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Blueberry consumption and metabolic syndrome

Submission date	Recruitment status	[X] Prospectively registered
28/02/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
03/03/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
13/03/2023	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The metabolic syndrome (MetS) is a constellation of risk factors that include obesity, high blood pressure, high blood lipids, and insulin resistance. MetS is also associated with decreased blood vessel function and alterations in intestinal (gut) permeability.
Increasing evidence indicates that diet and dietary bioactive compounds (e.g., polyphenols) can play a fundamental role in preventing and reversing most risk factors associated with the MetS, suggesting diet as a possible alternative to drug treatment. In particular, polyphenol-rich foods including blueberries may have potential health benefits against the development and progression of MetS. However, these effects need to be confirmed in human studies. At present, few human studies have been conducted evaluating the effect of blueberries on the risk factors associated with the MetS and the results are frequently not significant. No studies have evaluated the impact of blueberries on endothelial (blood vessel lining) permeability as well as intestinal (gut) permeability. The aim of this study is to explore the role of wild blueberries in normalizing MetS factors, improving endothelial function and permeability, and reducing inflammation, in people at high risk for heart disease.

Who can participate?
Men and women aged 40-65 years, overweight (BMI 25-30 kg/m²) and diagnosed with metabolic syndrome

What does the study involve?
Participants will be randomly allocated to drink 240 ml of a wild blueberry or a placebo (dummy) drink for 8 weeks. Blood, urine and feces samples will be collected at the start of the study and after 8 weeks. Blood vessel function markers will be measured at the start of the study, at 2 hours after blueberry/placebo intake, and at the end of the 8-week period, while body measurements and clinical and metabolic parameters will be assessed at the start and at the end of the study.

What are the possible benefits and risks of participating?
The daily intake of blueberry and polyphenols could have an overall beneficial impact on

metabolic syndrome markers. In addition, polyphenols may activate the body's defense mechanisms against oxidative stress and inflammation, contributing to the overall health benefit. There are no expected risks.

Where is the study run from?
1. DeFENS, Università degli Studi di Milano (Italy)
2. International Center for Assesment of Nutritional Status (ICANS), Università degli Studi di Milano (Italy)

When is the study starting and how long is it expected to run for?
November 2019 to January 2024

Who is funding the study?
Wild Blueberry Association of North America (USA)

Who is the main contact?
1. Dr Cristian Del Bo’, cristian.delbo@unimi.it
2. Prof. Dorothy Klimis-Zacas, dorothea@maine.edu
3. Prof. Alberto Battezzati, alberto.battezzati@unimi.it

Contact information

Type(s)
Principal Investigator

Contact name
Dr Cristian Del Bo'

ORCID ID
https://orcid.org/0000-0001-7562-377X

Contact details
Via G. Celoria 2
Milano
Italy
20133
+39 (0)250316730
cristian.delbo@unimi.it

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

Nil known

Study information

Scientific Title
The effect of wild blueberries on metabolic syndrome clusters: a new focus on endothelial permeability and functionality

Acronym
BLUMET

Study objectives
The present study attempts to test the hypothesis that wild blueberries are able to normalize metabolic syndrome risk factors, improve endothelial function and endothelial permeability, and reduce inflammation, in subjects at high risk for cardiovascular diseases.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/01/2022, the Ethics Committee of the University of Milan (Via Festa del Perdono 7, 20122, Milano, Italia; +39 (0)2 503 12667; comitato.etico@unimi.it), ref: 7/22

Study design
Controlled randomized crossover intervention study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Home

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Metabolic syndrome

Interventions
Thirty-two subjects with risk factors for metabolic syndrome will be enrolled and randomized using a computer random number generator to consume 240 ml/day of a wild blueberry drink (providing at least 560 mg of anthocyanins and 200 mg of chlorogenic acid) or placebo (a drink prepared to match macronutrient and calorie content and to have sensory characteristics similar

to the wild blueberry drink but without its bioactives). Each treatment will be 8 weeks long and separated by at least an 8-week wash-out period. At the beginning of each intervention period, an acute study will be performed in which subjects will consume a single portion of the wild blueberry drink.

Intervention Type
Other

Primary outcome measure
Acute study: improvement of vascular function measured as reactive hyperemia index (by EndPAT2000) at baseline and 2 hours after the intake of blueberry or placebo treatments

Chronic study: improvement of vascular function measured as reactive hyperemia index (by EndPAT2000) at baseline and after 8-week treatment with blueberry or placebo

Secondary outcome measures
The following list of markers will be measured at baseline (T0) and after 8 weeks (T8) of blueberry and/or placebo treatment:
1. Vascular function markers: vascular endothelial growth factor, vascular cell adhesion molecule-1, E-selectin, endothelin-1, endothelial nitric oxide/inducible nitric oxide measured in serum by ELISA kits
2. Digital augmentation index measured by EndoPAT2000
3. Blood pressure measured by a sphygmomanometer
4. Endothelial permeability markers: vascular endothelial cadherin, occludin, claudin 5 measured in serum by ELISA kits
5. Oxidative stress markers: endogenous and oxidatively-induced DNA damage measured in the buffy coat from blood by the comet assay
6. Inflammatory markers: tumor necrosis factor-alpha, interleukin-6, C-reactive protein measured in serum by ELISA kits
7. Intestinal permeability marker: serum and fecal zonulin measured by ELISA kits
8. Cardiometabolic markers: triglycerides, total serum cholesterol, low- and high-density lipoprotein cholesterol, glucose, insulin, c-peptide measured in plasma/serum by standardized techniques
9. Hepatic and renal function: serum creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase measured in plasma/serum by standardized techniques
10. Nutritional markers: anthocyanins (ACNs), vitamin C, folate, vitamin B12, measured in plasma /serum by high performance liquid chromatography mass spectrometry (HPLC/MS); glutathione (GSH/GSSG) measured in plasma/serum by ELISA kits
11. Food intake estimated by the use of food diaries and analysed by Metadieta software
12. Lipidomic, proteomic and metabolomic status measured in the buffy coat from blood using omics approaches (e.g., proteomic, lipidomic, metabolomic)

Overall study start date
11/11/2019

Completion date
31/01/2024

Eligibility

Key inclusion criteria
1. Women and men
2. Aged 40-65 years
3. Body mass index 25-30 kg/m²
4. Waist circumference ≥102 cm in men and ≥88 cm in women
5. High density lipoprotein cholesterol < 1.04 mmol/l in men and <1.30 mmol/l in women
6. Serum triglycerides ≥1.7 mmol/l or treatment with triglycerides-lowering drugs
7. Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment with blood pressure lowering drugs
8. Serum glucose ≥6.1 mmol/l or treatment with blood glucose-lowering drugs
9. No smokers

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
40 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
32

Total final enrolment
32

Key exclusion criteria
1. Obesity
2. Uncontrolled diabetes
3. Primary hypercholesterolemia
4. Dysthyroidism
5. Liver and renal disease
6. Gastrointestinal disorders
7. Antibiotic treatment
8. Use of supplements
9. Impaired cognitive function
10. Smokers
11. Allergy to blueberry and their products
12. Vegetarian, vegans, macrobiotic

Date of first enrolment
20/03/2022

Date of final enrolment

15/10/2023

Locations

Countries of recruitment
Italy

Study participating centre
University of Milan - DeFENS-ICANS
DeFENS: Via Luigi Mangiagalli 25
ICANS: Via Sandro Botticelli 21
Milan
Italy
20133

Sponsor information

Organisation
University of Milan

Sponsor details
Via Festa del Perdono, 7
Milan
Italy
20122
+39 (0)2 5032 5032
unimi@postecert.it

Sponsor type
University/education

Website
https://www.unimi.it/it

ROR
https://ror.org/00wjc7c48

Funder(s)

Funder type
Other

Funder Name
Wild Blueberry Association of North America

Results and Publications

Publication and dissemination plan
Planned publication of study results in high-impact peer-reviewed journals following trial completion. A protocol will be uploaded in the next few months of the study.

Intention to publish date
30/06/2024

Individual participant data (IPD) sharing plan
Data of the markers analysed will be available upon request at the end of the study from Dr Cristian Del Bo' (cristian.delbo@unimi.it). Data are anonymous and consent was obtained from participants

IPD sharing plan summary
Available on request