

The impact of cranberries on microbiome and brain in healthy ageing

Submission date 05/11/2018	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 13/11/2018	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 02/12/2022	Condition category Nervous System Diseases	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

In an ageing population the incidence of dementia is rapidly increasing and poses a significant financial, societal, and (above all) personal burden. Although some drugs exist for these conditions, they treat the symptoms rather than slow or reverse the progression of the underlying disease. Research studies are now focusing on alternative strategies to prevent cognitive decline. Nutrition is considered important for brain function throughout life, and findings from recent laboratory and human observational studies have suggested that compounds called flavonoids can improve brain function. Flavonoids are a group of nutrients found in all fruit and vegetables, as well as tea, coffee, and chocolate, and a large amount of these nutrients are particularly found in cranberry. Furthermore, gut bacteria have recently emerged as significant contributors to nutrition and health, and have even been suggested to influence brain functioning through complex connections between the gut and the brain. In addition to protection against cognitive decline, plant-derived nutrients such as flavonoids have been reported to affect the function, amount, and types of bacteria found in the gut. There have been no previous studies looking at the interactions of cranberry nutrients and gut bacteria, and furthermore their impact on cognitive function. The aim of this study is to test whether cranberry improves brain function and reduce disease-causing mechanisms in healthy older individuals, with a particular focus on the impact on gut bacteria.

Who can participate?

Healthy older adults aged 50-80 years

What does the study involve?

Participants are randomly allocated to be given either a freeze-dried cranberry powder or a 'placebo' powder matched for taste, colour, and energy content (but not containing any cranberry) to be taken twice daily with food over 12 weeks. Between the start and end of the 12-week study changes in the following are measured: cognitive performance (i.e. memory, attention, spatial navigation), types and amount of gut bacteria present, the structure and functioning of the brain, presence of markers of inflammation, cardiovascular health, and sleep and activity patterns. This is done by conducting cognitive testing, collecting health and background information using questionnaires, collecting blood (less than 2 tbsp.), urine, and stool samples, conducting magnetic resonance imaging (MRI) scans of the brain, providing

activity and sleep monitors to wear during the study, and collecting physical measurements including height, weight, and blood pressure. Participants come to the Clinical Research Facility at the Norwich Research Park on three occasions over about 13 weeks. Study visits include the screening visit, to make sure participants are able to take part in the study. It involves blood and urine samples being taken (to check liver and kidney function, as well as other markers of health), collection of physical measurements (height, weight, blood pressure), a cognitive test (to screen for existing signs of cognitive impairment), and some questionnaires asking about health and background. The baseline visit is the visit at the beginning of the main 12-week study where all the measurements are taken that the cranberry intervention could influence, including taking urine and blood samples (for more detailed nutrition, physiological, and genetic analyses), conducting some further, more specific cognitive testing (e.g. memory, attention), collecting a stool sample (to be collected at home and brought to the study in secure packaging provided), and conducting an MRI scan (to look at brain structure and function). The follow-up visit takes place immediately following the 12th week of the study and includes all the same measures as the baseline visit, including MRI scan, cognitive testing, and samples, in order to see if the cranberry has had an impact on any of these measures.

What are the possible benefits and risks of participating?

Participating in this study is on a voluntary basis, and participants will be able to withdraw from the study at any time without needing to give a reason. However, taking part will require a generous contribution of participants' time and effort, and as such, participants will receive £25 for completion of the study. The researchers plan to communicate findings from this study through peer reviewed scientific journals, internal reports, conferences and presentations to the public. In all instances, data will be strictly anonymous. In addition to participation in the research, the public may also be involved in dissemination of the findings

Where is the study run from?

1. University of East Anglia (UEA) (Lead Centre) (UK)
2. Norfolk and Norwich University Hospital (NNUH NHS Trust) (UK)
3. The Norwich Clinical Research Facility (NNUH NHS Trust) (UK)
4. Norwich Biorepository (NNUH NHS Trust) (UK)
5. Earlham Institute (UEA) (UK)

When is the study starting and how long is it expected to run for?

March 2018 to May 2020

Who is funding the study?

Cranberry Institute (USA)

Who is the main contact?

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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT03679533

Secondary identifying numbers
38546

Study information

Scientific Title

The impact of cranberries on the microbiome and the brain in healthy ageing: a feasibility intervention

Acronym

COMBAT

Study objectives

Healthy older adults will be provided with a high-polyphenol, freeze-dried cranberry powder study food to take daily for 12 weeks, following which it is hypothesized that there will be increased gut microflora diversity and quantity of health-promoting bacterial species as measured in stool samples, which will relate to improved brain function and cognition, and decreased biomarkers of disease processes related to neurodegeneration.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Health Research Authority, 22/03/2018, ref: 18/HRA/1339

Study design

Both; Design type: Treatment, Dietary, Case-controlled study

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Other

Study type(s)

Other

Participant information sheet

See additional files

Health condition(s) or problem(s) studied

Brain function in healthy older people

Interventions

Participants will be randomised using a computerised randomisation algorithm into one of two intervention arms: the active cranberry powder arm, or the placebo matched for colour, taste, and macronutrient content (but not containing any cranberry), to be taken twice daily with food over 12 weeks. Neither the participants nor the experimenters will know which one has been given during the study.

Once a potentially suitable participant has been established, they will be asked to come to the Clinical Research Facility at the Norwich Research Park on 3 occasions over approximately 13 weeks. Study visits will include:

1. The screening visit. This visit is to make sure participants are able to take part in the study. It will involve blood and urine samples being taken (to check liver and kidney function, as well as other markers of health), collection of physical measurements (height, weight, blood pressure), a cognitive test (to screen for existing signs of cognitive impairment), and some questionnaires asking about health and background.
2. The baseline visit. This is the visit at the beginning of the main 12-week study where the trialists will take all the measurements that the cranberry intervention could influence. They will be taking again a urine and blood sample (for more detailed nutrition, physiological, and genetic analyses), conduct some further, more specific cognitive testing (e.g. memory, attention), collect a stool sample (to be collected at home and brought to the study in secure packaging provided), and conduct an MRI scan (to look at brain structure and function).
3. The follow-up visit. This visit takes place immediately following the 12th week of the cranberry study. This visit will include all the same measures as the baseline visit, including MRI scan, cognitive testing, and samples, in order to see if the cranberry has had an impact on any of these measures.

Intervention Type

Supplement

Primary outcome measure

1. Gut microflora speciation and metabolism is measured by analysing stool samples at baseline and at the 12-weeks follow-up
2. Changes in hippocampal volume and other key brain structures measured using structural magnetic resonance imaging at baseline and at 12-weeks follow-up
3. Changes in cerebrovascular blood flow measured using magnetic resonance spectroscopy at baseline and at 12 weeks
4. Change in global cognition measured using the Addenbrooke's Cognitive Examination III at baseline and 12 weeks
5. Change in spatial navigation abilities measured using The Supermarket Test at baseline and 12 weeks
6. Change in spatial navigation abilities measured using the SeaHero Quest iPad app at baseline

and 12 weeks

7. Change in executive function and attention measured using the Trail Making Test and the Digit Span backwards test at baseline and 12 weeks

8. Change in visual memory performance measured using the Rey Complex Figure test at baseline and 12 weeks

9. Change in presence of circulating biomarkers of inflammation (hs-CRP) measured in blood samples taken at baseline and 12 weeks

10. Change in presence of circulating biomarkers of neuronal functioning and cognitive decline (BDNF) measured in blood samples collected at baseline and 12 weeks

11. Change in circulating biomarkers of lipid metabolism (total-, HDL-, LDL-cholesterol, triglycerides) measured in blood samples at baseline and 12 weeks

12. Regular dietary patterns measured using a food frequency questionnaire collected at baseline

Secondary outcome measures

1. Changes in energy expenditure and sleep measured using actigraphs worn for one week prior to baseline and one week prior to the 12 week follow-up visit

2. Genetics related to neurodegenerative disease detected using blood samples to be analysed for genes associated with neurodegenerative disease and dementia (e.g. C9ORF72, APOE-4) collected at baseline

3. Biomarkers of gut permeability and endotoxemia (LPS) measured in blood serum/plasma samples at baseline and 12 weeks

4. Levels of sunlight exposure measured using a brief questionnaire regarding levels of daily sunlight exposure, to be collected at baseline and 12 weeks

5. Sleep duration and quality collected using the Pittsburgh Sleep Questionnaire at baseline and 12 weeks

6. Sleep duration and quality measured using actigraphs worn by participants for one week prior to each baseline and 12 weeks follow-up visits

Overall study start date

23/03/2018

Completion date

21/05/2020

Eligibility

Key inclusion criteria

1. Aged between 50 and 80 years old

2. Male and female

3. Generally fit and healthy

4. Willing and able to provide written informed consent

5. Fluent in written and spoken English

6. Normal or corrected to normal vision and hearing

7. Understands and is willing and able to comply with all study procedures

Participant type(s)

Healthy volunteer

Age group

Adult

Sex

Both

Target number of participants

Planned Sample Size: 60; UK Sample Size: 60

Total final enrolment

60

Key exclusion criteria

Participants will be excluded from the study if they have any of the following:

1. Diagnosis of any form of dementia or significant neurological condition
2. Significant memory complaints
3. History or MRI evidence of brain damage, including significant trauma, stroke, learning difficulties or serious neurological disorder, including a loss of consciousness for more than 24 hours
4. Currently smoking or ceased smoking less than 6 months ago
5. Chronic fatigue syndrome, liver disease, diabetes mellitus, or gall bladder abnormalities
6. History of alcohol or drug dependency
7. Clinically diagnosed psychiatric disorder
8. Existing diagnosed gastrointestinal or gall bladder disorders
9. Known allergy to the intervention supplement
10. Any significant medical condition likely to affect participation
11. Currently a participant or have been a participant in any other study involving an investigational product within the last 4 weeks
12. Absence of a spouse to be a study partner with whom they are also currently living
13. Uncontrolled hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg)
14. Major cardiovascular event, such as myocardial infarction, within the last 12 months
15. Liver disease
16. Chronic fatigue syndrome
17. Diabetes mellitus
18. Participants will not be eligible for the study if they are prescribed any of the following:
 - 18.1. Blood pressure lowering medication
 - 18.2. Anti-depressants
 - 18.3. Anti-coagulants
 - 18.4. Anti-psychotics
 - 18.5. Cholinesterase inhibitors
 - 18.6. Anti-convulsants
 - 18.7. Non-steroidal anti-inflammatory drugs
19. Regarding supplements and diet, participants will not be eligible if they take and/or unwilling to stop taking the following:
 - 19.1. Flavonoid containing supplements (and unwilling to cease intake during, and 1 month preceding the trial) or unwilling to maintain existing intake of other supplements
 - 19.2. High flavonoid intake defined as > 15 portions of flavonoid rich foods per day
 - 19.3. Any other supplements that could have a significant impact on the outcome measures
20. Participants will not be eligible to undergo the neuroimaging component of the study if they have any of the following:
 - 20.1. Cardiac pacemaker
 - 20.2. Claustrophobia

21. To ensure safety within the MRI scanner, access to medical records or further inquiry will be required if participants indicate that they may have had any of the following:

- 21.1. Heart surgery
 - 21.2. Brain, head, spine or eye surgery
 - 21.3. Aneurysm clips
 - 21.4. Hydrocephalus shunt
 - 21.5. Metal dust or fragments in the eye
 - 21.6. Metal injuries (e.g. shrapnel, bullets, pellets)
 - 21.7. Electronic, mechanical, or magnetic implants
 - 21.8. Operations involving metal implants, plates, clips, stents, bands or expanders
 - 21.9. Operations within the previous 8 weeks
 - 21.10. Kidney problems
 - 21.11. Have had liver transplant or waiting for a liver transport
 - 21.12. Fits, blackouts, or epilepsy
 - 21.13. Piercings, hearing aids, dentures (to check if they are removable)
 - 21.14. Medication patches, tattoos, permanent eyeliner or makeup
22. For female participants:
- 22.1. Chance of pregnancy
 - 22.2. Breastfeeding
 - 22.3. Intrauterine contraceptive device (IUD)
23. For cases of operations, implants, or devices a surgeon's report will be requested from the participant's medical records, which will then be reviewed by the radiologist at NNUH before proceeding with the MRI scan. If participants are unable or unwilling to undergo an MRI scan, they are still able to participate in other components of the study

Date of first enrolment

02/10/2018

Date of final enrolment

31/12/2019

Locations

Countries of recruitment

England

United Kingdom

Study participating centre

University of East Anglia (UEA) (lead centre)

Norwich Research Park

Norwich

United Kingdom

NR4 7TJ

Study participating centre

Norfolk and Norwich University Hospital (NNUH NHS Trust)

Colney Lane
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Study participating centre**The Norwich Clinical Research Facility (NNUH NHS Trust)**

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Study participating centre**Norwich Biorepository (NNUH NHS Trust)**

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Sponsor information

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Sponsor type

University/education

ROR

<https://ror.org/026k5mg93>

Funder(s)

Funder type

Research organisation

Funder Name

Cranberry Institute

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United States of America

Results and Publications

Publication and dissemination plan

Results from this study will be presented at national and International conferences with a planned publication in a high-impact peer reviewed journal estimated for early 2021.

Intention to publish date

30/12/2021

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.2	20/03/2018	13/11/2018	No	Yes
Results article		19/05/2022	07/06/2022	Yes	No
Protocol file	version 4.0	07/05/2019	16/08/2022	No	No