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Developing chamomile as a potential long COVID therapy: clinical evaluation of Roman chamomile extract in healthy volunteers

Submission date
31/05/2023

Recruitment status
No longer recruiting

Registration date
12/06/2023

Overall study status
Completed

Last Edited
12/06/2023

Condition category
Signs and Symptoms

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Roman chamomile (Chamaemelum nobile [L.]) is a perennial herb of the Asteraceae family that is native to Southwest Europe, but found throughout Europe, North Africa, and Southwest Asia. The plant has a long history of traditional use to treat digestive related problems, including nausea, vomiting, heartburn, and gas. It also has proposed applications in anxiety, inflammation, and topical application for skin health.

Our pre-clinical research supports strong anti-inflammatory effects associated with treatment of human cells with an aqueous ethanol extract of Roman chamomile. Chronic inflammation is a major risk factor in many human conditions, ranging from cardiovascular disease through to metabolic health and cognitive health. Of particular relevance to the current study, our data suggests that Roman chamomile treatment may reduce the release of inflammation markers including vascular injury markers from vascular endothelial cells. In addition to providing potential benefits to cardiovascular health, given the proposed role of endothelial inflammation in the etiology of long COVID, the Roman chamomile extract may also be of benefit in the alleviation of long COVID symptoms.

The current study will assess whether oral consumption of the Roman chamomile extract results in the active constituents of the extract reaching blood. This will be assessed by the ability of blood plasma removed from healthy subjects taking the investigational product (or placebo) to attenuate the induction of the vascular injury marker VCAM-1 (as well as other inflammation markers) in endothelial cells in an ex vivo setting. The study will assess multiple doses of Roman chamomile extract to inform an effective dose for use in future human studies.

Chamomile has a long history of safe consumption, particularly as a common ingredient in herbal tea. The herb is Generally Recognized As Safe (GRAS) for use in food by the U.S. Food and Drug Administration (FDA) as a spice, seasoning, or flavouring agent. A report by the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC; 2011) concluded that no health hazards or side-effects were known to be associated with the proper administration of Roman Chamomile at the specified therapeutic doses of 1-4 g of dried plant material or 1-4 ml of

70% ethanol extract (1:1 extract ratio). The Drug Extractant Ration (DER) of the investigational product used in the proposed study is in the range of 7:1 to 10:1, so the highest dose tested of 200 mg is well within the equivalent range of Roman chamomile material defined above. It is, however, worth noting that in the absence of any data, the EMA recommended that Roman chamomile should be avoided by pregnant women, as well as individuals with a known hypersensitivity to any members of the Asteraceae family, and individuals susceptible to allergic reactions (e.g. asthmatics).

Who can participate?
Healthy young adults aged 18 - 35 years

What does the study involve?
Participants will be randomly assigned to one of eight arms, which represent four doses of Roman Chamomile extract by two sequence orders (active treatment followed by placebo, or placebo followed by active treatment), for a two-period crossover design. Each treatment period will last for seven days, with subjects visiting the site on days 1 and 7 for assessment and continuing to take the allotted treatment every morning on the intervening days. There will be a 14 day washout period between the two treatment periods.

What are the possible benefits and risks of participating?
Benefits: Participants will contribute towards a study that aims to demonstrate anti-inflammatory activities for Roman Chamomile extract, with potential applications in support for long COVID as well as other areas of human health.
Risks: Chamomile has a long history of safe consumption, particularly as a common ingredient in herbal tea. The herb is Generally Recognized As Safe (GRAS) for use in food by the U.S. Food and Drug Administration (FDA) as a spice, seasoning, or flavouring agent, and at the dosage range being assessed in the current study, does not have any known health hazards or side-effects according to a report by the European Medicines Agency (EMA) Committee on Herbal Medicinal Products. The study will require visits to the study site and blood tests.

Where is the study run from?
Sibelius Limited (UK)

When is the study starting and how long is it expected to run for?
December 2022 to July 2023

Who is funding the study?
1. Sibelius Limited (UK)
2. Balvi.io

Who is the main contact?
Dr Kieron Edwards, kieron.edwards@sibeliuslimited.com

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Si01-2023

Study information

Scientific Title
Assessing Roman chamomile extract for anti-inflammatory effects in healthy young adults: a randomised, double-blind, placebo controlled, cross-over study

Study objectives
Roman chamomile extract demonstrates anti-inflammatory potential in healthy humans

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/05/2023, Ethics Committee of the Faculty of Medicine of Sousse (Rue Mohamed Karoui Sousse 4002 Tunisie; +216 73 222 108; no email provided), ref: CEFMS 177/2023

Study design
Single centre interventional randomized double-blind placebo controlled cross-over study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
University/medical school/dental school

Study type(s)
Efficacy

Participant information sheet
Not available in web format, please use contact details to request participant information sheet.

Health condition(s) or problem(s) studied
Reduction in release of inflammation markers

Interventions
A total of 40 subjects will be randomised into one of four treatment arms each containing 10 subjects. Subjects will be randomly assigned to one of the eight study arm treatment sequences (4 treatment doses x 2 treatment orders) based on the order they are recruited in following a sequence generated by the randomizeBE library in R (version 4.3.0). The study participants and study site staff will remain blind to the treatment dose and sequence.

Each treatment arm will represent a different dose of the active treatment (Roman chamomile extract at 25 mg, 50 mg, 100 mg, or 200 mg), and the four arms will run as independent cross-over designs with the placebo (AB/BA).

The study will include two treatment periods of 7 days separated by a 14-day wash-out period. Half of the subjects in each arm will take the active treatment during the first period and the placebo treatment in the second period, with the other half of the subjects taking the treatments in the opposite sequence.

Subjects will take 2 capsules per day for seven days, with all treatments being made up to 200 mg total with the placebo and having identical appearance (Size 0, opaque, white capsules).

Intervention Type
Supplement

Primary outcome measure
Release of Vascular Cell Adhesion Molecule-1 (VCAM-1) from endothelial cells stimulated with LPS measured at 1h, 2h, and 4h post consumption of the treatments (versus 0h) on days 1 and 7 of the treatment periods using MSD V-PLEX Human assay kits (Meso Scale Discovery, Gaithersburg, MD, USA)

Secondary outcome measures
1. Release of further inflammation markers from LPS stimulated endothelial cells treated with plasma from subjects consuming the experimental treatment versus the placebo at one or more time-points post product administration (1h, 2h, and 4h) on days 1 and/or 7 of the treatment periods; including: TNFα, IL-1β, IL-6, IL-8, ICAM-1, CRP, and SAA measured using MSD V-PLEX Human assay kits (Meso Scale Discovery, Gaithersburg, MD, USA)
2. Blood plasma levels of CRP, IL-6, and TNFα at time 0h on days 7 versus day 1 of the treatment periods measured using MSD V-PLEX Human assay kits (Meso Scale Discovery, Gaithersburg, MD, USA)
3. Total antioxidant capacity of blood plasma at one or more time-points post product

administration (1h, 2h, and 4h) on days 1 and/or 7 of the treatment periods measured by the DPPH Radical Scavenging method
4. Inhibition of COX-1 and COX-2 by plasma from subjects at one or more time-points post product administration (1h, 2h, and 4h) on days 1 and/or 7 of the treatment periods measured using a Cox human inhibitor screening assay kit (Cayman chemicals; #701230)
5. Post-prandial blood glucose levels at one or more time-points post product administration (1h, 2h, 4h, and 24h) on days 1 and/or 7 of the treatment periods (fasted subjects to be given a standardized meal directly after the active treatment/placebo on test days) measured using a Glucose oxidase-phenol amino phenazone (GOD-PAP) method (#GL2623, Randox)
6. Mood assessed using the Bond-Lader Visual Analogue Scale (VAS) at timepoints 0h, 1h, 2h, and 4h on days 1 and 7 of each treatment period.
7. Sleep quality assessed by the Leeds Sleep Evaluation questionnaire on day 7 of each treatment period.

The below safety objectives will also be considered:
1. Serum ALT and AST levels at 0h and 4h time-point samples from days 1 and 7 of each treatment period for any evidence of acute or chronic liver toxicity from the treatment doses measured by spectrophotometric analysis using diagnostic kits (AL1200 and AS1202; Randox Laboratories, UK
2. Adverse events will be assessed by interviews with the study physician during participants visit to the study site on days 1 and 7 of each treatment period

Overall study start date
01/12/2022

Completion date
31/07/2023

Eligibility

Key inclusion criteria
1. Healthy young adults aged 18 - 35 years
2. Willing to participate and signed informed consent
3. Ability to understand the background and the purpose of the study
4. Willing to comply with the protocol and the study specific limitations
5. Body Mass Index between 18.5 and 30.0 kg/m² as measured within 30 days prior to start of study
6. Fasting Blood Glucose between 3.9 mmol/L and 5.6 mmol/L as measured within 30 days prior to start of study
7. HbA1c below 40 mmol/mol (5.7%) as measured within 30 days prior to start of study
8. No prior history of CVD

Participant type(s)
Healthy volunteer, Learner/student

Age group
Adult

Lower age limit
18 Years

Upper age limit
35 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Age <18 or >35 years
2. Body Mass Index <18.5 or >35 kg/m²
3. Type 2 diabetes
4. Type 1 diabetes
5. Resistant hypertension (systolic ≥ 150 and/or diastolic ≥ 90 mmHg) on at least 4 anti-hypertensive medications
6. Hypotension (systolic <100 and/or diastolic < 60 mmHg)
7. Recent operation <6 months
8. Known hyper- or hypothyroidism unless treated and under control (stable for more than 3 months)
9. Birth control pills intake (Contraceptive drugs)
10. Intake of any SAID or NSAID during 4 weeks before or during the study conduction, which may affect the inflammation markers
11. Intake of dietary supplements or homoeopathic remedies (e.g. vitamins, minerals, fish-oils) during 2 weeks before and during the study
12. Females pregnant or lactating or planning a pregnancy during study
13. Any known addiction to drugs and/or alcohol
14. Recent alcohol consumption of more than 21 units/week for more than 3 months
15. Intake of illegal drugs during 4 weeks before and during study conduction (e.g. cannabis, cocaine)
16. Any known allergies
17. On a strict diet or practicing sport extensively
18. Employees of sponsor or institutions conducting the study
19. Current participation in another clinical study
20. Inability or unwillingness of individual or legal guardian/representative to give written informed consent

Date of first enrolment
25/05/2023

Date of final enrolment
09/06/2023

Locations

Countries of recruitment
Tunisia

Study participating centre

Higher Institute of Nursing Sousse, The University of Sousse
Institut Supérieur des Sciences infermières
BP 141, Rue MOHAMED ELKAROUI
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Sponsor information

Organisation
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Sponsor type
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Funder(s)

Funder type
Industry

Funder Name
Sibelius Limited

Funder Name
Balvi.io

Results and Publications

Publication and dissemination plan
Planned publication in a high impact peer-reviewed journal

Intention to publish date
31/07/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to results publication

IPD sharing plan summary
Published as a supplement to the results publication