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Effects of a (poly)phenol-rich supplement on anthropometric, biochemical, and inflammatory parameters in participants with morbid obesity: Study protocol for a randomised controlled trial

Mercedes Gil-Lespinard [a], Carlos Bambarén Capurro [a], Mónica Montserrat [b], Núria Virgili-Casas [b], Raul Zamora-Ros [a,c,*]

[a] Unit of Nutrition and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain
[b] Endocrinology and Nutrition Service, Bellvitge University Hospital-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[c] Department of Nutrition, Food Sciences, and Gastronomy, Institute for Research on Nutrition and Food Safety (INSA), Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain

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ABSTRACT

Background: Morbid obesity (body mass index ≥40 kg/m^2) represents a severe health risk and implies the need of urgent therapeutic action. (Poly)phenols may play a relevant role in the management of this disease modulating physiological and molecular pathways involved in energy metabolism and adiposity. The purpose of this double-blinded, placebo-controlled, randomised trial is to determine if (poly)phenol supplementation, in combination with a dietary intervention, can improve anthropometric and cardiometabolic parameters in participants with morbid obesity.

Methods: Adults (n = 40) with morbid obesity, bariatric surgery candidates, will be recruited from the Bellvitge University Hospital, Spain, and randomly assigned (stratified by sex) to intervention (poly)phenol-rich supplement 1,200 mg/day + hypocaloric diet) or control group (placebo + hypocaloric diet) for 12 weeks. The primary outcome is body weight. Secondary outcomes are: other anthropometric markers and body composition measured through standardized methods and a bioimpedance analysis, cardiometabolic and inflammatory biomarkers, metabolic pathways, and gut microbiota diversity. Anthropometric parameters, dietary, physical activity and lifestyle questionnaires, blood pressure, and blood and urine samples will be collected at baseline, 6 weeks, and 12 weeks. Faecal samples will be collected at baseline and at 12 weeks. Informed consent of participants will be obtained before the start of the study.

Discussion:: The present study is expected to provide evidence on the effects of a combination of (poly)phenols on several well-established obesity and cardiometabolic markers, and to unravel possible underlying mechanisms by metabolomic analyses. Gut microbiota diversity will be considered as a potential future endpoint. The study will contribute to future strategies for prevention or treatment of obesity and related conditions.

1. Introduction

Obesity is a multifactorial disease defined as excess body fat accumulation, with a body mass index (BMI) higher or equal to 30 kg/m^2 [1]. It is considered to be one of the main risk factors for different chronic diseases such as type 2 diabetes, cardiovascular diseases and several types of cancer [2,3]. Worldwide, obesity has nearly tripled since 1975 [4]. The World Health Organisation reported in 2016 that 13% of world's adult population (aged 18 years and over) presented obesity [4]. In 2020, the European Health Survey estimated that about 16% of Spanish population presented obesity [5]. This condition is mainly a consequence of the high availability and consumption of low-nutritional quality and highly caloric foods, and the shift towards sedentary lifestyles [1]. Different health protection and promotion programmes have aimed to address this health problem. Unfortunately, the prevalence of obesity is reaching unprecedented levels, turning into one of the major

* Corresponding author. Department of Nutrition, Food Sciences and Gastronomy, Faculty of Pharmacy and Food Sciences, University of Barcelona, Avinguda Joan XXIII, 27-31, 08028, Barcelona, Spain.
E-mail addresses: rzamora@idibell.cat, rzamora@ub.edu (R. Zamora-Ros).

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global public health problems [1]. Morbid obesity is defined as having a BMI ≥40 kg/m^2 due to excess of body fat [6]. It is associated with several morbidities which are life-threatening, and indicates an urgent need of therapeutic action [6]. Body fat excess stimulates adipose tissue to release inflammatory mediators such as tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and reduces the synthesis of adiponectin increasing oxidative stress and leading to a pro-inflammatory state [7]. Systemic inflammation leads to higher risk of tissue damage and dysfunction, consequently increasing metabolic disorders and chronic diseases [7].

Traditionally, strategies to prevent or treat obesity have been focused on the intake of total energy, macro and micronutrients, or pharmacological and surgical interventions that tend to be expensive and invasive. Anti-obesity medications often deliver insufficient efficacy and dubious safety, and they mostly act as a complement to behaviour modifications [8]. A randomised clinical trials (RCTs) studying the effects of short-term anti-obesity medications alone (i.e., appetite suppressants) showed 5% weight reduction after 12 weeks versus placebo [9]. A recent meta-analysis of RCTs with serotonin receptor agonists (i.e., *locarserin*) provided for ≥1 year showed a modest improvement on body weight, but with loss of maintenance of weight reduction after a certain time-point. In addition, these types of anti-obesity medications can often be linked to neuropathies as they interfere with serotonin pathways [10]. As per surgical interventions, different interventional studies in participants with morbid obesity concluded that clinical significant weight loss and improvements in risk factors achieved with surgery can also be achieved with lifestyle interventions [11,12]. Although non-surgical interventions may result in weight regain, clinical significant weight loss is possible when the conservative treatment is well planned and can be sustained in the long-term [13]. Recently, the use of functional foods and their bioactive compounds is considered a new approach in the management of obesity [14]. Several investigations have suggested that dietary components such as (poly)phenols may play a relevant role [14,15]. (Poly)phenols are bioactive phytochemicals that are widely present in plant-based foods [16]. Approximately 500 different individual (poly)phenols have been identified and, according to their chemical structure, they can be classified as flavonoids, phenolic acids, stilbenes, lignans, and others [16]. In Europe, daily intake of these compounds has been estimated to be around 1 g, with phenolic acids and flavonoids representing the most abundant classes [17]. (Poly)phenols are partially absorbed in the small bowel, metabolized by phase I and II enzymes and excreted in the bile or urine [18]. Those that remain in the lumen are metabolized by the gut microbiota when they reach the colon, and their secondary metabolites (simple phenolic compounds) can be absorbed at this level [18]. Many studies on cellular and animal models have shown the anti-obesity effects of different (poly)phenols, such as lowering total energy intake, reducing fat and glucose uptake into adipose tissue, and increasing caloric expenditure and glucose uptake into skeletal muscle [19]. Studies in humans indicated that (poly)phenols could reduce or maintain body weight [12–14]. Results from the Netherlands Cohort Study [20] suggested that flavonoid intake may contribute to body weight maintenance, particularly in female participants. Similarly, three cohort studies including US health professionals showed that higher intakes of flavonoid-rich foods contributed to body weight maintenance [21]. Results from the EPIC cohort (unpublished results) showed that several classes, subclasses and individual (poly) phenols, particularly flavonoids, were associated with prevention of body weight gain over 5 years. A systematic review of interventional studies observed a reduction in body weight of 1.5 kg over 12 weeks for several RCTs, adding (poly)phenol supplementation in participants with overweight or obesity compared to placebo [22]. A recent systematic review of RCTs evaluated the effect of (poly)phenol supplementation in combination with hypocaloric diets or physical activity interventions on body weight and obesity parameters [23]. It concluded that isoflavone supplementation together with weight-loss therapies, especially physical activity, may promote weight reduction, particularly in post-menopausal women. Associations between other phenolic compounds and anthropometric parameters were not observed, but the majority of studies found protective changes in different parameters associated with obesity, such as insulin sensitivity and inflammatory biomarkers [23]. In light of this evidence, the hypothesis of the current RCT is that the addition of a (poly)phenol-rich supplement to a traditional body weight-loss treatment (hypocaloric diet) will favour weight loss and improve health parameters associated with obesity (e.g., lipid profile, inflammatory biomarkers, blood pressure, insulin resistance).

2. Methodology

2.1. Ethics and consent

The present study has been approved by the Bellvitge University Hospital Ethics Committee. All protocol modifications will be reviewed and approved by the ethics board. Written and voluntary consent will be obtained from each participant prior to the beginning of the study. The trial has been registered at www.ClinicalTrials.gov (NCT05428540).

2.2. Design, participants, and setting

This study is a double-blinded, randomised, placebo-controlled trial that will be conducted at the Bellvitge University Hospital in the Barcelona area, Spain. Forty adult participants (≥18 y) with morbid obesity (BMI ≥40 kg/m^2) referred to the Unit of Endocrinology and Nutrition of the hospital for a weight-loss treatment (in most of the cases prior to bariatric surgery), will be randomly assigned to an intervention or control group (n = 20 per arm). They will receive either a (poly)phenol-rich supplement (1,200 mg/day) or placebo, respectively, for 12 weeks, in combination with a hypocaloric diet. An overview of the study is presented in Fig. 1. To detail the study protocol, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [24] checklist was used (Table 1). Any protocol amendments will be discussed by the ethics committee before their application.

Before recruitment, a meeting with the medical staff from the Unit of Endocrinology and Nutrition will take place to widely discuss the aim, methodologies and technical aspects related to the development of this trial. After this meeting, the medical staff will start the assessment of potential participants and a detailed information sheet will be given to those plausible candidates meeting the inclusion criteria (see below). Candidates that demonstrate interest in the study will be given an informed consent reporting all the information on the intervention, and the protocol that they will be asked to undertake. Volunteers will be selected according to the inclusion and exclusion criteria (Table 2). Each participant enrolled will be assigned to an ID number and the encoding will be hidden to both the researchers involved in data collection and analysis, and the participants. All clinical and personal data of the participants will be collected and stored anonymously. The participants will be stratified by sex and randomly assigned to either supplement group (n = 20) or placebo group (n = 20).

2.3. Intervention

The trial duration will be 12 weeks. Each participant will attend three visits: baseline or visit 1 (V1, start of intervention), visit 2 after 6 weeks (V2), and visit 3 after 12 weeks (V3, end of intervention). Information regarding diet, physical activity, lifestyle factors, anthropometric measurements, blood pressure, and blood and urine samples will be collected in the three visits. In visits 1 and 3, faecal samples will be also collected. Recruitment and visits will take place in an outpatient clinic at the Bellvitge University Hospital. Trained staff will carry out questionnaires and anthropometric measurements, and fasting blood samples collection. Participants will bring 24 h urine and faecal samples collected the day before each visit (faecal samples only V1 and V3). Blood samples will be analysed in the clinical laboratory from the

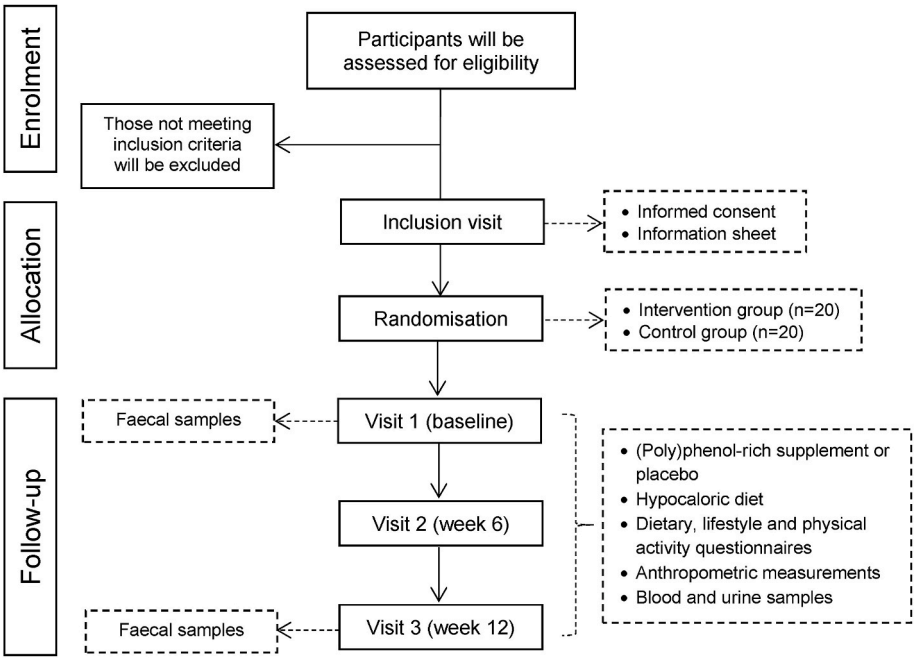

Fig. 1. Flow chart of the study design.

Table 1
Standard protocol items: recommendations for interventional studies (SPIRIT).

	Enrolment	Visit 1 (baseline)	Visit 2 (week 6)	Visit 3 (week 12)
Eligibility screening	X			
Informed consent	X			
Information sheet	X			
Capsules provision		X		
Hypocaloric diet explanation		X		
Dietary, physical activity, and lifestyle assessment				
Lifestyle and backgrounds		X		
Physical Activity		X	X	X
24-h Dietary Recall		X	X	X
3-day Dietary Record		X	X	X
Physical assessment				
Anthropometrics		X	X	X
Bioimpedance		X	X	X
Blood pressure		X	X	X
Biochemical assessment				
Blood lipids and sugar		X	X	X
Renal, hepatic, and thyroid function markers		X	X	X
Inflammatory biomarkers		X	X	X
Metabolomics		X	X	X
Microbiota composition		X		X

Table 2
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age ≥18 years.	Record of type I diabetes mellitus.
Body mass index ≥40 kg/m2.	Endocrinopathy-related obesity.
Derived to the Unit of Endocrinology and Nutrition (Bellvitge University Hospital) for a weight-loss treatment, in many cases prior to bariatric surgery.	Severe infectious process that may affect the inflammatory state during the 4 weeks prior to inclusion.
	Acute metabolic complications.
	Cardiovascular event in the 6 months prior to the study.
	History of liver disease.
	Pregnant, breastfeeding or wishing to be pregnant in the 12 weeks following inclusion.
	Recent history of neoplasia (<5 years) except skin cancer or melanoma.
	Use of oral or intravenous glucocorticoids for more than 14 consecutive days in the 3 months prior to the study.
	Alcoholism, drug addiction, or major psychiatric disorder.

hospital. Urine and faecal samples will be stored in the ultra-freezers of the Unit of Nutrition and Cancer at IDIBELL. Urine samples will be analysed by the Nutritional Biomarkers and Metabolomics group from the University of Barcelona, Spain. Faecal samples will remain stored for future microbiota analyses. All data collected will be recorded on the Research Electronic Data Capture (REDCap) software platform [25].

The (poly)phenol-rich supplement selected for the present study is based on a combination of individual compounds commonly used in previous trials, such as green tea extract, or blueberry extract, that proved to be effective for improvement of obesity parameters [26–29]. In addition, the inclusion of compounds from typical (poly)phenol-rich foods characteristic of the Mediterranean dietary pattern, such as olive oil, fruit and vegetables (particularly citrus fruit and onions), red wine and grapes, and whole grain cereals [30] was also considered. An identification of the specific compounds was carried out, and the precise amounts were calculated to formulate the supplement taking into consideration safety and effective dosages. In addition, the ~1,000 mg a day mean intake of dietary (poly)phenols from the European population was considered to calculate the (poly)phenol supplementation [31]. Here, we aimed to double this amount by including 1,200 mg of extracts with ~850 mg of (poly)phenols. The Centre of Functional Food Research and Development (CIDAF by its Spanish initials, Granada, Spain) performed the quality assessment of the raw material, evaluated the stability and purity of compounds, and developed both the supplement and the placebo capsules.

2.3.1. *Composition*

The supplement comprises seven different extracts: 400 mg of green tea extract (10% catechins and 75% epigallocatechin-gallate (EGCG)); 200 mg of blueberry extract (50% anthocyanidins), 100 mg of olive leaf

extract (20% hydroxytyrosol and derivates); 100 mg of rice bran extract (98% ferulic acid); 200 mg of *citrus aurantium* extract (50% hesperidin); 100 mg of *polygonum cuspidatum* extract (100% resveratrol); and 100 mg of *sophora japonica* extract (70% quercetin dihydrate).

Participants in the intervention group will take a 400 mg capsule three times per day with meals (breakfast, lunch and dinner), a total of 1,200 mg of a combination of extracts (~830 mg (poly)phenols) a day. The placebo capsules consist of microcrystalline cellulose 101 (Avicel PH-101) and will be taken by the control group under the same conditions as the intervention group. Both the supplement and the placebo are optically identical opaque bicoloured gelatine capsules to ensure the double-blind design.

2.3.2. Bioavailability and safety of compounds

The bioavailability of (poly)phenols in humans can be affected by a series of factors, including food availability, food processing related factors, food matrix, interaction with other compounds, host-related factors and (poly)phenol-related factors [32]. As to this last point, mechanistic studies reported that different (poly)phenols may present synergistic interactions when consumed together, enhancing their bioavailability and activity [33,34]. Absorption, digestion, metabolism and excretion among (poly)phenols might differ due to their structural diversity. The 7 compounds included in this supplement present heterogenic characteristics. Some of them with low molecular weight (e.g., ferulic acid) are easily absorbed through the gut barrier. In contrast, large molecular weight (poly)phenols (e.g., anthocyanidins) have a much lower direct absorption, but they can be partly absorbed in the colon as small phenolic acids after microbiota metabolization [35]. Bioavailability varies among the different subclasses, ranking from resveratrol (~75–90%) > tyrosols (~75%) > phenolic acids (~25–40%) > flavonols (~20–40%) > catechins (~15–40%) > flavanones (~8%) > anthocyanidins (~2%) [34,36–38].

To formulate this supplement, we reviewed studies in humans regarding safety and safe doses of the extracts and compounds chosen, as well as official reports from the European Food Safety Authority (EFSA) for specific compounds. All of the compounds selected for this supplement are included in the European Botanical Databases: the BELFRIT list from Belgium, France and Italy [39]; the German Stoffliste [40]; and the EFSA Compendium [41]. There are EFSA Scientific Opinion reports that support the safety of green tea catechins, (poly)phenols from olives (hydroxytyrosol and derivates) and resveratrol for human consumption [42–44]. As per other compounds, i.e., anthocyanins from blueberries and citrus fruit flavonoids (including hesperidin), different interventional studies in humans have reported safe doses or no adverse effects [45] [–] [47]. Ferulic acid has shown low levels of toxicity in animal models [48] and recent literature has linked this compound to low toxicity in humans [49]. As per quercetin, the Food and Drugs Administration determined that its use in different dietary products can be classified as Generally Recognized As Safe [50].

2.3.3. Hypocaloric diet

Participants will take the capsules together with a hypocaloric diet, developed by dietitians/nutritionists from both the Bellvitge University Hospital and the Bellvitge Biomedical Research Institute (IDIBELL). It consists of a 1,200 kcal/d hypocaloric diet and includes a large variety of foods to ensure that all nutritional requirements are covered. Previous evidence supports that low-calorie diets start with a 4 to 12-week weight reduction phase and should be planned in order to set energy deficit using diet upon principles of balanced nutrition, proportion of nutrients and meal replacements to make it easier to return to habitual diets [51]. Here, participants will be given a printed guide with general dietary recommendations, food choices and portions to follow. Table 3 summarises the hypocaloric dietary guide.

Table 3
Hypocaloric dietary guide: food groups and portions and general recommendations.

Food group	Portions/ day	1 portion equivalent to (example)
Carbohydrates	2	· 2 slices of wholemeal bread · 4 tablespoons of brown rice/quinoa/ pasta (cooked)
Proteins	2	· 4 tablespoons of pulses (cooked) · 100 g tofu/chicken/fish · 1 egg
Fruits	2	· 1 piece standard size (apple, pear, banana) · 2 pieces medium/small size (plum, kiwi) · 1 glass of berries · 1–2 slices of watermelon
Vegetables	3	· ½ plate cooked vegetables · 1 bowl raw vegetables · 1 big size (aubergine, courgette) · 2 small size (onion, tomato, carrot)
Dairy/plant-based alternatives	2	· 1 cup of milk/plant beverage (no added sugar) · 1 small pot of yoghurt (no added sugar) · 1 small pot of white cheese · 2 slices of cheese
Nuts and seeds	1	· 1 handful of nuts (no fried, no added salt/sugar) · 3 whole walnuts · 1 tablespoon of seeds
Olive oil	2	· 1 tablespoon of extra virgin olive oil

General recommendations.
· More: whole (less processed) food, and combination of natural colours and textures; home-made foods; safe water as main drink choice.
· Less: ultra-processed foods, added sugar and saturated fat, red and processed meat, alcohol and sweetened beverages.

2.4. Data collection

2.4.1. General information

During the baseline visit, participants' personal and lifestyle data, and personal and family medical record will be collected through an initial questionnaire.

2.4.2. Anthropometric measurements

The primary outcome of this study is to assess the effect of the supplement on body weight. Secondary outcomes include other anthropometric parameters and body composition. In the three visits, body weight and body composition will be measured by trained staff using a highly accurate Multi Frequency Segmental Body Composition Analyser. Moreover, an ergonomic measuring tape will be used to collect data on waist and hip circumferences, and an integrated measuring rod will be used to measure height.

2.4.3. Dietary intake assessment

Data on food intake will be assessed using a 3-day dietary record that participants must have completed prior to each visit. In addition, a 24-h dietary recall will be carried out during each visit by a trained dietitian. To estimate nutritional intake, the Nutritional Calculation Programme (PCN) Pro 1.0 from the University of Barcelona [52] will be used. (Poly) phenol intake will be assessed using the Phenol-Explorer database [53], following the methodology used in the EPIC study [54].

2.4.4. Physical activity

During the three visits, a trained dietitian will collect information on participants' physical activity level through a shortened Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire [55], including information on both leisure-time and occupational physical activity.

2.4.5. Blood pressure

During the three visits, both systolic and diastolic pressure will be measured to each participant by a trained dietitian, obtained in a resting, seated position using an OMRON HBP-1300 semi-automatic blood pressure monitor.

2.4.6. Blood samples

Fasting blood samples will be collected in the three visits. Trained nurses will extract 20 ml from the antecubital vein of each participant following standardized procedures. Samples will be stored and analysed in the clinical laboratory of the Bellvitge University Hospital. They will be centrifuged for 15 min at 5000 g, stored in two aliquots, and frozen at −80 °C until analysis. Through these samples, we will measure metabolic and functional markers [i.e., blood count, lipid profile, thyroid (thyroxine, thyrotropin), liver (transaminases) and renal (creatinine) function, glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), glycosylated haemoglobin, uric acid, and vitamin D) and inflammatory biomarkers (i.e., TNF-α receptor I and II, IL-6, adiponectin, and ultra-sensitive CPR].

2.4.7. Urine samples

In the three visits, participants will bring a 24-h urine sample. Three aliquots (2 ml each) will be stored at −80 °C in the ultra-freezers of the Unit of Nutrition and Cancer, IDIBELL. One aliquot will be used to measure cortisol in the clinical laboratory of the Bellvitge University Hospital, only for visit 1. Another aliquot will be used to perform a metabolomic analysis by the Nutritional Biomarkers and Metabolomics group from the University of Barcelona. About 500 metabolites (e.g., (poly)phenols and derived microbiota metabolites, organic acids, energetic and protein metabolism compounds) will be quantified using ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS). This will allow us to monitor metabolite alterations derived from the (poly)phenol-rich supplement and associate these changes with improvements in clinical and biochemical outcome measurements.

2.4.8. Faeces samples

Participants will bring a faecal sample in the first and third visit. These samples will be analysed in future microbiota studies. They will be kept stored at −80 °C in the ultra-freezers of the Unit of Nutrition and Cancer at IDIBELL.

2.5. Sample size, randomisation and statistics

In the statistical power study, a minimum of 18 participants per arm will be needed to detect, with a study power of 0.85, a variation of 5–10% in anthropometric and laboratory measurements, in a population with 10% standard deviation, assuming an alpha error of 0.05. Assuming a possible drop-out rate of 15%, the required sample size is 40, with equal number of participants in each group (n = 20). Participants will be randomly divided by using a computer random number generator, with an allocation ratio of 1:1 for intervention and control group. They will be stratified based on sex (male and female). Randomisation and allocation will be performed by the principal investigator of the trial and blinded to the participants and researchers involved in both data collection and analysis. Compliance will be assessed primarily through number of capsules left in the third visit – with a 75% of the capsules taken and a remaining of ≤25%. Secondarily, it will be assessed through the analysis of urinary poly(phenol) concentrations. Statistical analyses will be performed with R Software [56].

2.5.1. Intention-to-treat and per-protocol population

The main analysis will be performed according to the intention-to-treat (ITT) principle. In the ITT analysis, all patients will be analysed according to their initially assigned study arm at baseline, regardless of the adherence to the study protocol. Participants who withdrew consent or participants with a protocol violation concerning eligibility will be excluded from the ITT analysis. Participants with missing baseline information or lost to follow-up (no outcome data available at any time point: visit 2 and 3) will be excluded from the ITT analysis. Differences in participant characteristics between those lost to follow-up and those included will be assessed. Participants without protocol violations and meeting the requirements of compliance will be included for a per-protocol (PP) analysis (Fig. 2).

2.5.2. Superiority trial

This trial is designed to evaluate if the addition of a (poly)phenol-rich supplement to a traditional weight-loss treatment (hypocaloric diet) is superior to the conventional treatment alone.

2.5.3. Missing data

Different methodologies will be assessed to deal with missing data. The definitive decision will be made depending on the type of missing data and the robustness of results. A priori, it is not expected that the number of missing exceeds 10%.

2.5.4. Baseline characteristics

Baseline information of included participants will be reported per randomisation group. The following characteristics will be presented: age, sex, lifestyle factors, anthropometric parameters, energy and food group intake, and biochemical and inflammatory biomarkers. Categorical variables will be expressed as number and percentage of participants for each category. Continuous variables will be presented as mean ± standard deviation in case of normal distribution, and as median and interquartile range in case of non-normal distribution. Normality will be

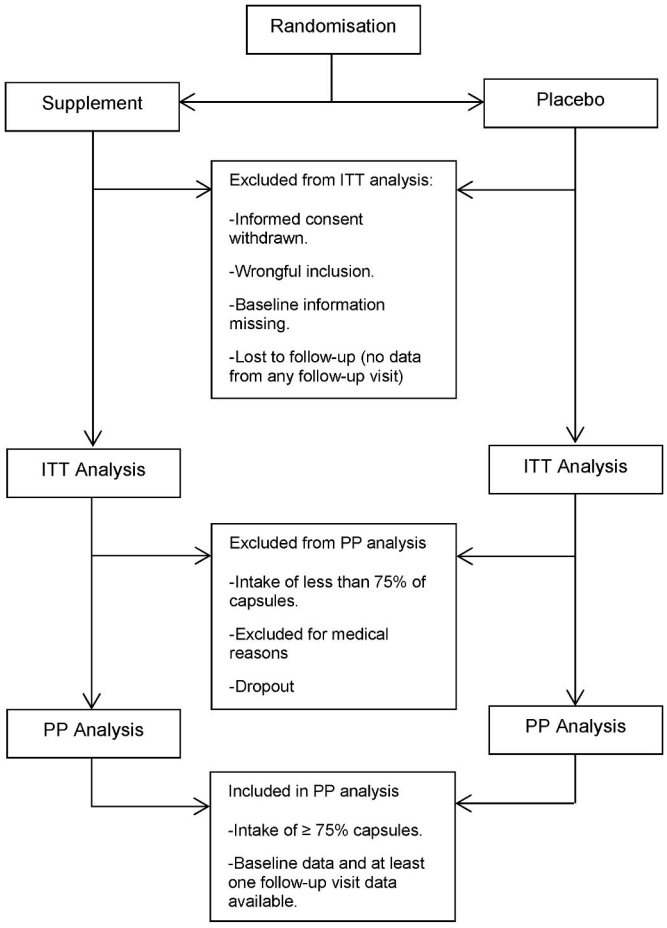

Fig. 2. Participant inclusion for intention-to-treat (ITT) and per-protocol (PP) analysis.

assessed by plotting distributions and by the Kolmogorov-Smirnov test. Differences between baseline characteristics of both groups will be assessed by the chi-square test or *t*-test for independent samples.

2.5.5. Outcome assessment

To analyse the differences in outcome variables between the two groups, the independent samples *t*-test will be used. Here, outcome variables will be expressed as differences between baseline and follow-up values (e.g., body weight change after 12 weeks). Besides, to assess pre- and post-intervention differences, the paired *t*-test will be used.

3. Discussion

This study will aim to evaluate the effects of a (poly)phenol-rich supplement, in combination with a hypocaloric diet, on anthropometric parameters, and cardiometabolic and inflammation biomarkers, in participants with morbid obesity. Previous evidence supports the association between the intake of different (poly)phenols, included in our supplement, and the improvement of several obesity parameters. For example, a combination of EGCG and resveratrol showed effectiveness downregulating pathways related to energy metabolism, oxidative stress, inflammation and immune system in participants with overweight and obesity [57]. Moreover, human intervention studies have shown individual anti-obesity effects of several (poly)phenol-rich foods including citrus fruits, green tea, berries, apples, and onions [14]. This is in line with what we propose to investigate in the current RCT. The main novelty of this intervention is precisely the combination of compounds that have shown to be effective alone (such as green tea catechins or blueberry anthocyanins) [17–20] and those that are included in a Mediterranean dietary pattern (such as citrus flavonoids, whole grain phenolic compounds, grapes and red wine resveratrol, and olive oil tyrosol) [30]. A recent review of RCTs on the effect of (poly)phenol-rich supplements combined with traditional weight-loss strategies (hypocaloric diet and/or physical activity interventions) on body weight loss and other obesity anthropometric parameters, concluded that (poly)phenol supplementation is not yet supported as a complementary approach for enhancing the effectiveness of traditional strategies [23]. Thus, through this study we aim to provide further evidence on this topic but studying participants with morbid obesity, a population with more need for treatment but for which evidence is still very little.

The sample size of this study has been calculated taking into account several assumptions, as mentioned above, to provide enough power to detect a mean difference in the primary outcome of 5–10% between the two groups. Sample size may be considered a limitation for some secondary outcomes and potential a posteriori subgroup analysis. Targeting bariatric surgery candidates with a BMI equal to or higher than 40 kg/m^2 may be a challenge when it comes to recruitment. Even so, this type of participant is often motivated and willing to participate, to have the opportunity to improve health, optimize quality of life, and lengthen lifespan [58,59]. Previous studies have reported that changes in body weight beginning at 2–5% can bring improvements in several associated risk factors [60,61]. Nonetheless, it should be bear in mind that weight loss *per se* should not be the only target, but general health improvement [61]. We will measure waist and hip circumference and therefore waist-to-hip ratio (WHR) as indicator of abdominal obesity and cardio-metabolic risk to provide a better assessment. In the EPIC study, a 5 cm larger waist circumference was associated with a 17% and 13% higher risk of death among men among women, respectively [62]. Likewise, a 0.1 unit higher WHR was associated with a 34% more risk of mortality among men and 24% among women [62]. Another characteristic that should be taken into consideration is that women are expected to outnumber men. In general, women tend to go through more frequent stigma experiences associated with body weight, often referred to negative beliefs/attitudes about the person, as well as perceived rejection, prejudice and discrimination (aroused from stereotypes and beliefs) [63]. In consequence, they are more likely to use weight loss programmes and strategies than men. Accordingly, despite not being a gender-based research, we will stratify randomisation by sex (female/-male) in order to create a balance between groups. As per risks associated with the intervention, ethical issues have been considered and according to the nature of the intervention, no side-effects are expected. Every potential participant will be provided with detailed information about it and informed consent will be obtained prior to inclusion. A major strength of this trial is its design: double-blinded, randomised, parallel, and placebo-controlled which enables to establish causation with an improved credibility and minimising biases. Through this trial, we may detect moderate/small effects that may be clinically relevant in participants with morbid obesity. The effects of (poly)phenols are usually stronger when measured in participants with higher needs; therefore, including participants with morbid obesity might allow us to see effects that may not be relevant after 12 weeks if measured in participants with small overweight or without excess of body fat, such as changes in cardiometabolic and inflammatory biomarkers. As length of the trial will be 12 weeks, the risk of loss to follow-up is very low. Moreover, as participants will be bariatric surgery candidates, we expect that the majority will accomplish adherence; the results of this trial will not affect participants' right to subsequently get the bariatric surgery according to medical opinion. This trial aims to be a pilot study that could open up new investigations. For example, it might be worth exploring their effectiveness in subjects with other degrees of overweight/obesity or in other outcomes, such as cardiovascular diseases or diabetes. Moreover, it could be interesting to test the efficacy of (poly)phenol-rich diets in future clinical nutrition research which could lead to enhancement of nutritional policies, as well as safer, more economic, and less aggressive approaches for morbid obesity treatment.

4. Conclusion

This study will evaluate the hypothesis that higher amounts of (poly)phenols could help reduce body fat, and therefore body weight, and lead to a cardiometabolic health improvement in participants with morbid obesity. Hence, this study will contribute to future strategies for prevention or treatment of obesity and related conditions.

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Authors' contributions

RZ-R and NV-C designed the study. RZ-R acquired the funding. MG-L, CBC and RZ-R wrote the study protocol. MM and NV-C will recruit the study participants. MG-L will conduct the trial and the statistical analyses. MG-L and CBC wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures will be conducted in accordance with the ethical standards for human subject research set forth in the Declaration of Helsinki. Written informed consent will be obtained from all participants included in this trial. This trial was approved by the Clinical Investigation Ethics Committee of the Bellvitge (PR082/22) and is registered in the ClinicalTrials.gov database (NCT05428540). Personal information about potential and enrolled participants will be

maintained in a database in order to protect subjects confidentially. Investigators will communicate trial results to participants, healthcare professionals and other relevant groups via publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

BMI	body mass index
CRP	c-reactive protein
EGCG	epigallocatechin-gallate
EPIC	European Prospective Investigation into Cancer and nutrition
HOMA-IR	homeostatic model assessment of insulin resistance
IDIBELL	Bellvitge Biomedical Research Institute
IL-6	interleukin-6
RCT	randomised controlled trial
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TNF-α	tumour necrosis factor-alpha
UHPLC-MS/MS	ultra-high-performance liquid chromatography coupled with triple quadrupole mass spectrometry

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