported using descriptive statistics by group.

8. Risks Assessment

The dietary supplements selected for this study are well tolerated, and the daily doses are within the FDA tolerated upper limits (where relevant). Minimal risk is foreseen for participants through their participation in the study. The most common side effect of dietary supplementation is gastrointestinal distress (for example, diarrhea) as a result of very high doses, particularly if a study participant has a previously unrecognized allergy or sensitivity. Should participants know that they have a sensitive stomach, it is recommended to take Elix Cycle Balance with a meal. Generally, participants are advised to take Elix Cycle balance with some fluid. Additionally, there is the possibility that participants may

experience rashes or hives, as well as headaches. Should these symptoms not dissolve after 3 days, participants will be advised to discontinue with the study.

In terms of confidentiality, there are minimal risks as all study participant information will be de-identified. Since this is a virtual study, no confidential or protected information would be taken outside of the standard. There is a slight financial risk to the participants in the rare event that the above complications occur requiring additional medical care.

9. Benefits Assessment

The benefits of using Elix that will be assessed within the scope of this study include:

- Brighter color of the menstrual blood
- Canceling fewer plans // missing on less work/productivity
- Decrease bloating
- Help regulate cycle
- Improve PMS symptoms overall
- Improvement of digestive function
- Increase energy & reduce fatigue
- Less clotting
- Fewer mood swings
- Lighter/less heavy periods
- Reduction of back pain
- Reduction of cramps
- Reduction of headache and menstrual migraines
- Increase libido
- Fewer body aches
- Less hormonal acne
- More balanced cycle
- Reduction in anxiety/stress

Participants are also contributing to the development and improvement of PMS and menstrual treatments, which some consider a benefit.

10. Payment and Remuneration

Upon completion of the study, patients will be compensated for their time with \$75 in the form of an Amazon gift card, plus receive 3 additional months on Elix Cycle Balance after the study is complete (total value \$200).

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