INFORMATION SHEET

An examination into the safety and efficacy of Khaya senegalensis on pain, physical and emotional wellbeing in women experiencing menstrual distress: a randomised, double-blind, placebo-controlled trial

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Background

Khaya senegalensis is a tree species native to Africa (and now also cultivated in Australia). Common names include African mahogany, dry zone mahogany, Gambia mahogany, khaya wood, and Senegal mahogany. Khaya senegalensis has traditionally been used to treat malaria, headaches, fever, rheumatism, and jaundice. It has also been used to treat menstruation pain, dysmenorrhoea, ovulation disturbances, and digestive pain and discomfort. In this study, the bark of Khaya senegalensis will be administered as it has anti-inflammatory and pain-blocking effects.

Because of its traditional use and research demonstrating it has anti-inflammatory and pain-blocking effects, we will investigate the effects of Khaya senegalensis on menstrual-related symptoms in women experiencing menstrual distress.

This study will be conducted by Dr Adrian Lopresti and Dr Stephen Smith (Clinical Research Australia).

Information about the funding source and declaration of interests

This study is funded by Bioactive Natural Health Pty Ltd., the company that produces and distributes the Khaya senegalensis tablets used in this study. However, this study is independently managed by Clinical Research Australia without external influence from Bioactive Natural Health Pty Ltd.

Aim of the study

We would like to know whether taking Khaya senegalensis tablets for one menstrual cycle can improve menstrual-related symptoms in women aged 18 to 50 years experiencing menstrual distress.

What does participation involve? **(see study flow chart on page 3)**

This study will comprise several steps as outlined below:

Step 1: Completion of initial online screening

This questionnaire consists of approximately 20 questions and takes approximately 5 to 10 minutes to complete. It provides us with information relating to the eligibility criteria. If, based on the screening questionnaire results, you are assessed as 'likely' eligible, you will be contacted for a phone interview. Ineligible volunteers will be informed by email that they do not fulfil the eligibility criteria.

Step 2: Phone Interview for an assessment of eligibility

If you are potentially eligible to participate in the study, you will be interviewed by a researcher. The interview will be conducted over the phone (approx. 15 minutes). The purpose of this interview is to obtain relevant background information (e.g., age, medication use, current treatments, menstrual symptoms, etc.), provide you with further details about the study and what the next step is in the

qualification process, and assess other relevant eligibility criteria. If you meet our eligibility criteria and agree to participate in the study, you will proceed to the next step.

Step 3: Completion of informed consent form (ICF)

You will be sent a follow-up email confirming your eligibility to participate in the study. You will also be sent an electronic version of the ICF. This ICF must be electronically signed and returned to us before proceeding further in the study.

After you have completed the ICF, we will post your study tablets, but you must not take them until you have completed step 4.

Step 4: Start daily monitoring of your symptoms

Every day, starting approximately 7 days before your period (bleeding/spotting) and until the end of your period (final day of bleeding) you will be required to complete daily records of your symptoms and intake of pain-relieving medication. This will be done electronically and needs to be completed every evening. This will take 2 to 5 minutes a day.

Step 5: Blood collection and complete online questionnaires

On the final day of your period (or 1 to 2 days before), you will need to attend your nearest Australian Clinical Labs (ACL) blood collection centre to have a blood sample collected from you. This blood sample needs to be collected from you before you start your tablets. The following markers will be measured: high-sensitivity C-reactive protein (a marker of inflammation), liver function, renal function, and complete blood count.

You will also be required to complete online questionnaires asking about your mood, wellbeing, and menstrual-related symptoms. This will take about 5 to 10 minutes.

Step 6: Take your tablets for one menstrual cycle (Khaya senegalensis or placebo)

You will be required to take your tablets from the end of your period (the day after you stop bleeding) to the end of your next period. For most women, this will be around 28 days.

In this study, we will be using a randomised, double-blind, placebo-controlled design. This means half of the participants will be placed on Khaya senegalensis tablets, and the other half will be placed on placebo (dummy) tablets.

Neither you nor the investigator will know which group you have been placed in. This random placebo allocation is important for us to assess the true effects of Khaya senegalensis on menstrual-related symptoms.

You will be required to take TWO tablets THREE times daily. Tablets should ideally be taken 6 hours apart. The first dose should be taken at approximately 8am, the second at 2pm, and the third at 8pm or 1 hour before bedtime. The tablets can be taken with or without food.

* Placebo involves providing a substance with no known treatment effects. In this case, the placebo will contain a plant-based gluten-free cellulose sourced from rice or corn.

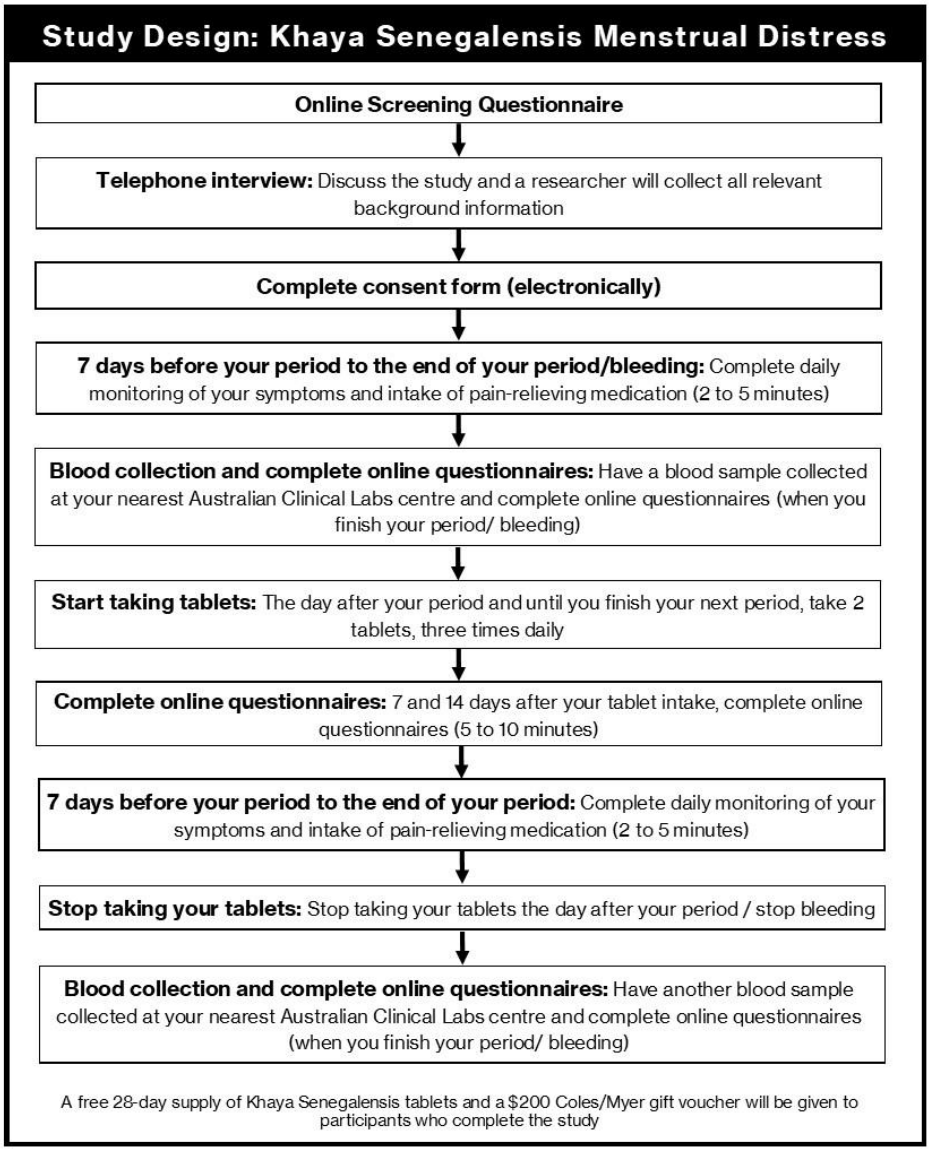
It is extremely important that you take these tablets every day. We will send you daily reminders to take your tablets every day.

Step 7: Complete online questionnaires 7 and 14 days after tablet intake

Once you start your tablets, you will complete online questionnaires that ask if you have experienced any adverse effects, symptoms, or illnesses that have appeared since starting your tablets, or if you have changed/started any new medications. On day 14, you will also be required to complete questionnaires about your menstrual symptoms, mood and general wellbeing. These questionnaires will take approximately 5 to 10 minutes to complete.

Step 8: Blood collection and complete online questionnaires

On the final day of your period (or 1 to 2 days before), you will need to again attend your nearest Australian Clinical Labs (ACL) blood collection centre to collect a blood sample. You will also be required to complete online questionnaires asking about your mood, wellbeing, and menstrual-related symptoms. This will take about 5 to 10 minutes.



Compensation for participating in this study

1. To compensate you for your travel costs and time associated with participating in this study, we will send you a $200 Coles/Myer Group gift voucher when you complete the study.
2. At the end of the study, volunteers placed in the placebo group will be offered a free 28-day supply of Khaya senegalensis supplements to try.

Criteria for inclusion/ exclusion in this study

To be included in the study, the following inclusion criteria must be met:

1. You are a menstruating women aged 18 to 50 years
2. You experience mild to moderately severe pain before and/or during menstruation, with a history of at least 3 months.
3. You experience physical and/or emotional symptoms associated with menstruation with a history of at least 3 months

4. You have a regular menstrual cycle length of 21 to 35 days
5. You are a non-smoker
6. You have a body mass index (BMI) between 18 and 30 kg/m^2
7. You have no plan to commence new treatments over the study period
8. You understand and are willing and able to comply with all study procedures
9. You are willing to provide a personally signed and dated informed consent form detailing all pertinent aspects of the trial

If any of the exclusion criteria below are met, you will not be suitable for participation in this study:

1. You suffer from recently diagnosed or unmanaged medical conditions including but not limited to: diabetes, hyper/hypotension, cardiovascular disease, gastrointestinal disease requiring regular use of medications, gallbladder disease/gallstones/biliary disease, autoimmune disease, cancer/malignancy, endocrine disease, or chronic/acute pain condition.
2. You are diagnosed with neurological or psychiatric conditions including but not limited to: psychiatric disorder (other than mild-to-moderate depression or anxiety), Parkinson's disease, Alzheimer's disease, intracranial haemorrhage, or head or brain injury.
3. You regularly take medications including but not limited to opioids, corticosterone, hormone-replacement therapy, and gonadotrophin-releasing hormone agonists.
4. You have changed your medication in the last 2 months or expect to change it during the study duration.
5. You are taking vitamins or herbal supplements reasonably expected to influence the study measures.
6. In the last month, you commenced or changed the dose of nutritional and/or herbal supplements that may impact on treatment outcomes.
7. You have planned a major lifestyle change in the next 2 months.
8. Your alcohol intake is greater than 14 standard drinks per week
9. You currently (or in the last 12 months) have used illicit drugs
10. You are pregnant, breastfeeding, or intend to fall pregnant during the study period.
11. In the last year or in the next 3 months, you have had significant surgeries (except exploratory surgery for endometriosis and other menstrual conditions undertaken/occurring before or after the study period)
12. You have participated in another clinical trial in the last month

Voluntary participation and withdrawal from the study

It is important that you understand that your involvement in this study is voluntary. While we are grateful to have you participate, we respect your right to decline. There will be no consequences to you if you decide not to participate, and this will not affect any future treatment/service. If you decide to discontinue participation at any time, you may do so without providing an explanation. If you withdraw, any assessments already conducted may continue to be used for analysis.

Please note that if you choose to commence a treatment to improve your cognitive performance or sleep or require treatment for any other condition during the study, this may result in withdrawal. Your health is the utmost priority, and your choice/need to commence a new treatment before completing this study is respected and supported.

Your privacy

Your privacy is very important to us. Your participation in this study and any information provided will be treated in a confidential manner. Your name and identifying details will not be used in any publication arising out of the research. Following the study, the data will be kept in a de-identified format, in a locked cabinet in the office of the Investigator and will be held for statistical analysis for future publication. Re-identifying codes will be retained for 6 months in case this is needed and will then be destroyed.

Possible benefits

The bark from Khaya senegalensis has antioxidant and anti-inflammatory effects and may be associated with several health benefits. If Khaya senegalensis supplementation is effective, it will provide us with a natural option to help reduce menstrual-related symptoms in women who experience menstrual distress.

Possible risks

Participation in this study carries little risk, and many measures will be in place to decrease the likelihood of potential risks.

Khaya senegalensis has a long history of use in traditional medicine. It is also available as an over-the-counter supplement in Australia. Khaya senegalensis is well tolerated, and although reported side effects are infrequent, there have been reports of mild digestive discomfort, such as stomach pain and bloating. No studies have reported any serious side effects from its intake, although this cannot be totally ruled out.

Daily Khaya senegalensis supplementation is not recommended during pregnancy; therefore, if you fall pregnant during the study, you must immediately stop taking your tablets and inform us as soon as possible. Falling pregnant during the study will result in your immediate withdrawal from the study.

Further details about Khaya Senegalensis and its intake are included in the 'Khaya Senegalensis Information Sheet'.

In this study, we will collect a blood sample from your vein (venepuncture). Although venepunctures are very safe, there is a possibility of developing bruising at the site of the needle puncture. This usually appears within 24 hours and may range in size from a small spot to a large purple bruise. While bruising can be unsightly, it is not dangerous and will slowly disappear over a few days. Very rarely, a small artery that contains blood at a much higher pressure than in veins will lie unusually close to or underneath a vein. In this situation, the artery may be accidentally punctured at the time of venepuncture. Bruising on the lower part of the arm over the next 2 to 3 days will likely develop. Again, this is not dangerous and will gradually disappear over a couple of weeks. Although extremely rare, some people may have a tiny branch of one of the sensory nerves of the arm running over the surface of the vein. Rarely, the needle will hit this tiny nerve on the way into the vein. This may cause a short, sharp electric-shock type pain. This may be all that occurs but, in some cases, a tingling type of pain may persist for 1 to 4 weeks as the nerve heals. This is inconvenient and may be unpleasant, but it eventually subsides. Another rare complication is for a small clot (or thrombus) to form in the vein at the site of the venepuncture. This is noticed as a small firm lump just under the skin at the venepuncture site. The lump may or may not be tender and will go away over a couple of weeks. Finally, although extremely rare, an infection at the site of puncture can occur. Please notify us immediately if this occurs. To minimise all these risks, blood collections will be collected by a qualified and experienced phlebotomist using current best practices.

What to do if you experience significant side effects

If you experience any significant illness, injuries, or side effects that have commenced since starting your tablets, please immediately contact Dr Adrian Lopresti or Dr Stephen Smith (contact details are below). You may be asked to stop participating in the study and to seek medical advice.

Dr Stephen Smith: Ph: 9448 7376 | Mob: 0412 813 518 | Email: steve@clinicalresearch.com.au

Dr Adrian Lopresti: Ph: 9448 7376 | Mob: 0411 969 797 | Email: adrian@clinicalresearch.com.au

Feedback on study results

It is estimated the results of this study will be finalised in late 2024. A summary of the results obtained from all participants in this study will be emailed to you when they have been published in a peer-reviewed journal (usually 6 to 12 months after the completion of the study).

Questions

If you would like to discuss any aspect of this study, please contact Dr Adrian Lopresti on 08 9448 7376.

We would like to thank you in advance for your assistance with this research project.

If you are interested in participating in this study, please contact Dr Adrian Lopresti on 9448 7376 or email adrian@clinicalresearch.com.au

This study has been approved by the National Institute of Integrative Medicine (NIIM) Human Research Ethics Committee (HREC) (Trial Reference Number: xxx_2024). If you have any

reservations or complaints about the ethical conduct of this research and wish to talk with an independent person, you may contact the NIIM Research Ethics Office (Tel. 03 9804 0646) or email hrec@niim.com.au). Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.