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Evaluation of the effects of cinchona supplementation on nutritional status and body composition in overweight/obese adults undergoing a hypocaloric diet

Submission date
14/07/2023

Recruitment status
No longer recruiting

Registration date
25/07/2023

Overall study status
Completed

Last Edited
01/08/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Obesity is a complicated and multifaceted disease that affects more than one-third of the global population. It is a significant risk factor for various illnesses like cardiovascular disease, type 2 diabetes, and cancer. Recently, there has been increasing interest in using nutraceutical products as supplements for preventing and treating obesity. Scientific studies have focused on understanding the functions of bitter taste receptors called TSR2R. These receptors are found in the stomach wall and the first part of the duodenum (the small intestine). Activation of a specific subtype of these receptors in the stomach wall leads to the release of the hormone ghrelin, which stimulates appetite. Activation of TSR receptors in the duodenum slows down the movement of food through the intestine and triggers the release of a substance called CCK, which signals feelings of fullness and satisfaction. Researchers have discovered that melatonin, a naturally occurring hormone, acts as a ligand (a molecule that binds to a receptor) for duodenal TSR receptors. This suggests that melatonin plays a role in regulating the metabolic cycle of these receptors. To find natural compounds similar to melatonin, a screening process was conducted, and alkaloids found in the bark of the Cinchona tree (specifically quinine, quinidine, cinchonine, and cinchonidine) were identified as promising candidates. These alkaloids have structural similarities to melatonin and are likely to act as receptor agonists, meaning they can activate the TSR receptors in the duodenum. In summary, obesity is a widespread disease that poses various health risks. Nutraceutical products are being explored as potential supplements for obesity management. Studies have shown that bitter taste receptors in the stomach and duodenum play a role in regulating appetite and satiety. Melatonin, as well as alkaloids found in Cinchona bark, are being investigated for their potential to act on these receptors in the duodenum and help regulate the metabolic cycle associated with obesity.

Who can participate?
Overweight/Obese (Body Mass Index 25-45 kg/m²) adults (aged 18-70 years old)

What does the study involve?
Patients are randomly divided into two groups and subjected to a low-calorie diet for 8 weeks. Specifically, the first group is treated with a low-calorie diet in association with Cinchona 400 mg twice daily; the second group is treated with a low-calorie diet and placebo (control group). Each subject will be given a self-assessment questionnaire based on a 5-point Likert scale to assess compliance with Cinchona intake, adherence to the diet, feeling of fullness, and recording of any adverse effects. Participants will be asked to maintain their usual patterns of physical activity throughout the study period.

Blood chemistry tests will be performed on all participants at T0 and 8 weeks to determine the following values: blood glucose, total cholesterol, HDL, LDL, triglycerides, creatininaemia, AST and ALT transaminase. The concentrations of hormones such as cholecystokinin and ghrelin are also examined. Body measurements will be taken at each time point. A taste test is performed at the beginning and end of treatment to assess the ability to perceive the bitter taste or not.

What are the possible benefits and risks of participating?
The project is based on the hypothesis that Cinchona will determine greater adherence to the low-calorie diet, regulating the sense of hunger and digestive functions, as well as the biochemical and hormonal parameters of overweight/obese subjects. There are no known risks to participants taking part in this study.

Where is the study run from?
Clinics of the Interdepartmental Program of "Diet Therapy in Transplantation, Renal Insufficiency and Chronic Pathologies", of the Department of Clinical Medicine and Surgery of the University of Naples "Federico II" (Italy)

When is the study starting and how long is it expected to run for?
May 2023 to October 2023

Who is funding the study?
1. University of Naples "Federico II" (Italy)
2. NGN Healthcare New Generation Nutraceuticals srl (Italy)

Who is the main contact?
Prof Bruna Guida, bguida@unina.it (Italy)

Contact information

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Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
n° 0029070 of 19/06/2023

Study information

Scientific Title

A randomized controlled trial to evaluate the effects of supplementation with Cinchona on nutritional status and body composition in overweight/obese adults undergoing a hypocaloric diet

Study objectives
The project is based on the hypothesis that Cinchona in the form of a gastro-resistant capsule of 400 mg (administered twice daily before main meals) will pass intact through the acidic barrier of the stomach and reaches the intestinal level to activate specific duodenal receptors that increase the secretion of cholecystokinin (CCK). The sense of satiety generated by these hormonal modifications should reduce hunger pangs as well as episodes of uncontrolled appetite in overweight-obese adult subjects, resulting in greater adherence to the hypocaloric diet.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 19/06/2023, Scientific Ethics Committee of A.O.U. Federico II – A.O.R.N. Cardarelli (Via Sergio Pansini, 5, Naples, 80131, Italy; +390817473433; segreteria@comitatoeticofedericoiicardarelli.it), ref: Protocol n° 204

Study design
Monocentric interventional single-blinded randomized controlled trial

Primary study design
Interventional

Study type(s)
Quality of life, Treatment

Health condition(s) or problem(s) studied
Overweight/obese adult subjects

Interventions
Obesity is a complex and multifactorial disease that currently affects more than one-third of the world's population, representing a key risk factor for numerous diseases, such as cardiovascular disease, type 2 diabetes mellitus, and cancer. Currently, there is a growing interest in supplementation with nutraceutical products for both the prevention and treatment of obesity. Scientific studies focusing on the biological functions of bitter taste receptors TSR2R expressed at the level of stomach wall and the first part of the duodenum have shown that activation of their subtype in the stomach wall leads to a release of the orexigenic hormone ghrelin, while activation of the TSR receptors in the first part of the duodenum causes a slowing of duodenal motility, which is associated with the simultaneous release of CCK, a substance that can initiate the satiety cycle. Available in vitro evidence on endogenous mediators capable of controlling the metabolic cycle of the two receptor subtypes highlight the role of melatonin as a ligand of duodenal TSR receptors. Therefore, a screening performed in order to identify natural molecules sharing structural similarities with melatonin allowed us to identify the alkaloids present in the bark of Cinchona (quinine, quinidine, cinchonine, and cinchonidine) as ideal candidates to act as receptor agonists of duodenal TSR.

Subjects will be treated with a low-calorie diet in combination with the intake of Cinchona in the form of gastro-resistant capsules administered twice daily one hour before main meals, or with the low-calorie diet and capsules with placebo only. The two interventions are described below.
1. Low-calorie diet: low-calorie, low-fat diet, according to LARN guidelines. The caloric restriction is 40% of total energy requirements and the macronutrient composition is approximately as follows: carbohydrates 55-60%, fats 20-25%, and proteins 15-20% of the daily calorie intake. In addition, participants are asked to maintain their usual level of physical activity.
2. Cinchona supplementation: participants in the intervention group are prescribed a low-calorie diet and asked to take 800 mg of Cinchona daily (400 mg before lunch and dinner). The substance used in the study is an extract from the bark of Cinchona Succirubra from the Rubiaceae family, which has a total alkaloid content of 2% of the dry weight. Treatment compliance was assessed by counting the number of tablets returned at the time of specified clinic visits. Each patient is given a sheet to record when they took Cinchona and any adverse events. Participants who do not take the capsule for two or more days will be classified as " non-compliant" and thus excluded from the study. All treatments were provided free of charge. All treatments were provided free of charge.
3. Placebo: 400 mg of maltodextrins twice daily.

The main objective of the study is to evaluate patients' adherence to the low-calorie diet and to determine whether the administration of a Cinchona-based dietary supplement can influence the feeling of satiety and food intake through the release of gastro-hormones cholecystokinin and ghrelin after two months of treatment. To this aim, each subject will complete a self-assessment questionnaire based on a 5-point Likert scale to assess compliance with Cinchona intake, adherence to diet, satiety, and the recording of any negative effects after 4 and 8 weeks.

Intervention Type
Supplement

Primary outcome(s)
1. Adherence to the low-calorie diet measured using a self-assessment questionnaire based on a 5-point Likert scale to assess compliance with Cinchona intake, and adherence to diet after 4 and 8 weeks
2. Feeling of satiety measured using a self-assessment questionnaire based on a 5-point Likert scale to assess compliance with Cinchona intake, and adherence to diet after 4 and 8 weeks
3. Negative effects measured using a self-assessment questionnaire based on a 5-point Likert scale to assess compliance with Cinchona intake, and adherence to diet after 4 and 8 weeks
4. Serum concentrations of gastrointestinal hormones cholecystokinin and ghrelin measured using Dot-Blot methods after two months of treatment

Key secondary outcome(s))
The secondary outcome measures following are assessed at 0, 4 and 8 weeks:
1. Anthropometric variables measured using height, weight, and waist circumference assessments
2. Body composition measured using bioimpedance analysis (BIA) with a 50 kHz tetrapolar bioelectrical impedance analyser (BIA 101 RJL, Akern Bioresearch, Florence, Italy). Total body water, fat mass and fat-free mass are extrapolated from the resistance and reactance values obtained with the BIA using the specific predictive equations
3. Plasma total cholesterol measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron International
4. High-density lipoprotein-cholesterol (HDL) measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron

International
5. Low-density lipoprotein-cholesterol (LDL) measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron International
6. Triglyceride levels measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron International
7. Aspartate transaminase (AST) measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron International
8. Creatine levels measured using a Diacron International Free Carpe Diem spectrophotometer (Grosseto, Italy), and commercially available kits from Diacron International
9. Serum cholecystokinin and ghrelin levels measured using commercial active ELISA kits (Hangzhou East Biopharm Co, LTD, USA)

Completion date
02/10/2023

Eligibility

Key inclusion criteria
1. Patients aged 18–70 years
2. Overweight/Obese subjects (Body Mass Index 25-45 kg/m²)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Total final enrolment
60

Key exclusion criteria
1. Participation in other clinical studies
2. Weight change greater than 3 kg in the last 2 months
3. Cancer or diagnosis of cancer in the last 5 years
4. Acute or chronic inflammatory and metabolic diseases (e.g. Crohn's disease, rheumatoid arthritis, etc.)
5. Patients with type 1 or 2 diabetes, treated with insulin and oral hypoglycaemic drugs

6. Patients with type 2 diabetes, treated with diet alone, can be included in the study
7. Patients taking weight loss medications (e.g. sibutramine, orlistat, rimonabant) and/or history of bariatric surgery
8. Use of hormonal therapies (estrogen, thyroxine, progesterone)

Date of first enrolment
25/06/2023

Date of final enrolment
10/07/2023

Locations

Countries of recruitment
Italy

Study participating centre
Department of Clinical Medicine and Surgery of the University of Naples "Federico II"
Clinics of the Interdepartmental Program of "Diet Therapy in Transplantation, Renal Insufficiency and Chronic Pathologies
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Sponsor information

Organisation
University of Naples Federico II

ROR
https://ror.org/05290cv24

Funder(s)

Funder type
University/education

Funder Name
Università degli Studi di Napoli Federico II

Alternative Name(s)

University of Naples Federico II, University of Naples, Federico II University of Naples, Università di Napoli, Università di Napoli Federico II, UNINA

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Italy

Funder Name
NGN Healthcare New Generation Nutraceuticals srl

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Bruna Guida, bguida@unina.it (Italy). Data shared will include demographic information, weight, height, BMI, lean body mass, fat mass, and biochemical analyzes (glucose, cholesterol, transaminases, uric acid, creatinine, ghrelin and cholecystokinin levels). These data will be shared at 12 weeks. Informed consent was required and obtained. Codes will be used to guarantee the anonymity of the participants.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/12/2023	13/12/2023	Yes	No
Results article		23/02/2024	01/08/2025	Yes	No
Participant information sheet	version 1.0	04/12/2022	25/07/2023	No	Yes
Participant information sheet	Information and expression of consent to the processing of personal data version 1.0		25/07/2023	No	Yes
Protocol file	Synopsis		25/07/2023	No	No