

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

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Registration date 04/11/2019	Overall study status Completed	<input type="checkbox"/> Protocol
Last Edited 01/12/2022	Condition category Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
		<input type="checkbox"/> 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

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
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 endothelial 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

Secondary study design

Randomised controlled trial

Study setting(s)

GP practice

Study type(s)

Prevention

Participant information sheet

No participant information sheet available

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 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 measure

At 16-weeks:

Epato-renal index, transaminases, gamma glutamyl transferase, measured by blood sample.

Secondary outcome measures

At 16-weeks:

EndoPat measures of Reactive vasodilatation, malondialdehyde levels, inflammation markers, measured by blood sample.

Overall study start date

01/02/2019

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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

80

Total final enrolment

80

Key exclusion criteria

1. Positive pregnancy test (β HCG) 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 intrauterine 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

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Sponsor type

Research organisation

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Funder(s)

Funder type

Research organisation

Funder Name

Nutramed Scarl, PON-MIUR 03PE000_78

Results and Publications

Publication and dissemination plan

We expect to publish data into peer-reviewed journal and as an oral communication or poster presentation in meetings related to NAFLD

Intention to publish date

30/01/2020

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