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The impact of cranberries on microbiome and brain in healthy ageing

Submission date
05/11/2018

Recruitment status
No longer recruiting

Registration date
13/11/2018

Overall study status
Completed

Last Edited
02/12/2022

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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

ClinicalTrials.gov (NCT)
NCT03679533

Protocol serial number
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

Study type(s)
Other

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(s)
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

Key secondary outcome(s))
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

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

Healthy volunteers allowed
No

Age group
Adult

Sex
All

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
United Kingdom

England

Study participating centre
University of East Anglia (UEA) (lead centre)
Norwich Research Park
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Study participating centre
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Sponsor information

Organisation
University of East Anglia

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

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?
Results article		19/05/2022	07/06/2022	Yes	No
Participant information sheet	version v1.2	20/03/2018	13/11/2018	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 4.0	07/05/2019	16/08/2022	No	No