ISRCTN33165861 https://doi.org/10.1186/ISRCTN33165861

The synergetic effect of Bergamot and Cynara Cardunculus extract on blood vessels in patients with type 2 diabetes and non-alcoholic fatty liver disease

Submission date
15/10/2019

Recruitment status
No longer recruiting

Registration date
04/11/2019

Overall study status
Completed

Last Edited
01/12/2022

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Non-alcoholic fatty liver disease (NAFLD) represents a considerable risk factor for cardiovascular diseases. NAFLD is worsened by the simultaneous occurrence of type 2 diabetes mellitus (T2DM) causing an enhancement of inflammatory and fibrotic processes. Although insulin resistance appears the link between NAFLD and TD2M, with current pharmacological treatments of TD2M failed to produce relevant benefits in preventing TD2M-related liver dysfunction. The effect of Bergamot and Cynara Cardunculus extract may have a positive effect on symptoms

Who can participate?
Patients over 18 with type 2 diabetes and non-alcoholic fatty liver disease

What does the study involve?
Patients will be randomly selected to receive effect Bergamot or Cynara Cardunculus extract, a mix of both, or placebo for 16-weeks. After this time the liver, kidney, and blood vessels will be evaluated for changes

What are the possible benefits and risks of participating?
The major benefits include improvement of liver functionality and overall a reduction of cardiometabolic risk prevention associated with reduced NAFLD. We do not expect risks for participants as the toxicological test for Bergacyn showed that the product, at very high doses, failed to produce any side effect. (See attached toxicology report).

Where is the study run from?
IRC-FSH University of Catanzaro, Italy

When is the study starting and how long is it expected to run for?
February 2018 to December 2019

Who is funding the study?
Nutramed S.c.a.r.l., Italy

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
219b/2018/CE

Study information

Scientific Title
The synergetic effect of Bergamot and Cynara Cardunculus Extract on vascular inflammation and endothelial dysfunction in patients with Type 2 Diabetes and NAFLD: a double blind, randomized, placebo-controlled study.

Acronym
BergaDiab

Study objectives

Bergamot Polyphenolic Fraction (BPF) and Cynara Cardunculus Extract (CyC) given alone or in combination (Bergacyn 50/50%) will have a hepatoprotective effect; correlate with reduction of oxidative stress/inflammation biomarkers; and improve entothelial dysfunction in patients with type 2 diabetes and NAFLD

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/09/2018, Ethics Committee of Calabria (Regione Calabria Comitato Etico Sezione Area Centro; A.O.U. Mater Domini in Via Tommaso Campanella, 115 Catanzaro; +39 (0)961-3604001; michelangelo.iannone@cnr.it), ref: 219b

Study design
Randomized double-blind placebo-controlled study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
NAFLD and endothelial dysfunction oxidative stress in type 2 diabetes

Interventions
Participants will be randomized using a random number generator in Excel software to receive oral administration of BPF (300 mg/daily; n=20), CyC (300 mg/daily; n=20) or a formulation of both extracts (Bergacyn; 150 mg + 150 mg/daily; n=20) or placebo (300 mg of maltodextrin; n= 20). Each participant will be required to maintain their habitual diet, physical activity during the study. The number of supplements not consumed and log reviews will be used to assess compliance. Participants returned at 16 weeks to provide a fasting blood sample and undergo liver ultrasound examination.

Following exclusion of subjects with excessive alcohol consumption and viral or autoimmune liver disease, NAFLD will be diagnosed by abdominal ultrasound, which is a widely accessible imaging technique with high diagnostic accuracy and reliability for the detection of fatty liver. An ultrasonographic examination will be performed by an experienced radiologist using a real-time scanner (3.5 MHz; Mod. Aplio, Toshiba, Japan) equipped with a convex-array probe. All subjects will be evaluated in the left lateral recumbent position of 15˚ - 20˚ to see the liver parenchyma and the right kidney cortex was seen contemporaneously.
The brightness of both zones will be examined. The liver will be recorded from the intercostal space, posing the region of interest (of 1.5 cm Å~ 1.5 cm) in the mid or anterior axillary line (seventh or eighth intercostal space).

The right kidney will be evaluated, highlighting the region of interest (0.5 cm x 0.5 cm) in the cortical zone. Hepato- Renal Index Difference (HRI-diff: Echo Levels in the Liver–Echo Levels in the Kidney) will be estimated using built-in software on the scanner enabling local measurement of attenuation in dB. Mild steatosis will be diagnosed for hyperechogenic liver tissue (compared with the kidney cortex) when the sonographic index results will be between 1 and 2. Values

between 2 and 2.5 will be indicative for moderate liver steatosis. Finally, hepatic steatosis will be diagnosed as severe when the hepatorenal ratio was > 2.5. In each case, the calculation of the hepatorenal index will be repeated at least twice.

Blood measurements:
At the baseline and after 16 weeks of the experimental protocol, a 12-h fasting morning blood sample will be collected, processed and stored at -80°C. All serum marker concentrations or activities will be measured using classical methods and commercial assay kits, according to the manufacturers' instructions. Assay kits for ALT, AST, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), SOD, GPx and MDA will be purchased from Novamedical, Italy. An ELISA kit for TNF-α will be purchased from Thermo Fisher Scientific (Milan). Chemiluminescence assay kits for serum liver fibrosis markers HA, PC III, and IV-C will be purchased from Sysmex (HQ: Kobe, Japan). Absorbance will be measured using a Bio-Rad 680 microplate reader (Bio-Rad Co., Hercules, CA, USA). Chemiluminescence intensity will be monitored on a luminescence reader (FlexStation 3, Molecular Devices, Sunnyvale, CA, USA).
All the laboratory tests will be performed in a blinded manner in respect to the assigned treatment.

Assessment of endothelial function:
Endothelial function will be assessed using the EndoPAT 2000 technique, which measures PAT using the reactive hyperaemia index (RHI, arbitrary units). Briefly, after 20 minutes of rest in a 45° angled inclined chair, at room temperature, the blood pressure cuff will be placed on the non-dominant upper arm (study arm), while the other arm will be used as the control. The hands will bewill be placed on armchair supports with the palm side down, as the fingers hung freely. The EndoPAT probes will be then placed on the tip of each index finger of both hands. After baseline recording, (five minutes on each arm), the arterial flow will be then interrupted in the experimental arm by rapidly inflating the cuff to occlusion pressure of 200 mmHg or 60 mmHg plus systolic blood pressure. After a five minutes occlusion, the cuff pressure will be rapidly deflated, and post-occlusion flow will be recorded for other five minutes in the experimental arm as well as the control arm.

Statistical analysis
For continuous variables, baseline differences between the BPF + CYC formulation and baseline levels will be assessed using Student’s t test for independent samples. Data analyses will be conducted using SPSS software (version 18.0)

Intervention Type
Supplement

Primary outcome(s)
At 16-weeks:
Epato-renal index, transaminases, gamma glutamyl transferase, measured by blood sample.

Key secondary outcome(s))
At 16-weeks:
EndoPat measures of Reactive vasodilatation, malondialdehyde levels, inflammation markers, measured by blood sample.

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. Men or women ≥ 18 years
2. Written informed consent
3. History of at least 12 months of type 2 diabetes mellitus
4. History of at least 12 months of NAFLD with no excessive alcohol consumption (less than 20 g /day for men and 10 g/day for women)
5. Fatty liver
6. Hepato-renal index between 2.5 and 3.5

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
80

Key exclusion criteria
1. Positive pregnancy test (ßHCG) performed at the selection visit or result not available, women who are pregnant, women who are breast-feeding, women of childbearing potential not using estro-progestative or progestative or intrauterine contraception, or women using estro-progestative or progestative or inteauterine contraception, but who consider stopping it during the planned duration of the study
2. History of alcoholism or drug abuse
3. Patients with viral or autoimmune liver disease
4. Patients unlikely to co-operate in the study or to comply well with the treatment or with the study visits
5. History of severe mental or psychiatric disorder, severe depression or history of severe depression, e.g. requiring an hospitalization or at high risk of suicide attempt
6. Participation in another study at the same time or within the preceding 30 days

Date of first enrolment
01/02/2018

Date of final enrolment
30/09/2018

Locations

Countries of recruitment
Italy

Study participating centre
IRC-FSH University of Catanzaro
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Sponsor information

Organisation
Nutramed Scarl

Funder(s)

Funder type
Research organisation

Funder Name
Nutramed Scarl, PON-MIUR 03PE000_78

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from sara.paone06@gmail.it on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		08/02/2020	01/12/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes