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Study of the efficacy of a food supplement based on extracts of lemon and orange, hesperidin and chromium for the maintenance of normal carbohydrate metabolism

Submission date
15/05/2025

Recruitment status
No longer recruiting

Registration date
17/06/2025

Overall study status
Completed

Last Edited
30/10/2025

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
The EPH35 study was created to find out if a dietary supplement made from lemon and orange extracts, hesperidin, and chromium could help people with slightly high blood sugar levels keep their glucose in a healthy range. The main goal was to see if the supplement could lower fasting blood sugar in people whose levels were a bit above normal (between 100 and 125 mg/dL).

Who can participate?
The study included 62 adults between the ages of 18 and 75 who were not diabetic but had slightly high fasting blood sugar. People with certain health conditions or who were taking diabetes medications were not allowed to take part.

What does the study involve?
Participants were randomly placed into one of two groups. One group took three tablets a day of the dietary supplement after meals, while the other group took a placebo (a tablet that looked the same but had no active ingredients). The study lasted six months. Blood sugar levels were checked at the start, after 90 days, and after 180 days. Other health markers like insulin, cholesterol, body weight, blood pressure, and signs of inflammation were also measured. Liver and kidney function were monitored to make sure the supplement was safe.

What are the possible benefits and risks of participating?
Participants might benefit from improved blood sugar control and better understanding of their health. The risks were low, but as with any supplement, there was a chance of side effects. All participants were monitored closely, and any issues were addressed by the study team.

Where is the study run from?
The study was carried out at the outpatient clinic of Dr. Agostino Greco in Caserta, Italy.

When is the study starting and how long is it expected to run for?
September 2022 to May 2024

Who is funding the study?
The study was funded by ESSERRE Pharma Srl, a company based in Rome (Italy). They provided the supplement and placebo free of charge.

Who is the main contact?
Dr Agostino Greco, alessandra.baldi.alimenti@gmail.com

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Public, Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
EPH35_01

Study information

Scientific Title
Study of the efficacy of a food supplement based on extracts of Lemon (Citrus limon (L.) Osbeck) and Orange (Citrus sinensis (L.) Osbeck), Hesperidin and Chromium, for the maintenance of normal carbohydrate metabolism through the reduction of mildly altered plasma glucose levels: a single-center, controlled, randomized, parallel-arm, double-blind clinical study

Acronym
EPH35

Study objectives
It was hypothesized that taking a food supplement based on Lemon (Citrus limon) and Orange (Citrus sinensis) extracts, Hesperidin and Chromium could contribute positively to the maintenance of normal carbohydrate metabolism. In particular, this combination was expected to be able to reduce slightly altered plasma glucose levels and bring benefits to the subject who took it.
The primary outcome of this clinical study was to evaluate the efficacy of the food supplement in the maintenance of normal carbohydrate metabolism by reducing plasma glucose levels in patients with impaired fasting plasma glucose (fasting plasma glucose between 100 - 125 mg /dL); the secondary outcomes were the 1) beneficial effect on carbohydrate metabolism, 2) beneficial effect on lipid metabolism, 3) body weight in terms of reduction of BMI (Body Mass Index) value, blood pressure values (diastolic and systolic pressure) and waist circumference , 4) levels of inflammation and 5) liver and kidney toxicity, improving the quality of life of the subjects with impaired fasting plasma glucose.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 15/03/2023, Comitato Etico Campania Nord - San Giuseppe Moscati (Contrada Amoretta - Città Ospedaliera, Avellino, 83100, Italy; +39 825/203025; comitatoeticoav@gmail.com), ref: CECN/2059

Study design
Single-center randomized controlled parallel-arm double-blind clinical trial

Primary study design
Interventional

Study type(s)
Efficacy, Prevention

Health condition(s) or problem(s) studied
Carbohydrate metabolism

Interventions
The study recruited 62 subjects (31 subjects per group), that were randomized into the following experimental groups:

GROUP 1: subjects who had to take two tablets of the food supplement based on extracts from Lemon (Citrus limon (L.) Osbeck) and Orange (Citrus sinensis (L.) Osbeck), Hesperidin and Chromium.
GROUP 2: subjects who had to take the placebo.

Each subject of the two experimental studies, after the administration of the food supplement or the placebo, underwent blood sampling as reported in the study layout.

The total duration of treatment was 180 days, with no follow-up period. The randomization sequence was generated by a statistician using STATA 16 software (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC), and subjects were assigned to each of the two treatment groups (dietary supplement and placebo) in a random and unpredictable manner using simple randomization (1:1 allocation ratio). This procedure minimizes the “selection bias”, i.e. systematic differences between the baseline characteristics of the groups being compared (prognostic and treatment response imbalance). The hiding of the randomization list protects the allocation sequence until assignment, and is stored in an inviolable place in the experimental center. Both the generation of the allocation sequence and the randomization list was separated through the use of sealed envelopes. These envelopes were prepared by a person not involved in the trial from a clinical point of view, must be opaque, sealed, stapled and numbered in order conforming to that of the randomization list, and subsequently stored in a sealed cabinet. The experimenter who enrolled the subjects, and who gave them one of the two treatments in comparison by opening the next envelope each time, remained unaware of the randomization list.

Intervention Type
Supplement

Primary outcome(s)
Measurement of fasting blood glucose in peripheral blood samples at baseline (t0), 90 days (t1), and 180 days (t2)

Key secondary outcome(s))
1. Glycated hemoglobin (HbA1c) levels are measured using high-performance liquid chromatography (HPLC) at baseline (t0), 90 days (t1), and 180 days (t2)
2. Fasting insulin levels are measured using immunoassay at baseline (t0), 90 days (t1), and 180 days (t2)
3. Insulin resistance is measured using the HOMA-IR index calculated from fasting glucose and insulin levels at baseline (t0), 90 days (t1), and 180 days (t2)
4. Total cholesterol is measured using enzymatic colorimetric assay at baseline (t0), 90 days (t1), and 180 days (t2)
5. LDL cholesterol is measured using direct enzymatic assay at baseline (t0), 90 days (t1), and 180 days (t2)
6. HDL cholesterol is measured using direct enzymatic assay at baseline (t0), 90 days (t1), and 180 days (t2)
7. Triglycerides are measured using enzymatic colorimetric assay at baseline (t0), 90 days (t1), and 180 days (t2)
8. Body mass index (BMI) is measured using weight and height data at baseline (t0), 90 days (t1), and 180 days (t2)
9. Systolic and diastolic blood pressure are measured using automated sphygmomanometer at baseline (t0), 90 days (t1), and 180 days (t2)
10. Waist circumference is measured using a standard measuring tape at baseline (t0), 90 days (t1), and 180 days (t2)
11. White blood cell count is measured using automated hematology analyzer at baseline (t0), 90 days (t1), and 180 days (t2)
12. Erythrocyte sedimentation rate (ESR) is measured using the Westergren method at baseline (t0), 90 days (t1), and 180 days (t2)
13. C-reactive protein is measured using high-sensitivity immunoassay at baseline (t0), 90 days (t1), and 180 days (t2)
14. Alanine aminotransferase (ALT/SGPT) is measured using enzymatic assay at baseline (t0), 90 days (t1), and 180 days (t2)
15. Aspartate aminotransferase (AST/SGOT) is measured using enzymatic assay at baseline (t0), 90 days (t1), and 180 days (t2)
16. Serum creatinine is measured using the Jaffe method or enzymatic assay at baseline (t0), 90 days (t1), and 180 days (t2)

Completion date
16/05/2024

Eligibility

Key inclusion criteria
1. Non-diabetic subjects, as determined by clinical history and information provided during recruitment, aged between 18 and 75 years.
2. Subjects with impaired fasting glucose (IFG) between 100 and 125 mg/dL.
3. Subjects able to understand and willing to sign the informed consent.

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
62

Key exclusion criteria
1. Aged < 18 and > 75 years
2. Subjects exposed to a high risk of cardiovascular events based on 8 risk factors (gender, age, diabetes, smoking habits, systolic blood pressure, total cholesterol, HDL-cholesterolemia and antihypertensive treatment) in accordance with the parameters of the Cuore project of the Istituto Superiore di Sanità (http://www.cuore.iss.it/sopra/calc-rischio.asp)
3. BMI > 30, indicated as the threshold value for the definition of an obese subject (https://www.salute.gov.it/portale/nutrizione/dettaglioIMCNutrizione.jsp?lingua=italiano&id=5479&area=nutrizione&menu=vuoto)
4. In drug therapy for diabetes even at low doses
5. Intake of blood glucose supplements in the two weeks prior to recruitment
6. Women who were pregnant, suspect they were pregnant or planned to become pregnant
7. Breastfeeding women
8. Blood donors in the three months prior to recruitment
9. Not self-sufficient
10. Who showed no inclination to collaborate
11. Who had difficulty reaching the reference facility within the expected times
12. Who were not considered suitable by the investigating physician due to the presence of other pathologies deemed incompatible with enrollment
13. With a history of allergy to the ingredients contained in the treatments under study (food supplement and placebo)
14. History of addiction or abuse of medications, drugs or alcohol
15. Smokers (electronic devices with nicotine or cigarettes)

Date of first enrolment
01/04/2023

Date of final enrolment
01/06/2023

Locations

Countries of recruitment
Italy

Study participating centre
Medical office
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Sponsor information

Organisation
ESSERRE Pharma S.r.l.

Funder(s)

Funder type
Industry

Funder Name
ESSERRE Pharma S.r.l.

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		14/10/2025	30/10/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes