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Effects of a liquid blend containing kava and kratom in healthy adults

Submission date	Recruitment status	[_] Prospectively registered
22/11/2024	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
26/11/2024	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
20/01/2025	Other	

Plain English summary of protocol

Background and study aims
This study aims to evaluate the safety and effects of Feel Free Tonic on cognitive function and mood in healthy adults. The study is designed to assess whether the tonic improves cognition and mood compared to a placebo while also evaluating its safety profile.

Who can participate?
Healthy males and females aged 21 to 55 years may participate if they meet the inclusion criteria. Participants should have a body mass index (BMI) between 18.5 and 29.9 kg/m², be non-smokers, and not have a history of significant health conditions, including psychiatric disorders, liver or kidney disease, or substance abuse. Individuals must also meet specific lifestyle requirements, such as consistent dietary habits.

What does the study involve?
Participants will undergo computerized cognitive testing, mood assessments, and safety evaluations, including vital signs, laboratory blood tests, and respiratory and oxygen measurements. Participants will be randomly allocated to receive placebo and low-dose test products in two sequences (placebo then low dose, or low dose then placebo) over two treatment periods separated by a washout period. An extension involves higher doses in open-label conditions. The entire study could span 6 to 20 weeks, with in-clinic visits for dosing and assessments.

What are the possible benefits and risks of participating?
While there are no direct health benefits, participants contributed to scientific knowledge that may advance the understanding of herbal supplements' effects on cognition and mood. Risks included potential side effects from the test product, such as nausea and diarrhea, and discomfort from blood test procedures.

Where is the study run from?
Apex Trials in Guelph, Ontario (Canada)

When is the study starting and how long is it expected to run for?
October 2022 to September 2024

Who is funding the study?
Botanic Tonics, LLC (USA)

Who is the main contact?
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Public, Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
B05-22-01-T0043

Study information

Scientific Title
A double-blind, randomized, controlled, crossover study to evaluate the effects of Feel Free Tonic on cognitive function and mood in healthy adults

Study objectives
The test product, Feel Free Tonic, at the dosages investigated, improves cognitive function and mood in healthy adults, compared to placebo. It also demonstrates a good safety profile that is comparable to placebo.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 01/08/2023, Advarra Institutional Review Board (Suite 300, 372 Hollandview Trail, Aurora, L4G0A5, Canada; +1 (0)905 727 7989; cirbi@advarra.com), ref: Pro00071515

Study design
Single-centre interventional double-blind randomized placebo-controlled crossover trial with an open-label dose escalation

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Safety and efficacy in healthy adults

Interventions
There were two study products, the placebo and the test product (Feel Free Tonic). The test product (Feel Free Tonic) was provided in three dosage levels: low dose (15 ml per day), mid dose (30 ml per day [15 ml BID]), and high dose (60 ml per day [30 ml BID]). The test product is a liquid blend containing kava and kratom, with 410 mg kava root extract and 840 mg dried kratom leaf powder per 15 ml liquid blend. Participants consumed a placebo and each dosage level of the test product daily for 6 consecutive days.

Participants were randomized in a 1:1 ratio to receive a placebo and low-dose test product in two sequences (placebo then low dose, or low dose then placebo) over two treatment periods separated by a washout period. After this crossover assessment period and another washout period, participants entered the open-label, dose-escalation assessment period where all participants consumed the other two dosage levels of the test product, the mid and high doses, over another two treatment periods separated by a washout period. Safety assessments of each dosage level of the test product were conducted to confirm that it is safe before the next dosage level is investigated.

Intervention Type
Supplement

Primary outcome(s)
Cognition is measured using the Computerized Cognitive Testing Battery at baseline and Day 6

Key secondary outcome(s))
1. Mood and mental health is measured using Mood and Mental Health Survey scores at baseline and Day 6
2. Mitragynine and 7-hydroxymitragynine pharmacokinetic profiles are measured using plasma concentrations at baseline, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, and 72.0 hours post-dose to determine maximum concentration (Cmax), time to peak concentration (Tmax), half-life (T1/2) and total systemic exposure (measured by area under curve (AUC) from 0-72 hours)
3. Kavain and dihydrokavain pharmacokinetic profiles are measured using plasma concentrations at baseline, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, and 72.0 hours post-dose to determine maximum concentration (Cmax), time to peak concentration (Tmax), half-life (T1/2) and total systemic exposure (measured by area under curve (AUC) from 0-72 hours)
4. The accumulation of mitragynine, 7-hydroxymitragynine, kavain, and dihydrokavain are measured using trough pre-dose plasma concentrations at baseline, Day 2, Day 3, Day 4, Day 5, and Day 6
5. Safety is assessed using:
5.1. Vitals (heart rate [HR] and blood pressure [BP]) at baseline, Day 7 and Day 9
5.2. Laboratory blood tests at baseline, Day 6, Day 7, and Day 9 unless otherwise specified
5.3. Hematology: hemoglobin, hematocrit, red blood cells (RBC), red cell distribution width (RDW), and RBC indices, which consist of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). Additionally, white blood cells (WBC) and their differentials (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) are measured, along with mean platelet volume (MPV), platelet count, and blood smear
5.4. Clinical chemistry: urea, creatinine with estimated glomerular filtration rate (eGFR), total bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), albumin, random glucose (baseline only), fasting glucose (serum, baseline and day 6 only), total protein, sodium, potassium, chloride, and thyroid-stimulating hormone (TSH, baseline only)
5.5. Respiratory rate [RR] and Oxygen Saturation (SPO2) at baseline, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, and Day 9
5.6. Subjective Opiate Withdrawal Scale (SOWS) and Clinical Opiate Withdrawal Scale (COWS) at baseline, Day 7, and Day 9
5.7. Adverse events (AEs) recorded throughout the study

Completion date
24/09/2024

Eligibility

Key inclusion criteria
1. Adults who are between 21 – 55 years of age (inclusive).
2. In good general health (no uncontrolled diseases or conditions) as deemed by the investigator and is able to consume the study product (consume approx. 15 mL/0.5 oz of either study product).
3. Naïve to kratom use or occasional kratom use (no more than once within 28 days prior to Visit 2).
4. Non-smoker (including nicotine vaping) and have not used any nicotine products (patches, gums etc.) for >3 months prior to Visit 2. Non-smoker is defined as someone who does not habitually/regularly use products containing nicotine.

5. Have a body mass index (BMI) range of 18.5 – 29.9 kg/m2 at Visit 2.
6. Individuals with childbearing potential must agree to practice an acceptable form of birth control for a certain timeframe prior to the first dose of the study product and throughout the study, including:
6.1. Use for at least 3 months prior to the first dose of study product: hormonal contraceptives including oral contraceptives, hormone birth control patch (e.g., Ortho Evra), vaginal contraceptive ring (e.g., NuvaRing), injectable contraceptives (e.g., Depo-Provera, Lunelle), hormone implant (e.g., Norplant System), or intrauterine devices (e.g., Mirena); or
6.2. Use for at least 1 month prior to the first dose of study product: double-barrier method, non-hormonal intrauterine devices (i.e., copper), or complete abstinence from sexual intercourse that can result in pregnancy; or
6.3. Vasectomy of partner at least 6 months prior to the first dose of study product.
Individuals with the potential to impregnate others must agree to use condoms or other acceptable methods to prevent pregnancy throughout the study. Complete abstinence from sexual intercourse that can result in pregnancy is also acceptable.
7. Agree to refrain from treatments and other items listed in Section 6.5 in the defined timeframe.
8. Agree not to donate blood until 3 months after the study completion.
9. Must have suitable veins for repeated venipuncture.
10. Have maintained consistent dietary habits (including supplement intake) and lifestyle for the last 3 months prior to screening and agree to maintain dietary habits and lifestyle throughout the study.
11. Willing and able to agree to the requirements and restrictions of this study, be willing to give voluntary consent, be able to understand and read the questionnaires, and carry out all study-related procedures.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
21 years

Upper age limit
55 years

Sex
All

Total final enrolment
54

Key exclusion criteria
1. Individuals who are lactating, planning to become pregnant during the study, or pregnant as confirmed by a positive pregnancy test during study visits.
2. Have a known sensitivity, intolerability, or allergy to any of the study products, their

excipients, or rescue medication.
3. Demonstrates a positive urine drug screen test for compounds listed in Table 8 3 or positive breath alcohol test.
4. Have abnormal RR or SpO2 measurements at the discretion of the investigator.
5. Is currently enrolled in another clinical trial or has received/used an investigational product in another research study within 28 days prior to Visit 2 for either the Main study or the Sub-study (except for participants who are willing to participate in both portions of the study, they may be screened for eligibility for the Main study after a minimum of a 2-week washout from the last visit of the Sub-study).
6. Individuals with an abnormality or obstruction of the gastrointestinal tract precluding swallowing (e.g., dysphagia) and digestion (e.g., known intestinal malabsorption, celiac disease, inflammatory bowel disease, chronic pancreatitis, steatorrhea).
7. Have Type I/Type II diabetes, high BP at visit 2 (≥140 systolic or ≥90 diastolic mmHg), or thyroid disease.
8. Have a history of heart disease, blood clotting disorders, renal or hepatic impairment/disease.
9. Have known genetic polymorphisms of CYP450, CYP3A4, CYP2D6, and/or CYP1A2 enzymes.
10. Individuals with active asthma or have experienced an asthma attack in the last 5 years.
11. Are receiving treatments for or have been hospitalized in the last 12 months for psychiatric disorders (e.g., depression, bipolar disorder, schizophrenia, etc.).
12. Have a history of cancer (except localized skin cancer without metastases or in situ cervical cancer) with recovery occurring within 5 years prior to the screening visit.
13. Reports significant blood loss or blood donation totaling between 101 mL to 449 mL of blood within 30 days prior to Visit 2 (either study) or a blood donation of more than 450 mL within 56 days prior to Visit 2 (either study).
14. Reports donating plasma (e.g., plasmapheresis) within 15 days prior to Visit 2 (either study).
15. Major surgery in 3 months prior to screening or planned major surgery during the study.
16. History of alcohol or substance abuse in the 12 months prior to screening (including having been hospitalized for such an in-patient or out-patient intervention program).
17. Evidence of addictive tendency as indicated by an LDQ score ≥21.
18. Currently consumes more than 2 standard alcoholic beverages a day.
Note: A standard alcoholic beverage is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor.
19. Any other medical conditions or use of medications/supplements/therapies that, in the opinion of the investigator, may adversely affect the participant’s ability to complete the study or its measures, pose a significant risk to the participant or compromise the quality of study data.

Date of first enrolment
08/08/2023

Date of final enrolment
30/06/2024

Locations

Countries of recruitment
Canada

Study participating centre

Apex Trials
Suite 203, 120 Research Lane
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Sponsor information

Organisation
Botanic Tonics, LLC

Funder(s)

Funder type
Industry

Funder Name
Botanic Tonics, LLC

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Ramsey Atallah (ratallah@botanictonics.com).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		13/12/2024	20/01/2025	Yes	No