Graham Kell, Psychologist (Provisional)
University of the Sunshine Coast
gbk001@student.usc.edu.au

A randomised placebo controlled clinical trial on the efficacy of *Caralluma* supplement for reducing anxiety and stress in healthy adults over eight weeks

Investigator: Graham Kell, Provisional Psychologist
Master of Clinical Psychology
University of the Sunshine Coast

Supervisors: Prof Mary Katsikitis, University of the Sunshine Coast
Amanda Rao, Managing Director, RDC Global

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Aims: The aim of this study is to conduct a preliminary investigation of Caralluma supplement to examine its efficacy for reducing anxiety and stress in healthy adults over eight weeks. The study will assess 1 g/day active treatment compared to placebo. Satiety will also be measured to investigate any correlation between treatment effect for anxiety / stress and self-reported reduction in appetite.

Design: The research design is a double-blind randomised placebo controlled clinical trial comparing the efficacy of CFE (1 g/day) to placebo by measuring self-reported anxiety and stress, and morning cortisol levels in saliva (nmol/L), before, during, and after treatment.

Hypotheses: It is hypothesised that a reduction in anxiety and stress (i.e., a decrease in negative anxiety scores and an increase in positives anxiety scores on the BAI, PSS, and PANAS and a decrease in morning cortisol levels (nmol/L, accounting for gender) over eight weeks would be significantly greater in the active treatment group than in the placebo group. Regarding Caralluma's effect on satiety, it is hypothesised that a decrease in the VAS score would be significantly greater in the active treatment group than in the placebo group. It is also hypothesised that a decrease in the VAS score for appetite would be positively correlated with a decrease in the anxiety and stress scales.

Introduction: The prevalence of anxiety disorders, combined with the private nature of the distress they cause, results in a large but silent affliction in society. Worldwide, mental health disruptions are the leading cause of disability (Beyond Blue, 2015). In Australia, depression and anxiety result in over six million lost working days, and an economic cost of $14.9 billion annually (White Cloud Foundation, 2015). Over two million Australian adults are diagnosed with anxiety in any one year (Australian Bureau of Statistics, 2008). All prevalence figures however, only account for diagnosed cases. It is arguable that this number would increase if it included people who experience mild to moderate anxiety or stress but are not clinically diagnosed with a disorder.

People who struggle to cope with daily life lack the treatments available to those with a diagnosed disorder. Prescription medications are often ineffective for these cases (ADIS International, 2007; Baumeister, 2012; Salum, Manfro, & Fleck, 2011), and the rates of

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remission tend to be low and the risk of relapse high (McDonald, 1997). Additionally, many find the adverse side effects of medications intolerable (Ferguson, 2001). The search for alternative treatments should therefore be a high priority in the management of mild to moderate anxiety and stress.

Caralluma fimbriata (CFE) is one such possible alternative. CFE, a cactus from India, has been used for centuries as a natural appetite suppressant. Recent studies measured its effects on satiety (Astell, Mathai, McAinch, Stathis, & Su, 2013) but Rajendran et al. (2014) also found evidence of anxiolytic effects in mice. In their study, pre-treatment with CFE was associated with statistically significant improvements in both nootropic (particularly memory) and anxiolytic activity for mice. When it comes to treatments, these are often mutually exclusive effects; anxiety medications (such as benzodiazepines) often worsen memory impairment. There are no pharmacological remedies that adequately treat anxiety co-presenting with cognitive deficits. Rajendran et al.'s research was clinically interesting since it suggested that CFE could be tested in this domain. Griggs, Su, and Mathai (2015) therefore investigated the efficacy of CFE for treating Prader-Willi Syndrome, which presents with deficits in these areas. Results were positive in behaviours relating to appetite, but the research did not isolate anxiety as an outcome.

This study will investigate the efficacy of CFE for reducing mild to moderate anxiety and stress over 8 weeks in otherwise healthy adults. This study will assess the efficacy of 1 g/day compared to placebo by measuring self-reported low mood and cortisol levels in saliva, before, during, and after treatment. Appetite will be monitored as a secondary outcome, to investigate any correlation between improvement in mood with changes in appetite.

Inclusion criteria: Participants will be included for assessment if they self-report mild-moderate anxiety (BAI >9<30), are not diagnosed with depression or a mood disorder, are otherwise healthy, and have given written informed consent.

Exclusion criteria: Participants will be excluded if they:

- are under 18 years of age
- have a known hypersensitivity to herbal drugs, or nutritional supplements;
- have been diagnosed with hypertension and are receiving medication;
- have a medical condition which, in the opinion of the investigator, makes them unsuitable or deemed unhealthy (including a BMI > 30);
- have currently or have a history of chronic alcohol and/or drug abuse;
- have participated in any other clinical trial during last 30 days;
- are currently participating in another clinical trial;
- have been diagnosed with a mood disorder;
- have minimal or severe anxiety on the Beck Anxiety Inventory (<10, or > 29);
- suffered severe PMS with mood or pain that would change during the study;
- suffered from any neurological disorder;
- are taking supplements that impact mood or appetite (e.g., St John's Wort, leptin);
- are already taking *Caralluma*.

Treatment: Two groups:

- 1 g/day active treatment group (500 mg morning and night)
- Placebo group

Duration: Eight weeks for each participant.

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Procedures: Written informed consent obtained from participants after an explanation of the study, including benefits and possible side effects of the treatment.

Screening:

- Demographics: Age, sex, weight, height, children (if yes, how many), whether they are smokers, drinkers (if yes, how many per week), and whether they exercise.
- History: Known medical conditions, medications, exclusion criteria checklist (see Screening interview script, and Participant demographics form).

Tools/instruments:

- Beck's Anxiety Inventory (BAI)
- Perceived Stress Scale (PSS)
- Positive Affect Negative Affect Schedule (PANAS)
- Salivary Cortisol test kit (Australian Clinical Labs)
- Secondary measure: Appetite using Visual Analog Scale (VAS)

Schedule:

	Baseline	Week 4	Week 8
Demographics	✓	×	×
Height	✓	×	×
Weight	✓	×	✓
BMI	✓	×	✓
Medications	✓	×	✓
Smoking	✓	×	✓
Drinking	✓	×	✓
BAI	✓	✓	✓
PSS	✓	✓	✓
PANAS	✓	✓	✓
Cortisol	✓	✓	✓
VAS (Appetite)	✓	✓	✓

Sample size: 120 participants

Recruitment: Participants will be recruited through voluntary sampling using RDC Global's clinical trial database, followed by digital advertising (RDC Global's Facebook advertising, and university emails). Letters of invitation will also available from RDC Global in Brisbane. This letter will also direct potential recruits to a dedicated website (anxietytrial.com.au) with information about the product, the clinical trial, and how to contact the investigator.

Randomisation: The sponsor will allocate the treatment containers to randomised groups (1 or 2) using Random Allocation Software version 1.0. Participants will be allocated containers in numerical sequential order (e.g., the 5th participant recruited will receive container 5, with enough capsules for the length of the trial). The randomisation code will be maintained by the sponsor to keep the investigators blind to active treatment allocation, and to facilitate randomisation code breaking in the case of adverse events. The investigator will be informed of treatment group allocation post-trial for statistical analyses.

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Safety: Product safety will be monitored by the investigator during interviews with each participant. The occurrence of any AE will be carefully monitored. If AE's are suspected, (1) Details will be recorded in the Adverse Event form, which will be forwarded to a medical consultant, (2) the participant will be asked to cease taking the treatment, (3) the sponsor and HREC will be notified, (4) the participant will be referred to a medical consultant for evaluation regarding whether the event constitutes an SAE. The sponsor will be asked to break the randomisation code, and the product allocation (active or placebo) will be made known to the referring medical consultant.

The risk of adverse effects to participants has been researched at the same doses proposed for this study. A 2013 study found Caralluma "was not associated with any toxicity or adverse events" (Odendaal, Deshmukh, Marx, Schauss, Endres, & Clewell, 2013). The study investigated in vitro mutagenicity, clastogenicity, death, toxicity, external, visceral, skeletal effects, and foetal abnormalities. A 2014 study found it to be safe for people for 60 days (the proposed intervention period) but stated that the long-term effects were not known and may depend on factors such as the user's age and health. It recommended not using the product if pregnant for precaution, so pregnancy will be an exclusion criteria in this study (Adnan, Jan, Mussarat, Tariq, Begum, Afroz, Shinwari, 2014).

The product will be produced in Australia by the Therapeutic Goods Administration's guidelines, under RDC Global's regulatory directives for: (1) 500 mg Caralluma adscendens var. fimbriata (measured equivalent of dry herb 6 g), with no gluten, lactose, egg, yeast, salt, preservatives, artificial colours, flavours or additives. (2) Placebo; equivalent maltodextrin in gelatine capsule.

Analysis: Change scores (delta) from baseline to week 4 and week 8 will be calculated for each individual to reduce within-group variability. Group means of the change scores will be assessed using mixed measures ANOVA with a Bonferroni post-hoc test, at $p < .05$. Correlation between appetite and anxiety and stress will be assessed using Pearson's r.