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Yerba Mate (*Ilex paraguariensis* St. Hill.) Tea May Have Cardiometabolic Beneficial Effects in Healthy and At-Risk Subjects: A Randomized, Controlled, Blind, Crossover Trial in Nonhabitual Consumers

Laura Bravo[1] | Sara Martínez-López[1,2] | Jose Luis Sierra-Cinos[2,3] | Raquel Mateos[1,4] | Beatriz Sarriá[1,2]

[1]Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN), Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain | [2]Department of Nutrition and Food Science, School of Pharmacy, Universidad Complutense de Madrid, Madrid, Spain | [3]Department of Health Science, School of Health Science, Universidad International Isabel I de Burgos (Ui1), Burgos, Spain | [4]CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

Correspondence: Laura Bravo (lbravo@ictan.csic.es)

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ABSTRACT

Yerba mate has been reported to have antihypertensive, hypocholesterolemic, antidiabetic, or antiobesity properties. Most evidences from human trials involved intakes of high amounts of mate by habitual consumers. Considering its increasing popularity, this study aimed at assessing the potential cardiometabolic effects of moderate intake of yerba mate by nonhabitual consumers. A randomized, crossover, controlled study was carried out in healthy and hypercholesterolemic subjects. Anthropometric parameters, blood pressure, blood lipids, glucose metabolism, inflammatory cytokines, chemokines, and different markers of endothelial function, as well as incretins, adipocytokines, and different hormones were measured at baseline and after 8 weeks consuming yerba mate or a decaffeinated isotonic drink (control). After daily consumption of three servings of mate tea, blood pressure, inflammatory cytokines, chemokines, and colony-stimulating factors decreased in all participants. LDL-C decreased in normocholesterolemic individuals, while the mate and control interventions elicited similar hypolipidemic action in the hypercholesterolemic group. Ghrelin and glucose-dependent insulinotropic polypeptide (GIP) significantly decreased after mate intake, while glucagon-like peptide 1 (GLP-1) and adipocytokines remained unchanged. Body fat percentage and tricipital skinfold decreased only in healthy subjects, with no effects on total body weight. In conclusion, yerba mate could exert cardiometabolic protective effects in healthy consumers and in subjects at moderate cardiovascular risk.

Trial Registration: This trial was retrospectively registered in ClinicalTrials (NCT06729905)

Abbreviations: ABTS, free radical scavenging capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease; DBP, diastolic blood pressure; d.m., dry matter; FRAP, ferric reducing–antioxidant power; G-CSF, granulocyte colony-stimulating factor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; HOMA-IR, Homeostasis Model Assessment of insulin resistance; hsCRP, high-sensitive C-reactive protein; ICAM-1, intercellular cell adhesion molecule-1; INF-γ, interferon gamma; MAFLD, metabolic-associated fatty liver disease; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MIP-1β, macrophage inflammatory protein-1β; NCDs, non-communicable diseases; ORAC, oxygen radical absorbance capacity; PAF, physical activity factor; PAI-1, plasminogen activator inhibitor-1; PP, (poly)phenol; QUICKI, quantitative insulin sensitivity check index; T2D, Type 2 diabetes; TE, Trolox equivalent; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

1 | Introduction

The prevalence of chronic non-communicable diseases (NCDs), including cardiometabolic pathologies like cardiovascular diseases (CVDs), Type 2 diabetes (T2D), as well as conditions like obesity, metabolic syndrome, or metabolic-associated fatty liver disease (MAFLD) among others, is increasing worldwide [1]. Changes in lifestyle and dietary habits to less healthy patterns are in the core of this negative trend, with increased sedentary behaviors and the shift from well-balanced diets like the Mediterranean or the Nordic diets to less healthy dietary practices that include increased consumption of ultra-processed foods [2, 3]. In turn, consumers' awareness on the importance of diet on health maintenance has also improved over the last decades, which sustains the growing demand of functional foods and nutraceuticals rich in bioactive compounds with health beneficial effects [4, 5]. There is increasing evidence from epidemiological and intervention studies showing that long-term consumption of (poly)phenol (PP)-rich foods has beneficial effects on the incidence of NCDs including several types of cancer, CVD, or T2D [6–10] associated to the multiple biological activities of PPs such as antioxidant, antiinflammatory, antiproliferative, proapoptotic, or modulating the gut microbiota. Among the most widely consumed PP-rich foods stand out beverages like coffee and tea, also rich in methylxanthines, that are the major contributors to PP intake in Western diets and with proven beneficial effects on different cardiometabolic diseases [11–13].

Another extensively consumed beverage in South America is yerba mate, prepared from the dried leaves of *Ilex paraguariensis* (St. Hil.), a plant species of the Aquifoliaceae family found in subtropical regions of South America. Yerba mate is produced mainly in Argentina, Brazil, Paraguay, and Uruguay, where mate is typically prepared as a hot water beverage (called *mate*, *mate cocido*, or *chimarrao* depending on the country) or a cold-water infusion called *tereré* [14–16]. The major consumers of mate are Uruguay, Paraguay, and Argentina, with annual per capita consumptions between 10.8 and 6.4 kg [4], and with estimated daily intakes of more than one liter per person [14]. Yerba mate is also exported to countries like Syria, Lebanon, United States, or Europe (mainly to Spain, Germany, and the Netherlands) [17], where its consumption is increasing due to its appreciated flavor and health properties. Indeed, the potential health effects of yerba mate have gained growing attention from the scientific community over the last years. Yerba mate is rich in phytochemicals like phenolic compounds, mainly hydroxycinnamic acids and flavonoids [18, 19], methylxanthines [19], and triterpenic saponins [20]. Although the beverage is prepared from the leaves like tea, the phenolic profile of yerba mate differs from green tea and resembles that of green coffee beans, being rich in hydroxycinnamates like monocaffeoylquinic acids (collectively known as chlorogenic acids) and dicaffeoylquinic acids, with important amounts of caffeine, which may account for mate's beneficial effects.

In vitro and preclinical studies have reported that mate promotes hypocholesterolemic [21, 22], hepatoprotective [23], antidiabetic [24, 25], antiinflammatory [26, 27], and antiobesity effects [28, 29], also having antiproliferative, cytotoxic [30, 31], and antioxidant properties [22, 23, 27, 30, 31]. Similarly, human intervention trials have shown health beneficial effects of yerba mate consumption decreasing blood cholesterol in dyslipidemic subjects and hypercholesterolemic patients on statin treatment [32], overweight women [33], and diabetic and prediabetic patients [34]. However, the hypolipidemic effects of mate are controversial, since other authors failed to observe changes in blood lipids after yerba mate consumption by hyperlipidemic subjects [35, 36]. On the other hand, yerba mate intake also promoted beneficial effects in T2D patients decreasing fasting blood glucose and glycated hemoglobin, although not in prediabetic subjects [34, 37]. Several studies also point to an antiobesity effect of yerba mate decreasing body fat percentage in overweight women, with higher benefits when yerba mate tea was combined with a hypocaloric diet decreasing also body weight, body mass index (BMI), and body circumferences [33]. Consuming yerba mate as a nutraceutical alone [38–40] or combined with other phytochemical-rich plants like guarana and damiana [41–43] has shown similar effects, decreasing body fat mass and body fat percentage, although with contradictory results on body weight loss. Finally, many studies reported the effect of yerba mate increasing serum antioxidant capacity and decreasing biomarkers of lipid and/or protein oxidation in healthy participants [44–47] and in subjects at cardiometabolic risk (dyslipidemic, overweight/obese, prediabetic, or diabetic subjects) [35–37, 48], although there is little information on the effect of yerba mate intake on inflammation [49].

All these evidences support the potential beneficial effects of yerba mate promoting protection against cardiometabolic diseases mainly in patients and at-risk subjects, although not all randomized clinical trials reported similar outcomes, in line with the well-established interindividual variability in the response to (poly)phenols' intake [6, 50]. Of note, except for the trials testing the antiobesity properties of yerba mate capsules, which were carried out in European or Korean populations, most of the human intervention studies on the health effects of yerba mate were carried out in countries where mate is commonly consumed. In such studies, the amount of yerba mate provided to the participants in the clinical trials resembled those of habitual mate consumption, in the range of 1 L/day of beverage prepared with 20, 50, or even 100 g of yerba mate leaves, which is far higher than habitual consumption of beverages like coffee or tea by Western populations. Thus, the question remains whether yerba mate could elicit similar cardiometabolic beneficial properties in a population not exposed to this beverage and consumed at doses habitual for other infusions within Western diets. The hypothesis is that both healthy and at-risk individuals might benefit from the consumption of yerba mate. The objective of the present study was to assess the health effects of regularly consuming yerba mate tea by nonhabitual consumers. To this aim, a randomized, controlled, crossover, single-blind, free-living intervention trial was carried out in apparently healthy (normocholesterolemic) subjects and in persons at moderate risk of developing CVD (hypercholesterolemic patients, not receiving statin treatment) who consumed daily three servings of yerba mate tea.

2 | Experimental Section

2.1 | Materials

Yerba mate, originally from Argentina, was purchased from a local supermarket in Madrid (Spain). It consisted of sachets

containing 3 g of dried roasted yerba mate leaves. Although the study was not blinded, to ensure it was an open-label study and participants did not know the brand of yerba mate used, tags were removed from the tea bags in a clean room, and yerba mate sachets were placed in blank containers before providing them to the participants in the trial. Solvents and reagents for the analysis of the phenolic composition of the yerba mate tea were of analytical (HPLC) grade and acquired from Panreac (Madrid, Spain). Standards 5-caffeoylquinic acid, caffeic acid, rutin, and caffeine were purchased from Sigma–Aldrich (Madrid, Spain), and 3,5-dicaffeoylquinic acid was from PhytoLab (Vestenbergsgreuth, Germany).

2.2 | Study Design, Subjects, Sample Size Calculation, and Recruitment

The study was a randomized, controlled, crossover intervention carried out in free-living healthy and at-risk (hypercholesterolemic) subjects. It was conducted at the Human Nutrition Unit (HNU) of the Institute of Food Science, Technology and Nutrition (ICTAN-CSIC). After a run-in stage (2 weeks), participants in each category (normo- and hypercholesterolemic) were randomly assigned in a 1:1 ratio to the test or control groups, so that half the participants consumed the yerba mate tea first while the other half had the control drink during the first intervention stage, that lasted 8 weeks. Then, a 2-week wash-out period followed before participants changed to consume the other beverage during the second 8-weeks intervention period. Participants had to consume three servings per day of the yerba mate tea or the control drink. Each serving of the yerba mate tea was prepared placing a sachet containing 3 g of dried yerba mate leaves in 150 mL of boiling water, brewing the beverage during 5 min before consuming it without added sugar or milk (if indispensable, due to the bitterness of mate, participants were allowed to add a small amount of sweetener). Volunteers consumed the tea three times per day, at breakfast, midmorning, and after lunch, emulating the usual times coffee or tea are normally taken by the Spanish population. The control drink was an isotonic drink free of sugars, polyphenols, and caffeine, which should be consumed three times a day instead of the yerba mate tea. During run-in and wash-out, volunteers only were allowed to drink water. Participants attended the HNU on three different days at baseline (at the end of the run-in), and at the end of each intervention stage. Fasting blood samples were collected as well as the dietary and physical activity questionnaires, and blood pressure and body weight, body composition, and anthropometric parameters were measured.

Participants were either healthy subjects or persons at cardiovascular risk, as determined by high blood cholesterol levels. Inclusion criteria were: men and women, 18–55 years old, with BMI between 20 and 25 kg/m^2, total cholesterol (TC) levels <200 mg/dL for the normocholesterolemic group, or between 200 and 240 mg/dL for the hypercholesterolemic participants. Exclusion criteria were: having impaired hepatic or renal function, or gastrointestinal disorders or other chronic pathologies/conditions (apart from high cholesterol levels in the at-risk group), food allergies/intolerances, smoking, vegetarians/vegans, pregnant/lactating women, on prescription drugs (including lipid-lowering agents, hypertensive drugs, etc.), having taken antibiotics 6 months before enrolment, taking vitamins, or other dietary supplements.

Changes in total blood cholesterol levels were established as the main variable for sample size calculation. Based on a difference between treatments of 6 mg/dL, a within-patient standard deviation of the response variable of 10, and considering that the study was randomized, controlled, and crossover, a sample size of 23 subjects per group was calculated. The statistical power was established at 80% and the confidence level at 0.95.

Recruitment was carried out through the website of ICTAN (www.ictan.csic.es), through e-mailing other professionals at ICTAN and CSIC, and to participants in previous intervention trials carried out at the HNU of ICTAN and who had signed their informed consent to be e-mailed informing them of future studies. Other forms of recruitment included offering informative talks between lectures at faculties of the University Complutense of Madrid (UCM) and placing advertisements at the University campus and in language and professional schools and medical centers.

Fifty-four subjects fulfilling the inclusion criteria accepted to participate in the study. Only two individuals withdrew due to personal and professional reasons. Of the remaining volunteers, 25 were normocholesterolemic and 27 were hypercholesterolemic. A flow chart of the recruitment process is shown in Supplementary Figure S1.

The study protocol was approved by the Clinical Research Ethics Committee of Hospital Universitario Puerta de Hierro (Madrid, Spain; approval ref. PI_42-12) and followed the guidelines laid down in the Declaration of Helsinki of 1975 (revised in 1983). Persons interested in participating in the study signed an informed consent before starting the intervention. The study was conducted between January 2012 and July 2013. The trial was retrospectively registered in ClinicalTrials (NCT06729905).

2.3 | Characterization of Yerba Mate Tea

The phenolic composition and caffeine content of the yerba mate tea were analyzed by HPLC-DAD according to previous analyses of different mate brands reported previously [19]. The tea was prepared as volunteers would consume it by adding boiling water to a 3 g/sachet and brewing during 5 min before removing the yerba mate. The beverage was left to cool to room temperature and filtered through a PVDF 0.45 μm filter before injection into an Agilent 1200 series liquid chromatographic system equipped with an autosampler, quaternary pump, and diode-array detector (DAD) (Agilent Technologies, CA, USA). Separation was performed on a Superspher 100 RP18 column (250 mm × 4.6 mm i.d., 4 μm, Agilent Technologies) preceded by an ODS RP18 guard column kept in a thermostatic oven at 30°C using a mobile phase consisting of 1% formic acid (Solvent A) and acetonitrile (Solvent B) at a flow rate of 1 mL/min. The solvent gradient increased from 10% to 20% Solvent B in 5 min, from 20% to 25% Solvent B over 30 min, 25% to 35% Solvent B over 10 min, then maintained isocratically for 5 min before returning to the initial conditions over 10 min. Chromatograms were recorded at 280, 320, and 360 nm, which are the maxima wavelengths of absorbance of

caffeine (λ_{max} 272 nm), hydroxycinnamic acid derivatives, and flavonols, respectively. For quantitative analysis, the external standard method was used. A standard curve of caffeine was used to quantify this methylxanthine; 5-caffeoylquinic and 3,5-dicaffeoylquinic acids were used to quantify mono- and diacyl derivatives of hydroxycinnamic acids, respectively; caffeic acid was used to quantify other caffeic acid derivatives and rutin to determine flavonol content.

The mate tea contained up to 74 mg/g dry matter (d.m.) of PPs, mainly hydroxycinnamic acid derivatives (Table S1). Of these, monoacylquinic acids were the main components of mate tea, outstanding the content of caffeoylquinic acids (50.65 ± 1.30 mg/g). Dicaffeoylquinic acids amounted to 13.03 ± 0.68 mg/g with appreciable amounts of free caffeic acid, caffeoylglucosides (up to 2.35 ± 0.06 mg/g), and caffeoylquinic lactones (0.46 ± 0.02 mg/g). Yerba mate also contained 7.41 mg/g of flavonoids, mainly rutin (6.03 ± 0.33 mg/g), followed by kaempferol glycosides (0.92 ± 0.08 mg/g) and minor amounts of quercetin glycosides (0.46 ± 0.02 mg/g). Finally, the caffeine content of the mate leaves was 7.34 ± 0.49 mg/g d.m., with minor amounts of theobromine (0.95 ± 0.01 mg/g). Considering the three servings drank by the volunteers during the mate intervention, the total amount of bioactive compounds consumed by the participants was 666.0 mg/day PPs and 66.1 mg/day of caffeine.

2.4 | Dietary Control and Compliance

Participants were instructed to maintain their habitual dietary habits without changes during the study, with the exception of consuming the yerba mate or control drink according to each intervention stage. In addition, to minimize the potential effects of PP- and methylxanthine-rich foods, coffee, tea, cocoa, and certain fruits and vegetables rich in phenolic compounds and especially foods rich in hydroxycinnamic acids were restricted during the study. Thus, whole wheat products, artichokes, aubergines, chard, broccoli, soya, oranges, mandarins, grapefruit, grapes, plums, or cherries were restricted, along with their derived products and beverages, including wine and juices. Apples, pears, pomegranates, as well as potatoes, white rice, or corn, were restricted to one serving per week. Participants were provided a list of alternative foods.

Diet was monitored by a detailed 72-h food intake dietary record comprising two working days and a holiday that volunteers had to fill in the week before each visit to the HNU. Participants were trained on how to fill in the questionnaire before starting the study, and they were asked to note down all foods taken, specifying when possible the ingredients, amounts, and serving weights, providing the labels of ready-to-eat foods consumed. Energy and nutrients (macro- and micronutrients) intake were estimated using the program DIAL (Department of Nutrition and Food Science, UCM and Alceingeniería, S.A., Spain).

Compliance with food restrictions and yerba mate intake was controlled by weekly phone calls to the participants and counting the number of yerba mate sachets returned after the intervention.

2.5 | Physical Activity

Participants were asked to maintain their habitual exercise level during the study. To monitor physical activity, volunteers answered a questionnaire informative of the activity performed in their occupation and leisure time. Volunteers recorded on three representative days of each stage of the study the minutes dedicated to working, sports, or other free-time activity as well as their sleeping time. Using the software ADN for Windows (version 3.1; Department of Nutrition, School of Pharmacy, UCM), a physical activity factor (PAF) was calculated. PAF corresponds to the activity level of each participant, estimated through the physical activity questionnaire and coefficients based on the Report of FAO/WHO/UNO [51].

2.6 | Body Weight and Anthropometric Measurements

Body weight was measured using a Tanita BC-418 MA tetrapolar segmental body composition analyzer (Tanita Corporation, Tokyo, Japan), which also provided information on body composition (total body and trunk fat percentage). Height was measured using a Holtain precision mechanical stadiometer (Holtain Ltd., Crymych, Wales, UK). BMI was calculated as [weight (kg)/height $(m)^2$]. Body circumferences (branchial, waist, abdominal, hip, and thigh circumferences) and skinfolds (tricipital and subscapular skinfolds) were measured using SECA 203 flexible tape (SECA Ltd, Birmingham, UK) and Harpenden skinfold caliper (HaB International Ltd., Southam, UK), respectively.

2.7 | Blood Pressure

After resting for at least 5 min, systolic (SBP) and diastolic (DBP) blood pressure were measured using an automatic arm sphygmomanometer (Pic Indolor Diagnostic, BS 150, Artsana, Italy) following the protocol established by the Spanish Society of Internal Medicine. Measurements were taken in both arms using a cuff of appropriate size, selecting the arm that showed a higher systolic value. Two more measurements were subsequently made on the selected arm waiting at least 3 min between measurements.

2.8 | Blood Sampling

Fasting blood samples were collected by a nurse from the nonprevailing arm using BD Vacutainer tubes (Becton, Dickinson and Company, New Jersey, USA) with EDTA or without anticoagulant to separate plasma and serum, respectively. Samples were immediately centrifuged after blood collection to collect plasma, whereas serum samples were maintained 30 min at room temperature after collection. Tubes were centrifuged for 10 min at 1500 × *g*, 4°C (Biofuge Primo R Heraeus centrifuge, IMLAB, Lille, France), and aliquots were separated and stored at −80°C until analysis.

2.9 | Blood Lipids and Liver Function

TC, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and phospholipids were determined in serum samples following methods recommended by Spanish Society of Clinical Biochemistry and Molecular Pathology using a Roche Cobas Integra 400 plus analyzer (Roche Diagnostics, Mannheim, Germany).

The enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were analyzed according to standardized spectrophotometric techniques using the Roche Cobas Integra 400 plus analyzer (Roche Diagnostics, Mannheim, Germany).

2.10 | Inflammatory Biomarkers, Chemokines, and Cell Adhesion Molecules

High-sensitivity C-reactive protein (CRP) was determined in serum using an automated ultrasensible turbidimetric method (Olympus AU2700 Biochemistry Analyzer, Olympus Iberia S.A.U., Barcelona, Spain) and expressed as mg/dL. Tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), and interleukins (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, and IL-13 were analyzed in plasma samples by multiplexing on a Bio-Plex MAGPIX system MP (Luminex Corporation, Austin, USA), using the Bio-Plex kit Pro Human Cytokine, Chemokine, and Growth Factor Assay Kit (Group I) (Bio-Rad Laboratories S.A., Alcobendas, Madrid). Results of the pro- and antiinflammatory cytokines were expressed as pg/mL.

Intercellular (intercellular cell adhesion molecule-1 [ICAM-1]) and vascular (vascular cell adhesion molecule-1 [VCAM-1]) cell adhesion molecules were analyzed in plasma using the Bio-Plex kit Pro Human Cytokine, Chemokine, and Growth Factor Assay Kit (Group II) from Bio-Rad. Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1β (MIP-1β) were analyzed in plasma using the Bio-Plex kit Pro Human Cytokine, Chemokine, and Growth Factor Assay Kit (Group I) from Bio-Rad. Plasminogen activator inhibitor-1 (PAI-1) was measured using the Bio-Rad Multiplex Diabetes kit also from Bio-Rad. Analytes were measured in duplicate on a MAGPIX Multiplex reader fitted to a Bio-Plex Pro Wash Station. Software Bio-Plex Manager MP (Luminex Corporation, Austin, USA) was used for data processing. Results were expressed as ng/mL or pg/mL.

2.11 | Glucose Homeostasis, Hormones, Adipokines, and Incretins

Fasting blood glucose concentration was analyzed in triplicate in serum using an enzymatic-colorimetric kit (GOD-PAP, Sprinreact, S.A.; Saint Esteve de Bas, Girona, Spain). Fasting insulin levels were analyzed in duplicate using the Bio-Rad Multiplex Diabetes kit on a Bio-Plex MAGPIX system MP (Luminex Corporation, Austin, USA). Using fasting glucose and insulin data, Homeostasis Model Assessment (HOMA) index to estimate Homeostasis Model Assessment of insulin resistance (HOMA-IR) was calculated according to Matthews et al. (1985) [52] as HOMA-IR = [Glucose (mg/dL) × Insulin (mU/L)]/405. In addition, the quantitative insulin sensitivity check index (QUICKI) was calculated as QUICKI = 1/[log insulin (mU/L) + log glucose (mg/dL)].

Different hormones, incretins, and adipokines of relevance were also measured using the Bio-Rad Multiplex Diabetes kit (Bio-Rad Laboratories S.A., Alcobendas, Madrid), namely glucagon, C peptide, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), ghrelin, leptin, resistin, and visfatin. Analytes were measured in duplicate on a MAGPIX Multiplex reader fitted to a Bio-Plex Pro Wash Station. Software Bio-Plex Manager MP (Luminex Corporation, Austin, USA) was used for data processing. Results were expressed as pg/mL plasma.

2.12 | Analysis of Antioxidant Capacity and Oxidation Biomarkers

Free radical scavenging activity of plasma was measured using the free radical scavenging capacity (ABTS) radical cation [53] and the oxygen radical absorbance capacity (ORAC) [54] methods, and the reducing capacity was determined by the ferric reducing–antioxidant power (FRAP) assay [55]. Trolox was used as standard and results were expressed as μM Trolox equivalent (TE). All samples were analyzed in triplicate on a Beckman DU 640 spectrophotometer (Beckman Coulter, California, USA). Lipid peroxidation was measured in serum by determining malondialdehyde (MDA) levels as described in Mateos et al. (2005) [56]. Concentrations of MDA were expressed as nmol/mL serum.

2.13 | Statistical Analysis

Results are presented as mean ± standard error of the mean, unless specified otherwise. Before statistical analysis of the results, normality of distribution and homogeneity of variance were verified using the Kolmogorov–Smirnov and Levene tests, respectively. A general linear model of the variance for repeated measures was used to assess the effects of consuming the yerba mate tea on the variables studied. The group (normocholesterolemic vs. hypercholesterolemic) was considered as an intraindividual factor. Differences within each group were further studied using paired t tests with Bonferroni corrections (Bonferroni post-hoc test). The significance level was set at $p < 0.05$. Statistical analyses were carried out using the program SPSS version 20.0 (IBM Company, NY, USA).

3 | Results

3.1 | Participants' Characteristic, Compliance, and Nutrients Intake

Baseline characteristics of the study population are shown in Table S2. Although we intended to achieve sex balance during recruitment, finally there were more women than men in both groups (15/10 women/men in the normocholesterolemic group, 17/10 in the hypercholesterolemic). There were no significant

differences among participants in both groups, who were young (although average age was a bit higher in the hypercholesterolemic group than in the normocholesterolemic, 34.1 ± 9.7 vs. 25.6 ± 6.7, respectively), had a normal weight (average BMI 23 kg/m^2), and were normotensive (average blood pressure range: SBP 115–120 mmHg, DBP 71–77 mmHg).

At the end of the study, only one volunteer returned some unused mate tea bags, which suggests an overall good adherence to the study protocol, also according to the weekly follow-up phone calls during the intervention reminding participants of food restrictions and to maintain other dietary and lifestyle habits unchanged. Questionnaires filled in during the study showed no changes in their physical activity, with a PAF ranging between 1.6 and 1.8, indicative of a light activity at work/university and during leisure time, with an overall moderate physical activity according to FAO/WHO/UNU Expert panel [51] (data not shown).

Dietary records showed no statistically significant differences in energy and nutrients intake between the normo- and hypercholesterolemic groups (Table S3). Similarly, the intake of energy, carbohydrates, dietary fiber, and lipids was maintained without significant changes throughout the intervention. Only protein consumption was lower after the yerba mate stage especially in the hypercholesterolemic group, in which intake of other macronutrients and energy also tended to decrease yet not reaching statistical significance. In both groups, the intake of saturated fatty acids (SFAs) was reduced during the intervention, especially during the mate consumption stage, although monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids and cholesterol intake were not changed (Table S3).

Data showed that the intake of energy, total carbohydrates (between 37% and 40% of total energy intake), and dietary fiber (14–16 g/day) were below the nutritional objectives for the Spanish population established by the Spanish Society of Community Nutrition [57]. Recommendations for this age group (average 25–34 years, Table S2) and with low to moderate physical activity were energy intake of 2700 kcal/day for men and 2070 kcal/day for women, 50%–55% of the total energy intake for carbohydrates, and 25 g/day and 35 g/day of dietary fiber for women and men, respectively. In turn, protein (ranging between 16% and 18%) and total fat (33% and 39%) intakes were higher than recommended (10%–15% and 30%–35% of the total energy intake, respectively). Consumption of cholesterol was lower than the limit of 300 mg/day recommended, as well as intake of PUFA (4.6%–5.3% of the total energy intake) that was within the 5% recommended. In turn, consumption of MUFA was below the objective of 20% of the energy intake (ranging between 15% and 18% in the studied population) and SFA (11.3% and 12.8%) were above the 7%–8% recommended. We did not assess the adherence to the Mediterranean diet, yet the data above suggest that participants did not comply with the recommendations for a well-balanced diet.

3.2 | Blood Pressure

Both healthy and hypercholesterolemic participants had SBP and DBP blood pressure levels within the normal range (Table 1). Blood pressure was higher in the at-risk subjects, reaching statistical significance for DBP. Mate intervention significantly decreased SBP and DBP, with noticeable reductions in the hypercholesterolemic subjects in which SBP decreased 8.2 mmHg and DBP 6.6 mmHg at the end of the mate intervention. In these participants, the control intervention also reduced blood pressure an average of 3.4 mmHg (Table 1). Heart rate was unaltered during the study in both groups of volunteers.

3.3 | Blood Lipids

As expected, the hypercholesterolemic group showed higher levels of TC, LDL-C, triglycerides, and phospholipids (Table 2), with similar HDL-C and VLDL-C concentrations compared to the normocholesterolemic subjects. Consumption of yerba mate tea during 8 weeks resulted in a significant decrease of LDL-C levels, without modifying other blood lipids and lipoproteins. In the hypercholesterolemic group, mate resulted in lower concentrations of blood lipids and lipoproteins (except VLDL-C) without modifying HDL-C levels. However, the control intervention also caused a similar response in the hypercholesterolemic patients (Table 2), pointing to an effect of the intervention per se rather than to a specific action of the yerba mate tea.

Liver enzymes were slightly, yet not statistically significantly higher in the hypercholesterolemic group (Table 2). Mate intervention resulted in decreased levels of ALT in the normocholesterolemic subjects.

3.4 | Inflammatory Biomarkers and Chemokines

Baseline levels of inflammatory cytokines were similar in normo- and hypercholesterolemic participants except for IL-2, IL-5, and IL-12 that were lower and IL-8 that was higher in the hypercholesterolemic group (Table 3). Consumption of yerba mate had a strong antiinflammatory effect, significantly decreasing plasma levels of all (but IL-2) interleukins as well as TNF-α and INF-γ in all participants. The concentration of the marker of acute inflammatory processes, high-sensitivity C-reactive protein (hsCRP), was also significantly reduced after the intake of yerba mate. The control intervention with the isotonic drink only had minor effects increasing the concentration of IL-8 and decreasing plasma levels of IL-5 and IL-12 in both experimental groups. However, these changes were not as remarkable as with yerba mate, pointing to a clear antiinflammatory effect of this beverage.

Several biomarkers of relevance on endothelial function and cardiovascular risk were measured and results are shown in Table 4. Mate intervention had no effect on the levels of vascular and intercellular cell-adhesion molecules (VCAM-1 and ICAM-1). In contrast, the levels of G-CSF and GM-CSF were diminished after yerba mate intervention, with reductions between 19.5% and 16.5% of G-CSF in normo- and hypercholesterolemic subjects with respect to baseline values, respectively, and more marked reductions in GM-CSF (27.8% vs. baseline in hypercholesterolemic and up to 56.9% reduction in normocholesterolemic subjects). MCP-1 also decreased after the yerba mate intervention, again with higher reductions compared to baseline values in the normocholesterolemic than in the hypercholesterolemic group (49.4% vs. 28.7%, respectively). MIP-1β, however, was not affected by

TABLE 1 | Effects of regularly consuming yerba mate on blood pressure and heart rate in normocholesterolemic and hypercholesterolemic subjects.

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
Blood pressure (mmHg)								
Systolic	112.77 ± 2.10	111.54 ± 1.81	109.93 ± 1.32	118.71 ± 2.70[a]	115.32 ± 2.35[a]	110.51 ± 2.25[b]	<0.001	N.S.
Diastolic	69.53 ± 1.18	69.07 ± 1.02	68.63 ± 0.81	76.19 ± 2.08[a]	72.78 ± 1.78[b]	69.56 ± 1.55[c]	<0.001	0.003
Heart rate (bpm)	67.83 ± 1.74	66.67 ± 1.76	65.91 ± 1.68	69.51 ± 1.52	70.14 ± 1.52	68.87 ± 1.24	N.S.	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column corresponds to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).
Abbreviations: bpm, beats per minute; N.S., not significant.

TABLE 2 | Effects of regular consumption of yerba mate on blood lipids (mg/dL) and liver enzymes.

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
Total-C	161.57 ± 4.40	162.50 ± 4.53	154.96 ± 4.58	230.38 ± 4.33[a]	217.71 ± 2.59[b]	214.29 ± 4.66[b]	<0.001	0.020
HDL-C	56.70 ± 2.64	57.41 ± 2.34	57.56 ± 2.36	63.13 ± 3.36	60.22 ± 2.31	62.04 ± 2.77	N.S.	N.S.
LDL-C	89.25 ± 3.94[a]	89.50 ± 4.05[a]	82.14 ± 3.60[b]	148.38 ± 4.31[a]	135.91 ± 3.43[b]	135.71 ± 3.98[b]	0.001	0.041
VLDL-C	14.24 ± 1.04	13.88 ± 0.80	13.72 ± 0.88	20.13 ± 2.03	17.61 ± 1.45	16.48 ± 1.39	N.S.	N.S.
Triglycerides	72.33 ± 5.29	71.33 ± 3.93	69.89 ± 5.66	103.29 ± 9.94[a]	84.43 ± 6.98[b]	86.95 ± 7.61[ab]	0.027	N.S.
Phospholipids	178.05 ± 5.92	180.74 ± 3.91	179.74 ± 5.25	225.38 ± 5.37[a]	210.00 ± 2.88[b]	220.24 ± 3.76[a]	N.S.	0.025
ALT (UI/L)	16.80 ± 1.25[a]	14.48 ± 1.04[ab]	14.88 ± 1.00[b]	21.36 ± 2.06	18.59 ± 1.33	19.27 ± 1.76	0.022	N.S.
AST (UI/L)	19.25 ± 0.71	17.83 ± 0.77	17.83 ± 0.87	20.86 ± 1.15	20.36 ± 0.73	20.41 ± 1.03	N.S.	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column corresponds to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N.S., not significant.

mate tea intake, although its values were significantly increased during the control intervention (Table 4). Changes in PAI-1 levels were also observed, with increased concentrations of this antifibrinolytic factor after mate consumption, reaching statistical significance in the hypercholesterolemic group.

3.5 | Glucose Homeostasis

Participants in this study had normal fasting blood glucose levels that were similar in normo- and hypercholesterolemic volunteers (Table 5). Consumption of yerba mate tea during 8 weeks resulted in a statistically significant reduction of fasting blood glucose, particularly in the hypercholesterolemic group (although it also tended to decrease in the normocholesterolemic subjects) and of insulin concentrations in the normocholesterolemic group (Tables 5 and 6). Yerba mate reduced insulin resistance and improved insulin sensitivity in both groups according to the HOMA-IR and QUICKI values, respectively, as shown in Table 5.

In line with the changes observed in insulin, glucagon levels also decreased in the healthy individuals according to the paired test but not in the hypercholesterolemic subjects after yerba mate intake (Table 6). In turn, C-peptide concentrations, slightly higher in the risk group, were not affected by the intervention. Fasting levels of incretins showed different statistically significant responses to the intervention. Attending to the Bonferroni test, GIP levels decreased after mate consumption in the normocholesterolemic group, while GLP-1 was not affected by yerba mate, although its levels decreased after the control intervention. Ghrelin also diminished during the study in the normocholesterolemic volunteers after the control and yerba mate stages, but not in

TABLE 3 | Effects of regularly consuming yerba mate on inflammatory markers (pg/mL).

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
IL-1β	5.28 ± 0.69^{a}	4.81 ± 0.45^{a}	2.56 ± 0.53^{b}	5.32 ± 0.66^{a}	5.76 ± 0.43^{a}	3.07 ± 0.51^{b}	<0.001	N.S.
IL-2	23.06 ± 3.63	13.35 ± 1.71	11.22 ± 3.79	14.47 ± 3.25	14.49 ± 1.53	17.40 ± 1.19	N.S.	0.032
IL-4	3.42 ± 0.39^{a}	3.23 ± 0.29^{ab}	2.24 ± 0.34^{b}	3.33 ± 0.34	3.38 ± 0.29	2.27 ± 0.30	<0.001	N.S.
IL-5	13.94 ± 1.14^{a}	8.47 ± 0.72^{b}	5.34 ± 1.13^{c}	11.33 ± 1.16^{a}	10.07 ± 0.73^{a}	6.64 ± 1.16^{b}	<0.001	0.038
IL-6	24.15 ± 2.48^{a}	18.07 ± 1.73^{a}	10.23 ± 1.56^{b}	18.72 ± 2.54^{a}	19.23 ± 1.77^{a}	9.49 ± 1.59^{b}	<0.001	N.S.
IL-7	14.01 ± 1.20^{a}	12.03 ± 0.90^{a}	7.94 ± 0.89^{b}	12.60 ± 1.28^{a}	13.19 ± 0.97^{a}	8.36 ± 0.96^{b}	<0.001	N.S.
IL-8	16.25 ± 6.12^{a}	30.68 ± 4.03^{b}	11.09 ± 2.82^{a}	35.35 ± 4.24^{a}	47.65 ± 2.79^{a}	12.06 ± 1.95^{c}	<0.001	0.017
IL-10	22.62 ± 3.59^{a}	18.08 ± 2.49^{a}	12.71 ± 3.18^{b}	19.48 ± 3.40	20.00 ± 2.36	14.09 ± 3.02	0.003	N.S.
IL-12	52.21 ± 5.63^{a}	36.42 ± 5.03^{b}	24.93 ± 5.09^{b}	45.99 ± 5.46^{a}	52.52 ± 4.88^{a}	22.42 ± 4.94^{b}	<0.001	0.023
IL-13	11.66 ± 0.96^{a}	11.53 ± 1.03^{a}	7.09 ± 0.93^{b}	11.35 ± 0.94^{a}	12.64 ± 1.01^{a}	7.15 ± 0.91^{b}	<0.001	N.S.
TNF-α	27.75 ± 2.43^{a}	25.28 ± 2.67^{a}	13.48 ± 2.29^{b}	23.09 ± 2.50^{a}	23.23 ± 2.28^{a}	14.46 ± 2.35^{b}	<0.001	N.S.
INF-γ	395.48 ± 37.50^{a}	307.94 ± 25.02^{a}	205.18 ± 32.69^{b}	331.46 ± 40.35^{a}	359.32 ± 26.92^{a}	199.77 ± 35.18^{b}	<0.001	N.S.
hsCRP (mg/dL)	0.040 ± 0.011	0.054 ± 0.013	0.031 ± 0.009	0.082 ± 0.023	0.062 ± 0.019	0.037 ± 0.008	0.031	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column corresponds to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).

Abbreviations: hsCRP, high sensitivity C-reactive protein; IL, interleukin; INF-γ, interferon gamma; N.S., not significant; TNF-α, tumor necrosis factor alpha.

the hypercholesterolemic group after yerba mate intake. As for the adipokines, resistin and visfatin were not affected during the study, with minor yet statistically significant changes in leptin levels observed after the control intervention.

3.6 | Serum Antioxidant Capacity and Lipid Oxidation

Serum antioxidant capacity increased after yerba mate consumption in normocholesterolemic and hypercholesterolemic subjects when measured by the FRAP method (Table S4), and also in the hypercholesterolemic group according to ORAC values. The ABTS method showed no statistically significant changes during the intervention.

Serum levels of the lipid peroxidation biomarker MDA showed a decrease in the normocholesterolemic subjects after both the control and yerba mate stages, while only mate decreased MDA levels in hypercholesterolemic subjects (Table S4). However, these differences did not reach statistical significance ($p = 0.07$).

3.7 | Body Weight and Anthropometric Parameters

The intervention with yerba mate had little effect on the measured anthropometric parameters (Table 7). There were no statistically significant changes in total body weight and body circumferences, nor in the waist-to-hip ratio (data not shown). In turn, yerba mate intake significantly decreased body fat percentage according to the general linear model of variance. Moreover, the normocholesterolemic subjects showed a significant reduction in this parameter as well as the tricipital skinfold in this group.

4 | Discussion

Most of the evidences on the health effects of drinking yerba mate comes from randomized clinical trials carried out in subjects with some cardiometabolic pathologies or at cardiometabolic risk, such as dyslipidemic, diabetic, prediabetic, or obese persons, typically consuming yerba mate in their habitual diets, since most of these studies were performed in South American countries. Such studies usually replicate or approximate the actual consumption patterns in those countries, with high daily intakes (1 L or more) of yerba mate prepared with high amounts of yerba mate leaves (50, 20 g/L) [32–34, 36, 37, 45, 46] which would provide high amounts of PPs and caffeine and are far from usual patterns of consumption of beverages like tea or coffee in Western populations. Therefore, considering the increasing consumption of yerba mate in the United States and European countries, among others, it was relevant to assess the potential health effects of its consumption under usual dietary patterns in Western countries. Coffee and tea consumption in the 10 European countries participating in the EPIC (European Prospective Investigation into Cancer and Nutrition) study ranged between <1 cup/day of coffee in Greece

TABLE 4 | Effects of yerba mate consumption on cytokines, chemokines, and cell adhesion molecules.

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
G-CSF (ng/mL)	43.31 ± 3.53	36.05 ± 3.08	34.86 ±4.51	38.01 ± 3.44	38.03 ± 3.00	31.74 ± 4.40	0.029	N.S.
GM-CSF (ng/mL)	253.69 ± 27.82[a]	221.36 ± 17.32[a]	109.22 ± 21.40[b]	220.33 ± 27.82	230.46 ± 17.32	159.03 ± 21.40	<0.001	N.S.
MCP-1 (pg/mL)	95.83 ± 6.18[a]	92.05 ± 4.34[a]	47.30 ± 4.98[b]	90.36 ± 6.48[a]	98.78 ± 4.56[a]	64.43 ± 5.23[b]	<0.001	N.S.
MIP-1β (pg/mL)	111.51 ± 6.11[a]	127.42 ± 6.55[b]	106.89 ± 7.21[a]	122.66 ± 7.29[a]	131.86 ± 6.68[b]	106.29 ± 7.37[a]	<0.001	0.038
PAI-1 (ng/mL)	3.49 ± 0.26	3.12 ± 0.24	3.89 ± 0.56	3.76 ± 0.28[a]	3.43 ± 0.26[a]	4.91 ± 0.65[b]	0.013	N.S.
VCAM-1 (ng/mL)	269.58 ± 8.79	266.22 ± 9.37	269.11 ± 10.81	251.51 ± 10.36	264.44 ± 11.04	251.61 ± 10.36	N.S.	N.S.
ICAM-1 (ng/mL)	199.40 ± 6.13	205.86 ± 5.47	196.19 ± 8.60	195.80 ± 5.86	198.39 ± 5.22	185.85 ± 8.22	N.S.	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column correspond to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; MIP-1β, macrophage inflammatory protein-1; N.S., not significant; PAI-1, plasminogen activator inhibitor-1; VCAM-1, vascular cell adhesion molecule-1.

TABLE 5 | Effects of yerba mate on fasting glucose and insulin levels and insulin resistance and sensitivity indexes.

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
Glucose (mg/dL)	74.39 ± 1.29	78.68 ± 1.92	71.77 ± 1.13	76.26 ± 1.75[a]	75.88 ± 1.54[a]	72.01 ± 1.28[b]	0.010	N.S.
Insulin (mU/L)	9.51 ± 0.45[a]	9.73 ± 0.34[a]	7.68 ± 0.52[b]	10.31 ± 0.56	10.12 ± 0.50	9.61 ± 1.03	0.039	N.S.
HOMA-IR	1.74 ± 0.07[a]	1.89 ± 0.81[a]	1.34 ± 0.09[b]	1.96 ± 0.13[a]	1.92 ± 0.11[a]	1.68 ± 0.20[b]	0.001	N.S.
QUICKI	0.35 ± 0.00[a]	0.35 ± 0.00[a]	0.37 ± 0.00[b]	0.35 ± 0.00[a]	0.35 ± 0.00[a]	0.40 ± 0.01[b]	0.001	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column correspond to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; N.S., not significant; QUICKI, quantitative insulin sensitivity check index.

to 4.4 cups/day in Denmark, and <1 cup/day of tea in Spain to 4.3 cups/day in the UK [58]. In terms of PP intake, coffee accounted for 35.9%–40.9% of the total PP intake and tea between 4.6% and 17.4% in the EPIC cohort [59], equivalent to 425–484 mg/day PPs from coffee or between 55 and 206 mg/day from tea considering an average daily intake of PPs of 1184.5 mg/day. In Spain, with an average consumption of 3 cups/day, coffee was the main source of dietary PPs according to the PREDIMED study [60], which estimated a daily intake of total PPs of 820 mg/day. However, published values of PP intake might be underestimated due to the complexity and variety of this group of bioactive compounds, the incomplete information available in food databases on the content and composition of PPs, and the inherent limitations of traditional methods used to collect dietary information [61], so higher actual daily intakes of total PPs cannot be ruled out.

TABLE 6 | Effects of regularly consuming yerba mate on incretins, adipokines, and other regulatory peptides and hormones (pg/mL).

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
Insulin	396.8 ± 18.9[a]	405.6 ± 16.5[a]	320.4 ± 29.3[b]	419.7 ± 22.7	427.4 ± 19.3	407.7 ± 35.9	0.039	N.S.
Glucagon	542.5 ± 19.2[a]	404.4 ± 11.0[b]	334.7 ± 42.5[c]	436.9 ± 20.5	403.6 ± 11.7	438.4 ± 25.1	<0.001	<0.001
C-Peptide	849.8 ± 58.8	935.4 ± 48.6	858.3 ± 75.2	1091.5 ± 64.2	917.2 ± 53.0	1046.8 ± 64.9	N.S.	0.010
GIP	321.3 ± 22.4[a]	296.2 ± 26.8[a]	234.1 ± 27.8[b]	274.1 ± 24.8	322.0 ± 29.6	314.4 ± 30.7	<0.001	N.S.
GLP-1	792.8 ± 56.5[a]	557.8 ± 39.5[b]	678.1 ± 60.7[ab]	591.7 ± 47.8[a]	459.4 ± 33.4[b]	575.1 ± 51.3[a]	<0.001	N.S.
Ghrelin	1236.0 ± 63.2[a]	933.7 ± 41.6[b]	1039.3 ± 74.8[b]	1006.0 ± 67.7	897.9 ± 44.6	1036.6 ± 80.2	<0.001	0.025
Leptin	2968.1 ± 395.9	2685.3 ± 400.4	3148.9 ± 495.8	3608.3 ± 395.9	2707.8 ± 400.4	3576.0 ± 495.9	0.009	N.S.
Resistin	3680.9 ± 192.3	3555.3 ± 225.0	3759.2 ± 509.1	3452.2 ± 206.6	3200.2 ± 241.7	3446.7 ± 244.1	N.S.	N.S.
Visfatin	3336.8 ± 316.4	2791.3 ± 367.6	2423.6 ± 830.7	2693.2 ± 339.9	3111.9 ± 394.9	2539.9 ± 892.3	N.S.	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column corresponds to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).
Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon like peptide-1; N.S., not significant.

TABLE 7 | Anthropometric variables after consuming yerba mate by normocholesterolemic and hypercholesterolemic subjects.

	Normocholesterolemic ($n = 25$)			Hypercholesterolemic ($n = 27$)			Yerba mate	Yerba mate*group
	Baseline	Control intervention	Mate intervention	Baseline	Control intervention	Mate intervention	*p*	*p*
Weight (kg)	63.01 ± 2.18	62.81 ± 2.24	62.73 ± 2.20	63.01 ± 2.82	62.91 ± 2.80	62.47 ± 2.85	N.S.	N.S.
Body fat (%)	22.82 ± 1.35[a]	23.66 ± 1.40[a]	21.27 ± 1.40[b]	26.17 ± 1.45	25.21 ± 1.36	25.38 ± 1.71	0.001	N.S.
Circumferences (cm)								
Waist	71.14 ± 1.45	71.44 ± 1.56	71.34 ± 1.49	76.76 ± 2.53	76.60 ± 2.51	75.96 ± 2.45	N.S.	N.S.
Hip	97.16 ± 1.13	96.70 ± 1.16	96.34 ± 1.25	96.08 ± 1.23	95.75 ± 1.22	95.76 ± 1.29	N.S.	N.S.
Thigh	52.00 ± 0.64	52.26 ± 0.59	51.84 ± 0.56	51.27 ± 0.96	50.90 ± 0.77	50.69 ± 0.81	N.S.	N.S.
Brachial	27.21 ± 0.49	27.38 ± 0.50	27.60 ± 0.49	27.18 ± 0.80	27.30 ± 0.81	27.25 ± 0.81	N.S.	N.S.
Skinfolds (mm)								
Tricipital	17.14 ± 1.22[a]	16.67 ± 1.18[ab]	16.12 ± 1.21[b]	16.12 ± 1.05	16.29 ± 1.22	16.01 ± 1.17	0.001	N.S.
Subscapular	10.78 ± 0.68	10.46 ± 0.62	10.53 ± 0.56	13.58 ± 1.25	13.10 ± 1.22	12.98 ± 1.10	N.S.	N.S.

Note: Data are presented as mean ± standard error of mean (SEM). The effects of consuming yerba mate were studied using the general linear model of the variance for repeated measures analysis. *p* values in the "Yerba mate" column correspond to the effect of the treatment, that is, consuming mate or the control drink (intrasubject factor); *p* value under the "mate*group" column correspond to the yerba mate x group (normocholesterolemic vs. hypercholesterolemic) interaction. Mean values within a row with unlike superscripts correspond to significant differences within either the normocholesterolemic or hypercholesterolemic group according to the Bonferroni test within either the normocholesterolemic or the hypercholesterolemic group ($p < 0.05$).
Abbreviations: N.S., not significant.

In the present study, consumption of 3 cups/day of yerba mate tea prepared from a total of 9 g of mate leaves in the three servings provided 666.0 mg/day of PPs and 74.6 mg/day of methylxanthines, which is assimilable to the amounts of PPs provided by nonalcoholic beverages (coffee and tea) estimated in the EPIC cohort [59] and to the 574 mg/day estimated in the UK population in a recent study using an ad hoc food frequency questionnaire designed to capture habitual PP intake [61]. As for caffeine, the amount provided by the three servings of yerba mate was within the lower limit of the estimated daily intake in the European adult population (37–319 mg/day) and much lower than the 400 mg/day assumed as safe for nonpregnant adults [62].

Substitution of the three daily servings of roasted coffee usually consumed by the Spanish population by yerba mate elicited beneficial cardiometabolic effects in both healthy, normocholesterolemic consumers, and in subjects at mild cardiovascular risk with moderate hypercholesterolemia, decreasing blood pressure, improving lipid profile and some markers related to endothelial function, with a modest effect on glucose homeostasis and body composition, yet a highly noticeable antiinflammatory effect in both groups of participants.

One of the effects most commonly associated to mate consumption in RCT is its hypolipidemic action. In the only study with normocholesterolemic participants, de Morais et al. [32] reported an 8.7% decrease in LDL-C levels in normolipidemic subjects compared to baseline values, which is similar to the 8.0% (−7.11 mg/dL) reduction in LDL-C observed in the normocholesterolemic participants in our study. These authors also reported between 8.1% and 8.6% reduction in LDL-C in dyslipidemic subjects measured on Days 20 and 40 of the intervention, respectively, and a further 10%–13.1% decrease in hypercholesterolemic patients on statin treatment (also on Days 20 and 40, respectively) after daily intake of 20–50 g yerba mate leaves. Again, these reductions in LDL-C were similar to the 8.5% (−12.67 mg/dL) decrease observed in the hypercholesterolemic subjects in the present study after 8 weeks, consuming mate tea prepared from 9 g/day of yerba mate leaves (Table 2). Other authors also reported similar reductions in LDL-C in T2D and prediabetic patients (7.4% and 7.3% decrease in LDL-C, respectively) [34] or in overweight women (6.5% reduction) after 12 weeks consuming 2 L/day of mate prepared with 100 g of yerba mate leaves [33], with higher reductions (up to 12.1%) when mate was combined with a hypocaloric diet. These authors also reported an 8.9% decrease of TC after mate intake and a 9.2% decrease in triglycerides when mate was consumed within the hypocaloric diet. These findings are in line with the results observed in the hypercholesterolemic subjects in the present study, with a 7.0% (−16.09 mg/dL) decrease of TC compared to baseline values or a noticeable 15.8% (−16.34 mg/dL) lower serum triglycerides concentrations. We did not observe any significant changes on HDL-C, in contrast with results reported in the literature showing decreasing [33, 63] or increasing [32, 34, 64] effects of yerba mate on HDL-C levels.

Overall, these outcomes would sustain a hypolipemic effect of yerba mate, in line with that observed for other foods rich in flavonoids, hydroxycinnamic acids, and other PPs as reported in several systematic reviews and meta-analyses of randomized controlled trials [65–67]. In support of this, a prospective trial in Paraguay involving 18 827 participants observed that heavy drinkers of yerba mate beverages consuming >1 L/day had lower TC and LDL-C than nonheavy drinkers consuming ≤1 L/day of yerba mate, although heavy male drinkers had higher triglycerides levels [68]. In contrast, a longitudinal study in both normolipidemic and hyperlipidemic participants failed to observe changes in blood lipids after consuming an instant yerba mate tea during 2 months [35], nor did another study in dyslipidemic subjects after drinking 1 L/day of mate during 3 months alone or in combination with a plant-rich dietary intervention [36], or in men predisposed to cardiovascular risk after consuming an encapsulated dry mate extract providing 581 mg/day of hydroxycinnamic acids during 4 weeks compared to the placebo. These neutral effects of yerba mate support the existing controversy on the actual the hypolipidemic effect of mate [64]. Indeed, in the present study after the control intervention with an isotonic drink, the lipid-lowering response observed in the hypercholesterolemic subjects was comparable to that elicited by yerba mate. Participants in the present study were instructed to maintain their habitual diet and lifestyle. According to the dietary questionnaires, although total energy intake was not changed in the hypercholesterolemic group during the study, there was a slight yet significant decreased in protein intake during the mate stage and a nonsignificant decrease in the intake of total fat, cholesterol, and fatty acids (significant for SFA) over the study (Table S3), also during the control stage, which might account for the observed hypolipidemic response in this group of volunteers.

Therefore, in spite of the clear hypolipidemic effect of yerba mate in the hypercholesterolemic subjects in comparison with baseline values, the similar response to the control intervention suggests that caution should be taken when referring to the hypocholesterolemic action of yerba mate. Our results agree with the findings of a recent systematic review and meta-analysis on the effect of yerba mate on lipid levels that failed to find differences in blood lipids when comparing yerba mate and control groups [69]. These authors remarked that differences between baseline levels could influence the findings on TC and LDL-C. Further research to elucidate the actual effect of yerba mate on blood lipids is needed.

A clear outcome of the present study is the hypotensive effect of yerba mate in the at-risk group of volunteers, with decreases of −8.2 and −6.63 mmHg in the SBP and DBP, respectively, compared to baseline, with final values of blood pressure comparable to those of the healthy volunteers (Table 1). Healthy, normocholesterolemic subjects also benefited from the hypotensive effect of yerba mate, although decreases in blood pressure were more modest in this group (SBP −2.84 mmHg and DBP −0.90 mmHg after yerba mate intake). These results are in line with those found by our team after the intake of a green/roasted coffee blend providing 445.2 mg/day of caffeoylquinic acids and 121.2 mg/day of caffeine [70]. In that study, reductions of −3.4 and −2.3 mmHg in SBP and DBP, respectively, were observed in normocholesterolemic participants and of −5.2 mmHg in SBP and −5.6 mmHg in DBP in hypercholesterolemic subjects after consuming the green/roasted coffee blend during 2 months. The stronger hypotensive effect observed after yerba mate intake in the present intervention in hypercholesterolemic participants might be attributed to the higher intake of PPs, to the additional presence of flavonoids in yerba mate compared to the green/roasted coffee blend (yerba mate providing 66.7 mg flavonoids/day in the present study), or to the lower intake of caffeine (66.1 mg/day). Although participants in the present trial were normotensive, this important reduction of blood pressure might contribute to a potential overall long-term cardioprotective effect of yerba mate consumption.

There is little information in the literature on the effect of yerba mate on blood pressure in humans; only Gerbara et al. [64] reported no significant changes in blood pressure nor heart rate in cardiovascular-risk male participants in their study with a dried extract of yerba mate. In an observational study in cardiology patients referred for a Holter monitory, habitual consumption

of yerba mate was not associated with changes in heart rate nor in the incidence of arrhythmias or ventricular extrasystoles [71]. Although not related to blood pressure or heart rate, Yu et al. reported interesting results from a randomized, double-blind, placebo-controlled parallel trial in subjects with high blood viscosity. In this study, intake of yerba mate tea prepared from 5 g/day of mate leaves improved parameters of blood viscosity and microcirculation, with increased levels of the vasodilator 6-keto prostaglandin F1α and decreased serum thromboxane B2 after 6 weeks of mate intake, pointing to a beneficial effect of yerba mate reducing key risk-factors of CVD [72].

Along with hypertension and elevated circulating lipid levels, inflammation plays an important role in cardiometabolic diseases. Specifically, atherosclerosis, which is the underlying cause of CVD such as coronary heart disease, peripheral vascular disease or stroke, couples dyslipidemia and inflammation, and it is regulated by multiple signals and mediators of leukocyte trafficking, cellular adhesion, and ultimate infiltration of vascular tissues in the initiation and progression of the atherosclerotic cascade [73, 74]. Therefore, it was important to study how yerba mate intervention could affect different inflammatory mediators like cytokines, chemokines, cell-adhesion molecules, or colony-stimulating factors mainly in the at-risk group of hypercholesterolemic subjects. Interestingly, yerba mate had a significant effect decreasing the levels of most of the analyzed ILs in both normocholesterolemic and hypercholesterolemic volunteers (Table 3). The response was comparable in both groups, with decreases ranging between 31.7% and 57.6% of the basal levels of IL-8 and IL-6, respectively, in the normocholesterolemic participants, and between 27.7% and 65.9% of the baseline values of IL-10 and IL-8, respectively, in the at-risk group. Proatherogenic ILs like IL-1β, IL-6, or IL-12 dropped to about half the baseline levels after mate intake but not after the control stage. However, antiinflammatory cytokines like IL-4 and IL-10 also decreased, although less markedly in the hypercholesterolemic subjects. Due to their potent proinflammatory and proatherosclerotic roles, the decrease of TNF-α and IFN-γ after intake of yerba mate is of special relevance. TNF-α induces other proinflammatory cytokines like IL-1β, IL-6, IL-8, and MCP-1, as well as cell-adhesion molecules, recruiting T cells and macrophages to the atherosclerotic lesion and further promoting the inflammatory cascade [74]. IFN-γ is also able to stimulate macrophages to secrete proinflammatory cytokines and promotes the uptake of oxidized LDL (oxLDL) by vascular smooth muscular cells and macrophages, developing into foam cells in the progression of atherosclerosis [74]. Therefore, the observed decreases of TNF-α and IFN-γ levels, close to −50% of the baseline values in the normocholesterolemic group and about −40% in the hypercholesterolemic one, might be associated to the observed reduction of IL levels and could be considered a protective effect not only against atherosclerosis and CVD but also on other inflammatory processes. This antiinflammatory effect of yerba mate was further confirmed by the reduction of plasma levels of hs-CRP (−22.5% vs. baseline values in the normocholesterolemic group and up to −55% in the at-risk volunteers, Table 3). Beyond its role as a biomarker of acute-phase inflammation such as in infection or tissue damage, CRP may also be involved in the atherosclerotic process, with a prothrombotic action mediating the release of tissue factor from vascular smooth muscle cells, increasing the antifibrinolytic activity of PAI-1 and resulting in an overall impaired fibrinolysis [75]. As such, the important reduction of this inflammatory protein supports a beneficial role of yerba mate.

Further, intake of yerba mate elicited significant reductions in G-CSF and GM-CSF in both normo- and hypercholesterolemic subjects (Table 4). These colony-stimulating factors are produced by different cell types, including immune cells (macrophages, T-cells, B-cells), endothelial cells, and vascular smooth muscle cells, with increased production under inflammatory conditions, being highly expressed in atherosclerotic plaques and with direct proinflammatory effects [76]. Indeed, targeting colony-stimulating factors as a novel therapeutic strategy against atherosclerotic plaque progression has been widely explored [76], highlighting the relevance of the findings of the present study with yerba mate.

Similar beneficial outcomes were observed after the consumption of yerba mate by normocholesterolemic and hypercholesterolemic subjects with a significant decrease of MCP-1 levels, as well as those of MIP-1β in normocholesteromic participants (Table 4). MCP-1 (CCL2) is one of the most studied chemokines due to its key role in the recruitment of monocytes into early lesions in atherosclerosis, thus initiating the monocyte–endothelial cell interactions in the early atherosclerotic process [77]. As MCP-1, MIP-1β has been localized in atherosclerotic plaques, being involved in the recruitment of peripheral monocytes into the vessel wall and playing a role in plaque formation [77]. In turn, none of the cell-adhesion molecules analyzed were affected by the intervention, with concentrations of VCAM-1 and ICAM-1 similar in both groups of volunteers and with no significant changes compared to baseline or control values (Table 4). The expression of these cell-adhesion molecules is triggered by TNF-α and, considering the reduced levels of this cytokine after yerba mate intake, no major effect on these molecules was expected. Importantly, the measured cell-adhesion molecules are the circulating, soluble forms that would increase in conditions of vascular inflammation upon cleavage of the membrane-bound forms in endothelial cells (VCAM-1), or in leukocytes, neutrophils, and endothelial cells (ICAM-1), being increased sICAM-1 and sVCAM-1 levels indicators of subclinical atherosclerosis and forecasts of cardiovascular morbidity and mortality [78]. Considering that even the at-risk participants were mildly hypercholesterolemic subjects not even on statin treatment, an established atherosclerosis condition with endothelial dysfunction and vascular inflammation was not expected. Therefore, all the effects of yerba mate on inflammatory and endothelial markers here discussed should be considered from a protective point of view, suggestive of a risk-reduction effect of yerba mate rather than as a therapeutic agent in an established or advanced stage of cardiovascular or other cardiometabolic conditions.

The only negative effect on these regulatory factors observed after yerba mate intake was related to the increased levels of PAI-1. PAI-1 regulates the fibrinolytic system attenuating plasminogen activation and subsequent fibrin degradation [79]. PAI-1, secreted from activated platelets, colocalizes on platelet-associated fibrin fibers to stabilize the thrombus, with elevated levels of PAI-1 detected within atherosclerotic plaques. As such, PAI-1 is a key protein in the progression of vascular events and is linked to both arterial and venous thrombosis. Therefore, the observed increase

of PAI-1 after yerba mate consumption can be considered an unfavorable outcome in relation to the potential cardioprotective effects of this beverage. However, plasma levels of PAI-1 were in the lower range of normal concentrations (between 5 and 20 ng/mL) [79], and therefore the observed increase after mate intake might be of no clinical relevance.

To the best of our knowledge, only one study assessed the effect of yerba mate on inflammatory cytokines in humans. In a pilot study in nine healthy men, Panza et al. [49] observed that consumption of 3 g/day of a soluble yerba mate tea during 1 week, providing 889.4 mg/day of PPs, resulted in lower serum TNF-α and IL-6 levels, in line with our results, although with no changes in IL-1β. However, the short duration and the small sample size of the study by Panza et al. confers a low level of evidence to their findings. The intervention also decreased the expression of NADPH oxidase subunit $p47^{phox}$ in leukocytes, supporting an antiinflammatory effect of short-term mate consumption. In the study by Martinez-Lopez et al. mentioned above with a green/roasted coffee blend, none of the cytokines, chemokines, cell-adhesion molecules, or colony-stimulating factors analyzed were affected by the coffee intake, except for IL-2, which levels decreased in the normocholesterolemic subjects [70]. IL-2 was the only cytokine that was not affected by yerba mate consumption in the present study. Coffee showed a potential antiinflammatory effect decreasing hs-CRP in both healthy and at-risk participants, which agrees with that observed in both groups of participants in the present trial (Table 3).

The effect of yerba mate intake on glucose homeostasis has also been scarcely explored in the literature. In a pilot study in 11 T2D patients and 11 prediabetic subjects, drinking during 2 months 1 L/day of mate prepared with 20 g of yerba mate leaves decreased fasting blood glucose and HbA1c levels in T2D patients and only HbA1c at Day 40 in the prediabetic participants [34, 37]. A more recent study using capsules containing a dried mate extract that provided 581 mg/day of PPs and 83 mg/day of methylxanthines during 28 days, fasting blood glucose decreased in men at CVD risk compared to baseline values, although there was no effect on oral glucose tolerance test (OGTT) [64]. In contrast, drinking an instant mate drink during 2 months had no effect on glucose levels in a longitudinal study in healthy and hyperlipidemic subjects [35]. Intake of one tablet/day combining yerba mate (500 or 1000 mg) with *Morus alba* (providing 2% I-deoxinojirimcina) and 100 µg chromium picolinate during 3 months by patients with impaired fasting glucose or impaired glucose tolerance was effective in decreasing fasting plasma glucose, HbA1c (with the 1000 mg dose only), triglycerides, HOMA-IR and improving insulin resistance. The higher dose of yerba mate also decreased blood cholesterol and LDL-C, CRP, and postprandial glycemia, yet no dose affected fasting plasma insulin, body weight, or body circumferences, again with no changes in OGTT compared to baseline [80, 81]. However, these results are not comparable with those reported here due to the additional pharmacological effect of the chromium picolinate and the bioactive compounds in *M. alba*.

In the present study, yerba mate had modest effects decreasing fasting plasma glucose concentrations −2.62 mg/dL in the normocholesterolemic subjects and −4.25 mg/dL (5.6% compared to baseline values) in the hypercholesterolemic participants. In the healthy volunteers, there was also a significant decrease in fasting insulin and glucagon levels (Tables 5 and 6). Although both groups of participants had normal basal glycemia, they benefited from the intake of yerba mate decreasing insulin resistance and improving insulin sensitivity as suggested by the HOMA-IR and QUICKI indexes, respectively, which might pose beneficial long-term protective effects against T2D. Indeed, in the mentioned cohort study in Paraguay, heavy drinkers of yerba mate had lower fasting blood glucose in spite of consuming more carbohydrates [68], and in a post hoc analysis in postmenopausal women in Brazil, heavy drinkers also had lower fasting blood glucose and fewer diagnosis of coronary disease, dyslipemia, and hypertension [82], supporting the beneficial effects of long-term yerba mate consumption.

Since GLP-1 levels were not affected by yerba mate intake (Table 6), the observed reduction on glucagon levels in the healthy volunteers after mate consumption does not seem to be related to this incretin, which is known for its insulinotropic and glucagonostatic effects, besides its anorexigenic properties slowing gastric emptying and reducing food intake [83]. In turn, fasting circulating concentrations of GIP decreased in the normocholesterolemic group after yerba mate intake, which might be associated to the lower insulin levels in these subjects considering the insulinotropic effect of GIP on pancreatic beta-cells. However, both GLP-1 and GIP are gut peptides secreted by the enteroendocrine system in response to nutrient ingestion, and thus the effect of mate on fasting levels of these incretins should be considered with caution. Nevertheless, bearing in mind that GIP promotes lipid deposition in adipose tissue and that excessive GIP may contribute to the pathophysiology of cardiometabolic conditions like obesity, insulin resistance, and MAFLD [84], the observed action of yerba mate decreasing fasting GIP levels might have importance in the prevention of these cardiometabolic traits. Novel therapies in the treatment of T2D and obesity dwell on the use of GLP-1 agonists and dual/triple agonists targeting GLP-1/GIP, GLP-1/glucagon, and GLP-1/GIP/glucagon receptors [85, 86]. Therefore, the role of yerba mate regulating these hormones and incretins merits further research, especially in the context of insulin resistance/T2D and obesity.

Likewise GIP, ghrelin levels also decreased in normocholesterolemic subjects after yerba mate intake (Table 6). Ghrelin, a gastrointestinal hormone released from the stomach, plays an important physiological role in energy homeostasis, with an orexigenic effect stimulating appetite, and promoting fat deposition in the adipose tissue and reducing energy expenditure [87]. Ghrelin is also involved in glucose metabolism, with an opposing role to that of GLP-1, inhibiting insulin and stimulating glucagon secretion, thus raising blood glucose levels and decreasing insulin sensitivity [88]. Therefore, the decreased levels of this gastric peptide might also be beneficial in glucose homeostasis and regulating body fat. It is interesting the fact that these effects of yerba mate on gastrointestinal hormones were mainly observed in normocholesterolemic and hardly not in hypercholesterolemic subjects. There are no previous studies on the effect of mate on incretins and other hormones of relevance on glucose and energy homeostasis. In a previous work with a green/roasted coffee blend rich in mono- and dicaffeoylquinic acids, thus partly resembling the composition of phenolic acids of yerba mate, coffee intake decreased glucagon levels as observed in the present study [89].

In turn, green coffee increased GLP-1 concentration compared to baseline values, not affecting GIP, contrary to what was observed in the present trial. Similarly, the green/roasted coffee blend decreased circulating levels of leptin and resistin in normo- and hypercholesterolemic subjects, and visfatin in normocolesterolemics only [90], whilst in the present intervention there were no significant changes in the adipokines resistin and visfatin, and only leptin increased slightly in normocholesterolemic subjects after yerba mate intake (Table 6), which might promote a satiating effect and would align with the decrease of the orexigenic ghrelin, although this did not apparently result in a decreased intake of total energy as shown in Table S3.

As discussed above, gastrointestinal hormones like ghrelin and the incretins GLP-1 and GIP have an important role not only on glucose metabolism but also on energy homeostasis and, primarily, on fat deposition on adipose tissue. The decreased levels of GIP and ghrelin might have contributed to the slight, yet statistically significant decrease of body fat percentage observed in the normocholesterolemic subjects, in spite of no further changes on total body weight or different body circumferences (Table 7). However, it is important to highlight that participants in the present trial were normo-weight, with a mean BMI of 23 kg/m^2. Therefore, the observed decrease of body fat percentage without a reduction of energy intake might be of special relevance for overweight/obese people and the role of the gastrointestinal hormones in this outcome merits future research.

The antiobesity potential of nutraceuticals containing yerba mate has been previously explored. Thus, consumption of capsules containing yerba mate (3 g/day) decreased body fat mass, body fat percentage, and waist-to-hip ratio in overweight and obese subjects without modifying visceral and subcutaneous abdominal fat area or body weight [38–40]. When yerba mate was combined with guarana and damiana (YGD), these capsules prolonged gastric emptying causing increased perceived satiety and reduced food and energy intake [41–43], as well as decreased total body weight [41]. In a postprandial study, YGD decreased the area under the curve (AUC) of ghrelin and elicited higher GLP-1 levels after breakfast than the placebo, supporting the anorexigenic effect of the herbal capsules containing yerba mate [43]. All other human intervention studies with yerba mate discussed above showed no effect on body weight or anthropometric variables [35, 63, 64, 80, 81]. Interestingly, one study in overweight women consuming during 12 weeks yerba mate prepared with 100 g/day of mate leaves showed decreased body weight, BMI, body circumferences, and waist-to-hip ratio only when a mate was consumed with a hypocaloric diet, with small increases or no changes when consumed without dietary counseling [33]. In turn, mate alone caused an important decrease on body fat percentage, higher than that observed in the mate + diet group. This agrees with the finding of the present study and points to a direct effect of yerba mate on body fat mass without changes on lean body weight.

Among the best-studied properties of yerba mate is its capacity to increase plasma or serum antioxidant capacity, with almost all human studies backing up this property of PP-rich yerba mate, enhancing gene expression and/or the activity of antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase, and paraxonase [PON]-1 or PON-2) [35–37, 44–47] in different population groups (i.e., healthy individuals, T2D patients, dyslipidemic, or overweight/obese participants). However, some studies did not observe changes in biomarkers of macromolecules' oxidative damage like lipid hydroperoxides, carbonyl groups, or conjugated dienes [35, 36, 46]. In line with this, outcomes from the present study sustain the antioxidant capacity of yerba mate increasing serum FRAP and ORAC values, with a decrease in the levels of MDA close to statistical significance ($p = 0.07$, Table S4).

Beyond the antioxidant potential of yerba mate, most of the observed effects associated to mate consumption can be related to its high content in phenolic compounds, mainly monocaffeoylquinic (chlorogenic) acids and dicaffeoylquinic acids, with minor amounts of flavonols (Table S1). Chlorogenic acids have potent antihypertensive actions elicited by complementary mechanisms such as increasing nitric oxide (NO) bioavailability, thus promoting vasodilation, as well as through direct vasorelaxant effects acting on the endothelium-derived relaxing factors involved in nitric oxide synthase (NOS), cyclooxygenase (COX), and endothelium-derived hyperpolarizing factor (EDHF) pathways, or by inhibiting angiotensin-converting enzyme (ACE) [91, 92]. The hypotensive effect of chlorogenic acids would overcome the pressor effect of caffeine, although it is now known that caffeine can both increase and decrease blood pressure acting as an antagonist of adenosine receptors A_1R, $A_{2A}R$, and $A_{2B}R$ [93]. Besides, regular consumption of caffeine would result in the development of tolerance to this methylxanthine, which explains the lack of pressor effect of caffeine in habitual consumers [93]. Although participants in the present study refrained from consuming coffee or other caffeine-containing beverages 2 weeks before starting the study and during the whole intervention (including the wash-out period), no pressor effect was observed upon consumption of caffeinated yerba mate and, in turn, a clear hypotensive effect was observed, likely due to the contribution of hydroxycinnamic acids in yerba mate.

Hypertension, diabetes, or hypercholesterolemia are important risk factors associated to CVD and endothelial dysfunction, characterized by decreased NO bioavailability, increased production of reactive oxygen species (ROS), accumulation of oxLDL in the vascular wall, production of proinflammatory cytokines, chemokines, cell-adhesion molecules, etc. Chlorogenic acid has antiinflammatory functions inhibiting the synthesis and secretion of inflammatory mediators like TNF-α, IFN-γ, IL-1β, IL-6, IL-8, or prostaglandin E2 by modulating key signaling pathways, including NF-κB, MAPK, Nrf2, and others [94], also inhibiting the expression of VCAM-1, ICAM-1, and E-selectin [92]. Therefore, the potent antiinflammatory action of yerba mate here observed can be associated to its phenolic acid content.

Hydroxycinnamic acids, as other PPs, including flavonols present in yerba mate, also have hypolipemic, antiadipogenic, and antidiabetic potential acting by different mechanisms. They inhibit lipogenesis through the inhibition of hepatic enzymes involved in cholesterol and fatty acid synthesis (3-hydroxy-3-methylglutaryl coenzyme A [HMG-Co-A] reductase and fatty acid synthase [FAS], respectively), and increasing energy metabolism (β-oxidation of fatty acids) by stimulating the expression of peroxisome proliferator-activated receptor alpha (PPAR-α) and downregulating sterol regulatory element-binding protein (SREBP)-1C and related molecules in the liver [95, 96]. PPs also affect

glucose absorption inhibiting digestive enzymes (α-amylase, α-glucosidase) and interacting with sodium-dependent glucose transporter 1 (SLGT1) in the intestine, reducing gluconeogenesis by inhibiting glucose-6-phosphatase, modulating incretins, stimulating the translocation of glucose transporter 4 (GLUT4), increasing glucose uptake in peripheral tissues (muscle and adipose) and improving insulin sensitivity [95, 97].

However, in spite of the extensive knowledge on the health-promoting effects of hydroxycinnamic acids and other PPs supporting their mediating action on the outcomes observed in the present study, the potential contribution of other bioactive components in yerba mate should not be overlooked. Caffeine can also decrease lipogenesis by modulating gene expression of key enzymes and transcription factors, decreasing lipid accumulation and body weight gain, increasing energy expenditure via enhanced lipid β-oxidation and decrease energy intake, with beneficial effects against T2D by increasing insulin secretion and insulin sensitivity as well as improving glucose tolerance [98, 99]. Similarly, the triterpenic acids in yerba mate, ursolic and oleanolic acids, can also have antiinflammatory effects and endothelial-protective actions decreasing TNF-α, IL-1β, IL-6, and MCP-1 via inhibition of NF-κB signaling, modulating lipid metabolism by inhibiting FAS, with antihypertensive action associated to modulation of the renin–angiotensin system and natriuretic hormone, and with antidiabetic potential via inhibition of α-amylase, α-glucosidase, as well as inhibition by oleanolic acid of the NF-κB, MAPK, and NLRP3 inflammasome pathways and upregulation of the HO-1/Nrf2 pathway [100]. Therefore, although less studied than PPs, their potential contribution to the health-promoting effects of yerba mate merits future research.

The present work has several limitations. We did not explore the response of the intestinal microbiota to the yerba mate intervention, which has not been tackled in the scientific literature [101] in spite of the complex, yet determinant impact of the gut microbiota on the bioavailability and health effects of dietary PPs [102]. We did not analyze the circulating phenolic and methylxanthine metabolites in the participants in this trial. However, in a previous study, we established the bioavailability and pharmacokinetics of yerba mate PPs in healthy individuals [103]. Up to 34 phenolic-derived metabolites were identified in biological fluids, including noncatabolized hydroxycinnamate derivatives, Phase II conjugated metabolites from the hydrolyzed parent compounds, and microbiota-derived catabolites. The major circulating metabolites were dihydroferulic, dihydroisoferulic, and dihydrocaffeic acids and their Phase II sulfated and glucuronidated metabolites, with appreciable concentrations of dihydroferuloylquinic acids, always in the μM range. Phase II metabolites of free caffeic and ferulic acids as well as of the flavonols quercetin and kaempferol were also detected in plasma. The most abundant urinary metabolites were dihydrocaffeic acid-3-sulfate, feruloylglycine, and dihydroferulic acid-4-sulfate, along with many microbiota-derived catabolites, although with appreciable excretion of sulfated caffeic and ferulic acids and free caffeoyl- and feruloylquinic acids, supporting the absorption of the parent hydroxycinnamates yet in minor amounts. Overall the bioavailability of yerba mate's phenolic compounds was low, about 13.2% of the ingested dose, but the presence of μM concentrations of PPs metabolites in plasma supports the association of the effects here reported to these bioactive compounds.

As strengths of this study can be pointed out its design, as a well-powered, randomized, controlled, and crossover trial, with a close follow-up of participants' adherence. It is a novel study, exploring for the first time the impact of consuming yerba mate by nonhabitual consumers following an intake assimilable to habitual consumption patterns in Western countries of caffeinated beverages like tea or coffee. It also explored the effect of mate tea in a normal (healthy) population and in subjects at mild risk of CVD, who might benefit from easy, accessible dietary interventions such as the consumption of yerba mate tea to decrease cardiometabolic risk factors. Of note, multiple biomarkers of clinical relevance were measured, many for the first time in studies with yerba mate, including an extensive panel of cytokines, chemokines, adhesion molecules, incretins, and hormones, further contributing to the novelty of the present study.

5 | Concluding Remarks

For the first time in a European population of nonhabitual consumers of yerba mate, regularly drinking 3 servings/day of yerba mate tea prepared from 9 g of mate leaves showed potential health benefits both in subjects at moderate cardiovascular risk and in healthy consumers. Yerba mate consumption could exert cardiometabolic protective effects by decreasing blood pressure and promoting potent antiinflammatory responses in both groups of participants, improving different modulators of endothelial function. Yerba mate also had hypolipidemic action, decreasing LDL-C in healthy individuals and TC, LDL-C, and triglycerides in hypercholesterolemic subjects, although the similar hypolipidemic effect of the control intervention in this group calls for caution on the relevance of this outcome. Yerba mate intake also modulated fasting plasma levels of glucose, insulin, and glucagon, yet with different responses in both groups of participants. The effect of mate on gastrointestinal peptides like GIP and ghrelin might account for the decrease of body fat percentage, although the antiobesity effect of yerba mate was not supported by changes in total body weight or body circumferences. Further research on the health effects of yerba mate in the context of chronic NCDs like T2D or obesity is warranted.

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Ethics Statement

The study protocol was approved by the Clinical Research Ethics Committee of Hospital Puerta de Hierro (Madrid, Spain; approval ref. PI_42-12) and followed the guidelines laid down in the Declaration of Helsinki of 1975 (revised in 1983). Persons interested in participating in the study signed an informed consent before starting the intervention. The study was conducted between January 2012 and July 2013.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/mnfr.70065.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.