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Protocol

Consumption of coffee enriched with cocoa and cinnamon by hypertensive women (Ecardio-CACACA): study protocol

Consumo de café enriquecido com cacau e canela por mulheres hipertensas (Ecardio-CACACA): protocolo de estudo

Consumo de café enriquecido con cacao y canela por mujeres hipertensas (Ecardio-CACACA): protocolo de estudio

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Abstract

Objective: To analyze the effect of consuming different coffee formulas enriched with cocoa and cinnamon on cardiovascular, glycemic and anthropometric biomarkers in hypertensive women, during 12 weeks.

Methods: Double-blind randomized clinical trial, of the factorial type, to be carried out in Basic Health Units, in a city in the interior of Ceará, with a sample of 90 people. Eligible participants will undergo two assessments (before and after) to measure clinical and laboratory cardiovascular, glycemic and anthropometric biomarkers. Randomization will be by strata, according to the stage of hypertension, and allocation will be by blocks. Participants will be instructed to drink coffee formulas twice a day (breakfast and lunch), in concentrations of 10g (coffee), 5g (cocoa) and 3g (cinnamon), prepared with 50 mL of hot water. For data analysis, repeated measures ANOVA (> 2 groups) will be considered, and in case of statistically significant associations (P< 0.05), linear regression will be performed. With this, it is intended to know which is the most effective fortified coffee formula for the control and/or reduction of cardiological, glycemic and anthropometric biomarkers.

Descriptors: Coffee; Cacao; Cinnamomum zeylanicum; Hypertension; Clinical study.

Whats is already known on this?
Coffee, cinnamon and cocoa are effective in reducing cardiovascular and glycemic biomarkers, as well as reducing adiposity, in people with chronic non-communicable disease.

What this study adds?
Enriching coffee with other foods (cinnamon and cocoa) can contribute to better management of cardiovascular and glycemic problems, giving nurses greater autonomy in their clinical practice.

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Resumo

Objetivo: *Analisar o efeito do consumo de diferentes fórmulas de café enriquecidas com cacau e canela sobre biomarcadores cardiovasculares, glicêmicos e antropométricos em mulheres hipertensas, durante 12 semanas.* ***Métodos:*** *Ensaio clínico randomizado duplo-cego, do tipo fatorial, a ser realizado em Unidades Básicas de Saúde, em uma cidade do interior do Ceará, com uma amostra de 90 pessoas. Os participantes elegíveis passarão por duas avaliações (antes e depois) para mensuração de biomarcadores cardiovasculares clínicos e laboratoriais, glicêmicos e antropométricos. A randomização será por estratos, de acordo com o estágio da hipertensão, e a alocação será por blocos. Os participantes serão orientados a tomar as fórmulas de café duas vezes ao dia (café da manhã e almoço), em concentrações de 10g (café), 5g (cacau) e 3g (canela), preparados com 50 mL de água quente. Para análise dos dados, será considerada a ANOVA de medidas repetidas (> 2 grupos), e em caso de associações estatisticamente significantes (P< 0,05), será realizada regressão linear. Com isso, pretende-se conhecer qual é a fórmula de café enriquecido mais eficaz para o controle e/ou redução de biomarcadores cardiológicos, glicêmicos e antropométrico.*

Descritores: *Café; Cacau; Cinnamomum zeylanicum; Hipertensão; Estudo clínico.*

Resumén

Objetivo: *Analizar el efecto del consumo de diferentes fórmulas de café enriquecido con cacao y canela sobre biomarcadores cardiovasculares, glucémicos y antropométricos en mujeres hipertensas, durante 12 semanas.* ***Métodos:*** *Ensayo clínico aleatorizado doble ciego, de tipo factorial, a ser realizado en Unidades Básicas de Salud, en un municipio del interior de Ceará, con muestra de 90 personas. Los participantes elegibles se someterán a dos evaluaciones (antes y después) para medir biomarcadores cardiovasculares, glucémicos y antropométricos clínicos y laboratoriales. La aleatorización será por estratos, según el estadio de la hipertensión, y la asignación será por bloques. Se indicará a los participantes que tomen fórmulas de café dos veces al día (desayuno y almuerzo), en concentraciones de 10g (café), 5g (cacao) y 3g (canela), preparadas con 50 mL de agua caliente. Para el análisis de datos, se considerará ANOVA de medidas repetidas (> 2 grupos), y en caso de asociaciones estadísticamente significativas (P< 0,05), se realizará una regresión lineal. Con ello, se pretende conocer cuál es la fórmula de café fortificado más eficaz para el control y/o reducción de biomarcadores cardiológicos, glucémicos y antropométricos.*

Descriptores: *Café; Cacao; Cinnamomum zeylanicum; Hipertensión; Estudio Clínico.*

INTRODUCTION

Enriching coffee with the addition of other foods and/or substances is promising, both from an industrial and therapeutic point of view.[1,2] Evidences have shown that foods such as coffee and cocoa have a favorable effect on human health, as a result of preventive action and control of chronic diseases, such as diabetes, metabolic syndrome, hypertension and other health problems.[3,4]

Coffee seems to have the potential to act as a nutraceutical (anti-inflammatory, anti-diabetic, anti-obesity, antioxidant, and hypolipidemic functions) and an important food additive.[5] In turn, cocoa is rich in polyphenols capable of increasing mitochondrial activity, performing that of the GLUT4 receptors in skeletal muscles and decrease IgE concentration, as well as improve neural efficiency and inhibit nuclear factor κB. These mechanisms favor, respectively, weight reduction, improvement of insulin resistance, treatment of allergies, modulation of mood and counter inflammation.[6,7]

Another product that can be highlighted is cinnamon. In this sense, systematic reviews, including meta-analysis, indicate that this spice reduces some cardiological biomarkers, such as triglycerides, not interfering with cholesterol levels (low-density lipoprotein cholesterol – LDL-C or high-density lipoprotein – HDL-C).[8,9] A more recent review also highlighted the benefit of this supplementation on systolic (SBP) and diastolic (DBP)[11] blood pressure, biomarkers of inflammation and oxidative stress.[12] Regarding blood glucose, consumption of cinnamon was effective in reducing plasma glucose and glycated hemoglobin.[10] Such bioproducts are part of the list of possibilities that Integrative and Complementary Practices provide for a more autonomous and evidence-based assistance that nurses can use in primary care units.

Thus, based on the above, hypertensive and diabetic patients may benefit from supplementation with these types of products.[13] However, none of these studies analyzed and/or compared the effect of these combined foods in relation to glycemic and cardiovascular biomarkers and to the level of adiposity in hypertensive people.

In this perspective, the production of foods that benefit the health of people with hypertension appears as a good strategy for prevention, restoration or health promotion. Therefore, this production must follow an experimental design.

It is relevant, in the development and optimization of foods, the experimental design with factorial schematization, when one is interested in knowing and measuring the effect of components of the formula (predictive variables) on a certain product (outcome).[14,15] In this case, classically, researchers choose to develop factorial schemes, in which only one predictor factor (ingredient) varies at a time, keeping the others constant. Thus, to delimit the ideal level of the food formula, it is necessary to conduct several

experiments, which are more expensive. Furthermore, this strategy is also inadequate because it does not consider the joint interaction between all the factors.[14]

Therefore, in this research, the factorial scheme with mixture planning will be considered, simultaneously varying all the components of the fortified coffee in order to reduce the number of experiments and identify a product with the best functional characteristics.[14] Furthermore, this type of strategy minimizes the possibility of underestimating the effect of isolated nutrients in relation to cardiovascular risk compared to other food components.[16]

In the case of coffee, it is recommended to study the effect of its use on psychological, hormonal and metabolomic parameters, with the aim of listing more robust and conclusive evidence.[17] For cocoa, conducting clinical trials can be an opportunity to clarify its endothelial and antioxidant effects, as well as insulin resistance and glucose tolerance, which are still inconclusive.[18,19]

It is also underlined that, given the magnitude of arterial hypertension on the world stage, associated with the great demand for care on the part of nurses, especially those who work taking care of this disease in Primary Health Care, the elaboration of integrative and complementary practices with therapeutic potential, such as the consumption of coffee, cinnamon and cocoa, emerges as an important strategy to be adopted by this professional. In fact, these natural inputs may be opportune to boost the protagonism of nurses, as well as add skills and abilities to the performance of these professionals, increasingly directing them to advanced practice nursing.

Therefore, the aim of this study will be to analyze the effect of consuming different coffee formulas enriched with cocoa and cinnamon on cardiovascular, glycemic and anthropometric biomarkers in hypertensive women for 12 weeks.

METHODS

Design

This will be a randomized, double-blind, phase II, factorial (3x) clinical trial, ideal when the intention is to evaluate multiple components (and their interactions) of an intervention with a good statistical approach. The research will be carried out in Basic Health Units in the city of Eusébio, Ceará, Brazil. The Basic Health Units will be selected by drawing lots, considering only those that have at least one Family Health Strategy team in two shifts (morning and afternoon), in attendance from Monday to Friday.

In total, 90 women diagnosed with arterial hypertension for at least six months, registered and monitored at health units and using antihypertensive drugs should participate in the study – according to the due sample calculations. The choice for developing the study only with the female public was because this is the population that most use health services, as well as the disparity between men and women in terms of blood pressure values.

This study complies with ethical guidelines. The study was approved by the Research Ethics Committee of the Universidade da Integração Internacional da Lusofonia Afro-Brasileira, under opinion number 5.865.185/2023, and registered with the Brazilian Network of Clinical Trials (ReBEC), under number: U1111-1290-6529, and acronym Ecardio-CACACA.

For greater transparency and quality of the research, Table 1 summarizes the recruitment, initiation of intervention and evaluation schedule, according to the Standard Protocol Items: Recommendations for International Trials guidelines (SPIRIT).[20]

Table 1. Schedule of recruitment, allocation, intervention and evaluation of treatments. Fortaleza, Ceará, Brazil, 2023.

			Study Period		
	Recruitment	**Allocation**	**T0 (*baseline*)**	**Weekly**	**T90 (*outcome*)**
Eligibility Assessment	X				
Term of Consent	X				
Allocation of groups		X			
Intervention					
Control group*			X	X	X
Experimental group 1**			X	X	X
Experimental group 2***			X	X	X
Assessment					
Adverse events				X	X
Laboratory variables			X		X

Anthropometric variables	X	X	X
Clinical variables	X	X	X
Socioeconomic variables	X		

Legend: T0 – baseline (before the beginning of the intervention), T90 – after 90 days of the beginning of the interventions. *Control group (100% Arabica coffee, 40g/day); **Experimental group 1 (100% Arabica coffee, 40g/day + 100% cocoa, 10g/day); ***Experimental group 2 (100% Arabica coffee, 40g/day + cinnamon, 6g/day).
Source: authors (2023).

Data collection

Data collection will be carried out after recruiting participants, for a total of 90 days – given the length of study. It will be carried out in Basic Health Units, in rooms reserved for the study, on previously scheduled days and times. At the time of collection, previously trained members of the research group will conduct an interview to collect socioeconomic and clinical data and assess anthropometric markers. At T0 (baseline) and T90 (final), a laboratory hired to collect the blood of research participants will be available in a reserved room, in order to carry out the analysis of cardiovascular and glycemic biomarkers. In addition, the collection will continue with weekly visits, to be scheduled in the homes of the participants in this research. At that moment, blood pressure, heart rate and capillary blood glucose will be measured, for example. Furthermore, possible adverse events and further guidance regarding the study will be provided at these times.

Study variables: baseline and post-intervention

- Socioeconomic variables (baseline only): family economic income will be investigated; years of study; marital status; type of work; skin color; and who they live with.
- Clinical variables: questions such as physical exercise will be investigated; duration of arterial hypertension; family history of hypertension; medications in use; if they have an allergy; place where medication is obtained; frequency of medical consultations or with another health professional to monitor the disease; use of integrative and complementary practices, in particular, herbal medicine for any clinical condition. In addition, blood pressure, heart rate (at rest) and pulse pressure will be measured, as well as a digital puncture to measure capillary blood glucose and uric acid (values between 2.4 and 5.7 mg/dL being considered normal). The measurement of these variables will be done via a portable device, through the analysis of a blood sample.
- Anthropometric variables: waist circumference measurements will be investigated; neck circumference; thigh circumference; abdominal circumference; hip circumference; height; weight; body mass index; central adiposity index; waist-hip ratio; triceps skinfold; the supra iliac; abdominal; suprascapular; and body fat percentage.
- Laboratory variables: fasting blood glucose tests will be collected; HbA1c; triglycerides; total cholesterol; homocysteine; apolipoprotein B; protein C; uric acid; fructosamine; creatinine; fasting insulin; and the calculation of the HOMA-IR index.

Outcomes

The primary outcome will be related to the reduction of laboratory levels of cardiovascular predictors (triglycerides, total cholesterol, homocysteine, apolipoprotein B, protein C, uric acid, and creatinine). Secondary outcomes will be linked to the assessment of the reduction in glycemic levels and body adiposity.

Study participants

Women with a diagnosis of arterial hypertension, registered and monitored in the Basic Health Units of the city of Eusébio will be able to participate in the study. Recruitment will be based on the list made available by the coordination of Primary Care in the municipality of women with hypertension. Recruitment will be carried out at least 10 days before the beginning of data collection, by community health agents from each unit.

Eligibility criteria

To participate in the study, participants must be between 18 and 80 years old, be female, have a telephone number for contact, not be allergic to products derived from cocoa, coffee and/or cinnamon, have been diagnosed with arterial hypertension for at least six months, reside in the health territory where

the study will be carried out and possess a Mini-Mental State Examination sufficient to answer the study questions.

Exclusion criteria will be: patients who make prolonged use of glucocorticoids and/or psychotropics; users of more than three different classes of antihypertensive drugs; have diabetes (type 1 or 2); being pregnant or lactating; having osteoporosis; having undergone surgeries in the last 30 days prior to data collection or having postoperative restrictions; being a smoker; and having significant liver, kidney and/or cardiovascular alterations that may be aggravated by the thermogenic influence of the inputs/products used.

As for the discontinuity criteria, these will be: if a participant wishes to withdraw from the study for any reason; serious adverse events or unusual changes in laboratory tests; patient who takes another type of herbal medicine during this study for therapeutic purposes; patient who reports not having taken the formula for a period equal to or longer than five consecutive days.

Sample size

The number of participants per group (three interventions) was calculated considering a factor analysis of repeated measures using ANOVA. For that, we consider: Effect size: 0.8; $\alpha = 0.05$; $\beta=0.8$ in a layout of three groups and nine measures (considering blood pressure and cardiovascular predictors as the main outcome). The n of each estimated group was 24, 20% will be added to this value, considering losses during follow-up. Therefore, the final sample will consist of 90 patients, divided into three intervention groups. The calculation was performed using the free software GPower 3.0, using the t test for independent samples.

Randomization and allocation of participants

The randomization of the subjects will be of the strata type. Lists will be created based on the stage of hypertension (Stage 1 Hypertension; Stage 2 Hypertension and Stage 3 Hypertension) and, subsequently, blocks of three participants will be recruited for a simple draw, which will designate the allocation group the participant will be part of.[21] To guarantee the secrecy of the participants' allocation, this step will be carried out by an external professional, in order to guarantee that the investigator does not interfere to which group each participant will be allocated (Formula 1, Formula 2 and Formula 3), until this person (participant) has entered the study. After this stage, a member of the research group will deliver a box containing the sachets with the formulations to each participant. In this, there should be a number registered next to the name of each participant.

The registration of the numbers of each patient will be done in writing and electronically. The printed records will be stored in a folder containing the documents of the study participants. Electronic records will be entered into an Excel® spreadsheet. A copy of the written records will be sent to the study supervisor/coordinator. Each patient's identification number will be listed and recorded by a member of the research group. Thus, the member will know which group each participant will be in. The list of numbers assigned to each patient shall be printed and kept in a sealed envelope, under the responsibility of the associate. And a copy will be placed in another sealed envelope and will be under the responsibility of the study advisor/coordinator.

The researcher will also record the data in an Excel® spreadsheet, save it on a personal computer and include the records online, in a "cloud", with a login and password exclusively owned by the researcher. The main researcher will only know which group each participant was allocated to at the end of the intervention period.

Intervention and follow-up

Participants will be allocated into three different groups (control group, experimental group 1 and experimental group 2). The intervention will last for 12 weeks (90 days), and each participant will receive a total of 180 sachets (divided into three boxes, each with 60 sachets), containing different formulations, as shown in Table 2. The groups' packaging will be identical and will not specify the contents of the formula. Each participant must take two sachets a day, reconstituted in 50 mL of hot water, at the time of ingestion. It will be recommended to take a sachet at breakfast time, in the morning shift, and another after lunch, in the afternoon shift. The intervention time was chosen based on other evidence in the literature and considering the time of change in HbA1c.

Table 2. Coffee, cinnamon and/or cocoa formulas, according to allocation group. Fortaleza, Ceará, Brazil, 2023. (*n*= 90)

Formula	Groups		
	Control Group (n= 30)	Experimental Group 1 (n= 30)	Experimental Group 2 (n= 30)
Cinnamon (*C. zeylanicum*)	-	-	6 grams
Cocoa (100%)	-	10 grams	-
Arabica coffee (100%)	20 grams	20 grams	20 grams

Source: authors (2023).

The choice of dosage and times were based on suggestions from previous researchers. It is stipulated that the minimum daily intake of polyphenols should be 1 gram. However, the amount of polyphenols when consuming one to three cups of coffee a day (101-337 mg/day) already brings cardiovascular benefits, especially in terms of blood pressure, lipid profile and homocysteine.[22,23] Consumption of different types and sources of polyphenols during a meal does not create any kind of competition during absorption in the intestinal lumen (enterocytes). Furthermore, there is no consensus that bovine milk (usually consumed at breakfast) interferes with the bioavailability of polyphenols.[22] Therefore, coffee intake during the two main meals of the day will be indicated.

A new box will be delivered, at intervals of 25 to 29 days, by researchers and community health agents from the Basic Health Units. In addition to the method of preparation, participants will receive guidance on keeping the sachets at room temperature and not making any changes to their diet to gain or reduce weight, so as not to change the amount of calories ingested.[23] The remaining sachets will also be counted for measuring adherence. In addition, all patients will be encouraged to continue taking their medications routinely, following the recommendations of their treating physicians. Participants will be instructed on how to take the sachets. The products will be arranged in sachets and packed in identical boxes, containing a label with information on dosage, product shelf life (greater than the intervention period) and return date. Each vial will be numbered to facilitate the process of randomization of participants. To promote the retention of participants, there will be weekly telephone follow-up.

Patients will be encouraged not to change their physical activity or eating routine during the data collection period. All participants will be informed about the risks and benefits of the study and will be aware that they can leave the study at any time and for any reason. After recruitment, evaluation of the participation criteria and acceptance of the participants to be part of the study, the researchers will set a date to start data collection. The collection will be divided into two stages. In the first, participants will be instructed about the study and will collect all socioeconomic, clinical, anthropometric and laboratory variables. To assess adherence, the Morisky test will be applied.

All treatments will be carried out by a group of nurses, who will undergo a training and calibration exercise in the initial phase of the study. The main researcher will carry out the intervention and data collection and will not know which group will lead. Blood samples (10 mL) will be collected after 10 to 12 hours of fasting. Samples will be centrifuged at room temperature at 3,000rpm for 10 minutes to separate serum from blood cells. The tests will be determined by the colorimetric enzymatic method, with commercially available kits (Pars Azmun Co., Tehran, Iran) in an automated analyzer (Abbott, model Alcyon 300, Abbott Park, IL). As for HOMA-IR, it will be calculated by multiplying glucose by insulin (µUI/mL), both in fasting conditions, and dividing by 22.5 – the established cut-off point was 2.5. Venipuncture, manipulation and analysis of biological samples will be performed by trained professionals and the analyses will be conducted in a clinical analysis laboratory with the CONTROLLAB quality seal, intermediated by the Brazilian Society of Clinical Pathology and Laboratory Medicine and by the quality seal of the National Quality Control Program.

The results of the blood tests will be given to the participants after the complete review of the study is done, in order for participants not to jump to conclusions about the intervention, so that they do not start using cinnamon (or not) without knowledge of the true effectiveness. Between T0 and T90 collections, research group members will visit patients weekly. In these visits, the related adverse events and the measurement of previously mentioned clinical data will be explored. The investigator will analyze, through discussion with the patient, the occurrence of adverse events during each visit and record the information. Adverse events will be recorded with the instrument and registration number of each participant. Adverse

events will be described by duration (start and end dates and times), severity, outcome, treatment, and relationship to study drug or, if unrelated, possible cause.

Prior to undertaking any study-related activity, the written informed consent and authorization must be signed and dated by the patient. If the patient is not literate, the term will be read by a data collector or by the main researcher, and then the signature will be removed on request. Consent must be obtained before undertaking any study-related collection activities. After collection, data analysis, writing of technical documents, and results will be disclosed to patients and professionals involved in this study. In addition, the data will be provided to the Brazilian Ministry of Health for future investments in this area.

Blinding

Due to the objectives of the study, the identity of the test and control treatments will not be known by the principal investigator, data collection personnel, laboratorial analysis laboratory or patients. The following study procedures will be applied to ensure triple blinding of study treatments. Furthermore, access to the randomization list will be strictly controlled. The treatment received by each person will be revealed after the completion of the clinical intervention and after completing the study database. During the study, blinding can only be broken in emergencies when knowledge of the patient's treatment group is necessary for patient management. When possible, the investigator should discuss the emergency with the treating physician before revealing which group the patient is in. Participants will be taken off study medication if necessary for their safety, or if the participant requires emergency surgery and information is requested about all treatment interventions – this is expected to occur very rarely if ever. Only in the event of an emergency where the participant cannot be adequately treated without knowing the identity of the study medication will this be disclosed.

Data analysis

A database will be built in an Excel® spreadsheet with double typing, followed by validation. Measures of central tendency and dispersion will be generated. The normality and homoscedasticity of the variables will be analyzed based on the Kolmogorov-Smirnov and Levene tests, respectively. Based on this information, we will enter the general linear model and repeated measures ANOVA (> 2 groups). In cases of associations of $p< 0.05$, linear regression will be performed.

Bias control

In order to minimize possible biases, the following covariates will be investigated: (1) Age: up to 30 years old; 31-65; > 65 years (model 1); (2) Sedentary lifestyle: yes or no (model 2); (3) Use of antihypertensive medication: yes or no (model 3).

CONTRIBUITIONS

Contributed to the conception or design of the study/research: Araújo MFM. Contributed to data collection: Lira Neto JCG. Contributed to the analysis and/or interpretation of data: Lira Neto JCG, Araújo MFM. Contributed to article writing or critical review: Lira Neto JCG, Araújo MFM. Final approval of the version to be published: Araújo MFM, Teixeira CRS, Paula ML, Serra MAAO.

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