INFORMATION SHEET

An examination into the anti-stress and anti-fatigue effects of an ashwagandha extract (NRAHG001) in stressed adults: a randomised, double-blind, placebo-controlled trial

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You are invited to participate in this study.

Background

Ashwagandha (*Withania Somnifera*) is a plant that has been used in traditional medicine to improve mental and physical wellbeing. There have been several studies demonstrating its positive effects on mood, energy, and general wellbeing. In this study, we are interested in investigating its effects on mood, fatigue, and the body's ability to respond to stress. We are also interested in trying to understand how ashwagandha may work in the body to improve mood and wellbeing. As a result, we are inviting you to participate in this 4-week, randomised, double-blind, placebo-controlled study.

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 Natural Remedies Pvt Ltd, the company that produces the ashwagandha extract used in this study. However, this study is independently managed by Clinical Research Australia (CRA) without external influence from Natural Remedies Pvt Ltd.

Aim of the study

We would like to know whether taking an ashwagandha extract (NRAHG001) for 4 weeks can improve mood, fatigue, and resiliency to stress in adults experiencing high stress. To help understand how ashwagandha works in the body, we will also assess changes in blood and saliva markers associated with stress, mood, and general wellbeing.

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 results of the screening questionnaire, 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 initial 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. 20 minutes). The purpose of this interview is to obtain relevant background information (e.g., age, sex, illnesses, medication use, etc.), provide you with further details about the study, and assess other relevant eligibility criteria.

If you have qualified, you will be notified immediately, and a face-to-face appointment at our office in Duncraig will be arranged for 3 to 14 days later.

Step 3: VISIT 1: Face-to-face assessment (approx. 30 mins)

During this meeting, the following tasks will be completed:

1. Complete the informed consent form
2. Measurement of your weight, height, and blood pressure
3. Blood sample collection: a researcher trained in venous blood collection will collect a blood sample from your vein. We will use this blood sample to measure several markers associated with mood, stress, and cognitive performance. We will also investigate whether concentrations in these blood markers change over time.
4. Complete self-report questionnaires assessing your mood and fatigue
5. Provision of 4-week supply of study capsules

Step 4: 4-week intake of capsules (ashwagandha or placebo)

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

Neither you nor the investigator will know which group you have been allocated to. This random placebo allocation is important for us to assess the true effects of ashwagandha on stress, mood, and fatigue.

You will be required to take ONE capsule, every morning, with or without food.

** Placebo involves providing a substance with no known treatment effects. In this case, the placebo will contain cellulose (a type of fibre).*

It is extremely important that you take these capsules every day.

Step 5: Complete daily mood ratings

Every evening at approximately 7pm, you will be sent a notification to your mobile phone to complete 3 ratings of your mood for the day. You will also need to indicate whether you took your capsules. This will take less than 1 minute.

Step 6: VISIT 2 (DAY 7): Face-to-face assessment (approx. 60 mins)

This visit will occur after taking your study capsules for 7 days. The following tasks will be completed:

1. Return your capsules so we can complete a capsule count
2. Respond to questions about any illnesses, side effects, and changes in your medications or supplements
3. Measurement of your weight and blood pressure
4. Complete self-report questionnaires assessing your mood and fatigue
5. Complete the Cold-Pressor Test. This test involves the following tasks:
    a. Place your hand in cold water (7 degrees Celsius) for up to 3 minutes. This procedure can be stressful and will induce a moderate pain sensation. You can remove your hand anytime if the pain is unbearable and then return it when you are ready.
    b. Have your facial expressions recorded during the 3-minute Cold-Pressor Test. Changes in your facial expression will be used to provide an assessment of your stress response. This recording will be immediately deleted after coding has been completed.
    c. Complete stress and fatigue ratings before, immediately after, and 10, 20, and 30 minutes after the test.
    d. Have a watch placed on your wrist that measures your pulse rate, skin temperature, and sweat response. This will be worn before the test and for 30 minutes after the test.
    e. Collect a saliva sample before the Cold-Pressor Test and 30 minutes later.
    f. Have your blood pressure measured before, immediately after, and 10, 20, and 30 minutes after the test.

Visit 2 will occur between 1 and 5 pm, and you must refrain from consuming food or drink for at least one hour before the visit. You must also avoid any alcohol intake on the day of testing and not consume any caffeinated beverage for at least 4 hours before the visit.

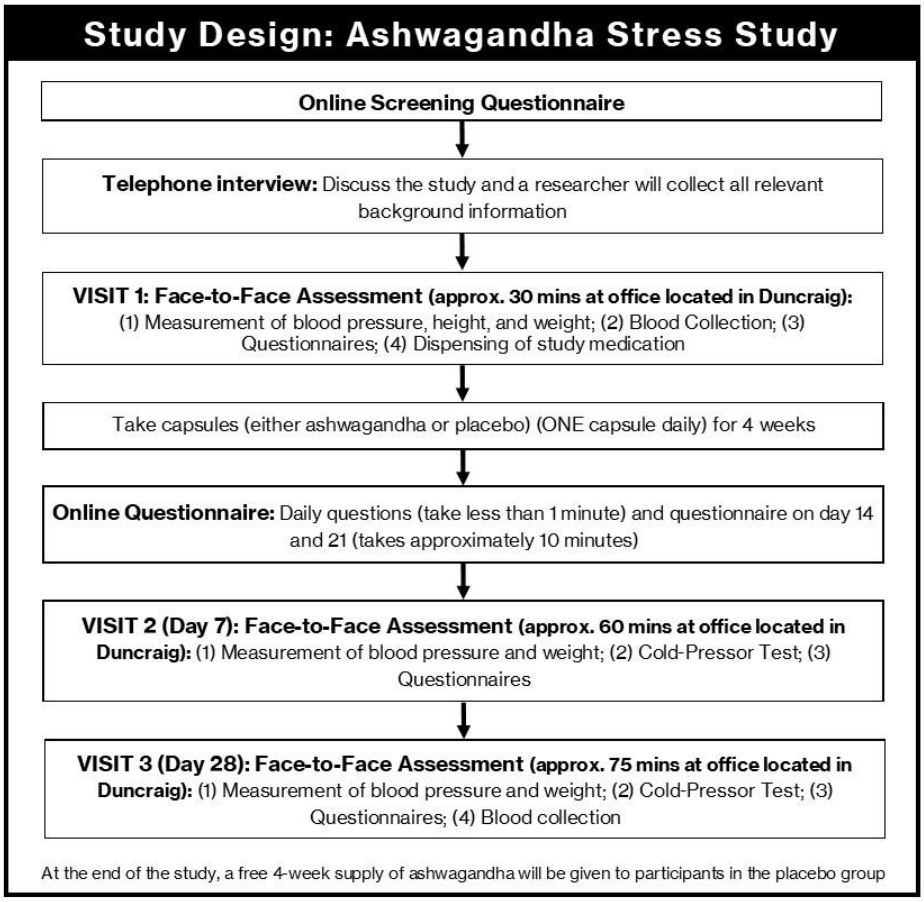
Step 7: Complete online questionnaires on days 14 and 21

At weeks 2 and 3 (days 14 and 21), you will complete an online questionnaire that assesses your mood and fatigue. You will also complete online questionnaires that ask if you have been experiencing any adverse effects associated with your capsule intake, experienced any illnesses, or changed/started any new medications or supplements. These questionnaires will take approximately 10 minutes to complete.

Step 8: VISIT 3 (DAY 28): Face-to-face assessment (approx. 75 mins)

This visit will occur after taking your study capsules for 28 days. The following tasks will be completed:

1. Return your capsules so we can complete a capsule count
2. Respond to questions about any illnesses, side effects, and changes to your medication or supplement intake
3. Measurement of your weight and blood pressure
4. Complete self-report questionnaires assessing your mood and fatigue
5. Complete the same Cold-Pressor Test that was completed at visit 2
6. Have a blood sample collected from your vein.



Compensation for participating in this study

1. To compensate you for your travel costs and time associated with participating in this study, at visit 1 we will give you a $30 gift voucher, at visit 2 a $60 gift voucher, and visit 3 a $100 gift voucher.
2. At the end of the study, all volunteers placed in the placebo group will be offered a free 4-week supply of ashwagandha capsules 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 generally healthy adult (male or female) aged between 18 and 65 years.
2. You are currently experiencing high stress.
3. You have a body mass index (BMI) between 18 and 35 kg/m^2.

4. You are a non-smoker.
5. You have no plan to commence any new treatments over the study period.
6. 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 a recently diagnosed or unmanaged medical condition including, but not limited to, diabetes, hyper/hypotension, cardiovascular disease, gallbladder disease, autoimmune disease, endocrine disease, or cancer/ malignancy.
2. You have been diagnosed with a neurological or psychiatric disease (other than mild-to-moderate depression or anxiety) and/or neurological condition/ disease (e.g., Parkinson's or Alzheimer's disease).
3. You regularly take medications including but not limited to anticonvulsants, benzodiazepines, opioids, corticosteroids, or immunosuppressants.
4. You have changed your medication (dose or type) in the last 3 months, or you expect to change it during the study.
5. Current use of supplements that contain ashwagandha or other supplements that may affect treatment outcomes.
6. In the last month, commenced or changed the dose of nutritional and/or herbal supplements that may impact treatment outcomes.
7. You plan on making major lifestyle changes in the next 2 months.
8. You drink more than 14 standard servings of alcohol per week.
9. You currently (or in the last 12 months) have regularly used illicit drugs
10. You are pregnant, breastfeeding, or intend to fall pregnant during the study period.
11. You have had a significant surgery in the last 12 months or have a surgery planned during the study period.
12. You have participated in any other clinical trial in the 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 to not 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 treatment to reduce your stress, improve your mood, or increase your energy; 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

Ashwagandha intake is associated with several positive effects on mental and physical wellbeing. However, the quality of different extracts can vary. If this ashwagandha extract is found to be effective, it will provide us with a natural option for treating mood, stress, and energy issues in people experiencing high stress.

Possible risks

Ashwagandha is considered safe and is well-tolerated by most users. It is used throughout the world as a health supplement and is commonly used in Ayurvedic medicine. In this study, we will be using 30mg a

day, although up to 5000mg has been used in some trials. Even though reported side effects are infrequent, mild nausea is the most common complaint. No studies have reported any serious side effects from its intake, although this cannot be totally ruled out.

The cold-pressor test involves placing your hand in cold water for up to 3 minutes. This is likely to induce mild pain in participants. However, you can remove your hand from the cold water if the pain is unbearable. A researcher will always be present during the cold-pressor test for support.

In this study, we will collect a blood sample from your vein (venepuncture). Although venepunctures are very safe, there is a possibility of 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, injury, or side effects from taking your capsules, please contact Dr Adrian Lopresti or Dr Stephen Smith immediately (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 2025. 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.

Questions

If you would like to discuss any aspect of this study, please feel free to contact the principal investigator, 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: 0153E_2025). If you have any reservation or complaint 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 e-mail hrec@niim.com.au). Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.