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Review Article

A 3-Arm Placebo Randomized Controlled Trial Was Conducted To Evaluate The Impact Of Montmorency Tart Cherry And Blueberry Juice On Cardiometabolic Outcomes In Healthy Individuals.

Sinclair Jonathan, Gareth Shadwell, Stephanie Dillon, Robert Allan, Bobbie Butters and Lindsay Bottoms.

First Affiliated Hospital of Peking University, China.

Abstract

Cardiometabolic illness is the leading cause of global mortality and healthcare expense. Although pharmaceutical therapies are successful in the short term, their long-term efficacy is unclear and accompanying adverse effects are worrying. Montmorency tart cherries and blueberries contain significant quantities of anthocyanins, making them promising natural remedies for cardiometabolic disease. This project proposes a randomized controlled experiment to evaluate the impact of Montmorency tart cherry and blueberry juice on cardiometabolic outcomes compared to a placebo. This 20-day, parallel, single-blind, randomized, placebo-controlled experiment will enroll 45 participants.Participants will receive either 60 mL of Montmorency tart cherry juice, blueberry juice, or a placebo with a cherry/blueberry flavor. The study's primary outcome is the difference in systolic blood pressure between groups at baseline and after intervention. Secondary outcome measures will include differences in anthropometrics, energy expenditure, substrate oxidation, haematology, blood pressure/resting heart rate, psychological well-being, and sleep efficacy. The statistical analysis will be done on an intention-to-treat basis. This study has received ethical approval from the University of Central Lancashire's Health Research Ethics Committee (ref: HEALTH 0016) and is registered as a trial. The study's findings will be published in a renowned peer-reviewed journal.

INTRODUCTION

Cardiovascular disorders, type 2 diabetes, and related cardiometabolic diseases are the leading causes of global death and healthcare costs [1]. Cardiometabolic syndrome symptoms include hypertension, obesity, insulin resistance, atherogenic dyslipidemia, low high-density lipoproteins, high triglycerides, adiposity, high body mass index, big waist-to-hip ratio, and impaired glucose regulation [2]. To date, various pathophysiological biomarkers have appeared in the literature, with indications of oxidative stress. Nitric oxide and inflammation are identified as essential factors contributing to the clinical presentation of cardiometabolic illness [3, 4]. Angiotensin-converting enzyme inhibitors, betablockers, calcium antagonists, diuretics, and lipid-lowering medications are common traditional treatments for cardiometabolic disease [5]. Although these drugs are beneficial for treatment, Angiotensin-converting enzyme inhibitors, betablockers, calcium antagonists, diuretics, and lipid-lowering medications are common traditional treatments for cardiometabolic disease [5]. Although these drugs are beneficial in treating and preventing cardiometabolic disease, their long-term effects and cost-effectiveness have yet to be proven [6]. Additionally, major unfavorable side effects are common [7]. Recent research indicates that 84% of adults over the age of 57 take prescription medications on a daily basis, emphasizing the need for natural, cost-effective solutions to control cardiometabolic disease [8].

Improved eating habits have been shown to improve cardiometabolic health and are recommended as the major therapy for preventing and managing the condition [9]. Dietary interventions are more cost-effective and safer than short-term pharmacological drugs for treating and preventing metabolic disease, providing a clear rationale for their adoption (10). Fruit and vegetable-rich diets have been linked to reduced risk of cardiometabolic illness [11]. Maintaining a high-fruit and vegetable diet over time is challenging [12], so dietary supplements may be a more tempting option. Anthocyanins, prevalent in a variety of fruits and vegetables, contribute to their dark colors [13]. Anthocyanins found in Montmorency tart cherries, blueberries, strawberries, cranberries, and blackcurrants (dark fruits) have been linked

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to improved cardiometabolic health [14-16]. However, most peer-reviewed studies have focused on tart cherries. Supplementing with anthocyanin-rich tart cherries has been proven to reduce oxidative stress and inflammation [17,18-20], whereas blackberry supplementation increases fat oxidation rates [21]. Improved fat oxidation during rest and physical activity can lead to long-term alterations in body mass and composition, as well as improved insulin sensitivity [22]. Supplementing with anthocyanin-rich foods may enhance body composition and insulin management by increasing fat oxidation during rest and moderate activity. Anthocyanin-rich fruits have anti-inflammatory, anti-oxidative, and substrate trafficking effects that target chronic low-grade inflammation, pro-oxidant, and lipid-attenuating status, which are key factors in cardiometabolic pathophysiology [23]. However, analogous research on the impact of anthocyanin-rich fruit supplementation on cardiometabolic outcomes have generated mixed results. Tart cherry juice supplementation has not been demonstrated to improve cardiometabolic indices such as blood pressure and lipids, according to some research.Studies have shown improvements in insulin tolerance, cholesterol, systolic blood pressure, and low-density lipoprotein (LDL) cholesterol [24-27, 28-29]. Research on the effectiveness of various anthocyanin-rich supplements is mixed, with some indicating good effects on cardiometabolic outcomes [30-34] and others having no effect [35-38]. Currently, no randomized intervention trials have compared the effectiveness of various anthocyanin-rich fruit supplements on cardiometabolic outcomes. Research indicates that anthocyanin levels in dark fruits, including blueberries, are comparable to or higher than those in tart cherries [16]. Further research into this area could have practical and clinical implications.

Aims And Objectives

The study aimed to examine the effects of 20 days of twice-daily Montmorency tart cherry or blueberry juice supplementation on cardiometabolic health markers in healthy people with placebo. This randomized experiment aims to assess the effect of tart cherry and blueberry supplements on systolic blood pressure compared to placebo. The secondary goal is to evaluate how sour cherry juice and blueberry supplementation affect additional risk factors for cardiometabolic illness.

Hypotheses

The primary outcome shows that both Montmorency tart cherry and blueberry supplement groups reduce systolic blood pressure compared to the placebo, although there are no differences between the groups. Secondary results show that the Montmorency tart cherry and blueberry groups enhance cardiometabolic health measures compared to the placebo, although there are no significant differences between the two supplement groups.

MATERIALS AND METHODS

Described According To The Updated Guidelines For Reporting Parallel Group Randomized Trials [39]

Study Design And Setup

This study is a 20-day parallel, single-blind, randomized placebo-controlled trial (Figure 1). Following eligibility screening and enrollment, participants will learn about testing equipment, questionnaires, and procedures. A computer software (Random Allocation Software) will randomly assign participants to one of three groups: Montmorency tart cherry, blueberry or placebo. Cardiometabolic health and other indicators will be measured at baseline and 20 days after the intervention. The key outcome measure for cardiometabolic health trials is the difference in systolic blood pressure across groups from baseline to post-intervention [27]. Secondary outcome measures will be betweengroup variations in anthropometry, energy expenditure, and substrate oxidation.

Participants

Inclusion Criteria

Must be 18 years old or older, non-smoker, BMI < 30, and able to provide informed permission.

Exclusion Criteria

Pregnancy - Over 65 years old - Diabetes or uncontrolled hypertension Allergies to cherries or blueberries - Frequent consumption of blueberries or cherry products - Lack of regular medicine or antioxidant supplementation

Sample size

Power calculations were performed for the major outcome variable, which was the difference in systolic blood pressure between groups. A sample size of 45 is required for 80% power to detect a minimum significant clinical difference (MCID) of 6 mmHg between groups [40], with a predicted standard deviation of 5.5 mmHg in each group [41]. This assumes a 10% loss to follow-up rate.

Recruitment

Participants are likely to primarily come from the UK city of Preston and neighboring areas. Recruitment will take place through posters on university campuses, local workplaces, and social media marketing. Individuals interested in participating can email the research team for further information and questions about the study. Participants will be invited to attend an eligibility, enrollment, and familiarization session at the University of Central Lancashire.

Dietary Interventions

After the baseline data collecting session, participants will be given either Montmorency tart cherry, blueberry, or placebo concentrate. Participants will take 30 mL of supplement diluted in 100 mL of water twice day, once in the morning and again in the evening [27]. All supplements will be chilled throughout. A 30 mL dose of Montmorency tart cherry concentrate (energy: 102 kcal, carbohydrates: 25 g, sugars: 18 g, protein: 1.10 g, fiber: 2.6 g) contains approximately 320 mg of anthocyanins, as per the manufacturer (ActiveEdge, Hanwell, UK). Similarly, considering the manufacturers To prepare the placebo, mix 100% unflavored maltodextrin carbohydrates (MyProtein, Cheshire, UK) into drinking water using a magnetic stirrer (Stuart Scientific, UK) and stir bar (Fisher Scientific, Waltham, MA, USA). To generate a placebo concentrate, 666 g of maltodextrin will be mixed with water, yielding 20 g per 30 mL serving, similar to Montmorency tart cherry or blueberry concentrates. To match the color of the Montmorency tart cherry concentrate, an equal amount of red and black food coloring will be added, as well as an equal amount of red, blue, and black food coloring for the blueberry supplement. Add 1 mL of cherry or blueberry flavor drops (MyProtein, UK). Participants in the study will be advised to continue their usual diet and exercise regimens, and refrain from taking multivitamin or antioxidant supplements [24]. During the post-intervention data collecting session, participants will be requested to return any un-used supplements to the laboratory. This will determine the volume of supplement/placebo consumed (mL) and the percentage compliance in each group. To assess blinding effectiveness, participants will be asked to identify their assigned trial arm at the end of the post-intervention data collecting session. Both groups will be followed for loss of follow-up and any adverse outcomes.

Data Collection

Lab Visit Data

Measurements will be taken at the University of Central Lancashire's physiology lab twice, once at baseline and once after intervention. The University of Central Lancashire's laboratories are fully accredited by the British Association for Sport and Exercise Sciences. This means that they have undergone rigorous inspections, have reliable and well-maintained equipment, have qualified staff, and follow proper health and safety procedures.

Anthropometric Measurements

Body mass index (kg/m2) will be calculated using anthropometric measurements of mass and stature (without shoes). The stadiometer (Seca, Hamburg, Germany) will be used to measure stature, while weighing scales (Seca 875, Hamburg, Germany) will be used for mass measurement. Body composition will be measured using a phase-sensitive multifrequency bioelectrical impedance analysis device (Seca mBCA 515, Hamburg, Germany) [43]. This will enable for quantification of percentage body fat (%) and fat mass (kg). To calculate the waist-to-hip ratio, measure the waist circumference at the midpoint between the inferior margin of the last rib and the iliac crest, and the hip circumference at the point of maximum protrusion of the buttocks, without compressing the soft tissues [44].

Energy Consumption and Substrate Oxidation

During testing, respiratory gases will be collected using a gas analysis device (MetaLyser 3B, Cortex Biophysic, Leipzig, Germany). The University of Central Lancashire laboratory is air-conditioned and maintains a constant temperature of 20C. To measure resting energy expenditure and substrate oxidation, participants will lie supine for 20 minutes, with data retrieved and averaged over the last 17 minutes [45]. Resting fat and carbohydrate oxidation rates (g/min) will be measured using published stoichiometric formulas (Equations (1) and (2)), assuming little protein consumption [46].

Hematological Testing

Capillary blood samples will be taken via finger-prick using a disposable lancet and cleaned with a 70% ethanol wipe. Capillary triglyceride, total cholesterol, and glucose levels (mmol/L) will be measured using three handheld analyzers (MulticareIn, Multicare Medical, Washington, DC, USA) and a single handheld analyzer (HemoCue, Ängelholm, Sweden). LDL cholesterol (mmol/L) will be calculated using the Anandarja et al., [49] formula, which takes total cholesterol and triglycerides as inputs. In addition, HDL cholesterol (mmol/L) will be determined by rearranging the Chen et al., [50] equation to make HDL the product of the formulas.

Blood Pressure and Resting Heart Rate

After the resting energy expenditure test, blood pressure and resting heart rate will be measured while sitting erect. The study will use a non-invasive automated blood pressure monitor (OMRON M2, Kyoto, Japan) to measure peripheral systolic and diastolic blood pressure, as well as resting heart rate, in accordance with European Society of Hypertension standards [52]. Three readings will be collected, separated by a 1-minute interval [53]. The mean of the last two readings will be used for analysis.

Questionnaires

Sleep quality is reduced in patients with cardiometabolic disease [54], however dietary polyphenols [55] and Montmorency tart cherry supplementation have been shown to improve sleep quality and alleviate symptoms of insomnolence [56-57]. To evaluate sleep quality, we will use the Pittsburgh Sleep Quality Index [58], the Epworth Sleepiness Scale [59], and the Insomnia Severity Index [60]. These questionnaires will be used together to provide a comprehensive understanding of sleep efficacy. Research indicates that individuals with cardiometabolic disease have reduced psychological well-being [61], while a high intake of

dietary polyphenols has been linked to improved markers of psychological wellbeing [62].

Data Management

Data will be collected and stored in compliance with the Data Protection Act 2018. Data will be entered into electronic spreadsheets and saved on a secure university server using Microsoft OneDrive. All data will be kept secret and anonymized for review. Data and papers will be securely stored in a secured file cabinet throughout the study. After the study, the data will be transmitted to the University of Central Lancashire Research Data Archive (CLOK) and stored for 5 years. Electronic data will be erased after a specified period, while hard copies will be disposed of privately.

Statistical Analysis

All experimental data (save for subjective judgments of trial arm allocation) will be continuous and reported as mean and 95% confidence intervals. To compare the three groups at baseline, we will use linear mixed models with fixed factors and random intercepts based on participant information. The intervention-based data will be analyzed on an intention-to-treat basis, with all randomized participants included in the final analysis to the extent possible. Additionally, to assess the impact of the intervention on all outcome indicators,

The three groups will be compared using linear mixed models, with group as a fixed factor and random intercepts by participants. Baseline values will be changed as a continuous fixed covariate. In linear mixed models, the mean difference (b), t-value, and 95% confidence intervals will be provided. The effectiveness of blinding will be evaluated using a chi-squared (X-2) test. All analyses were performed using SPSS v27 (IBM, SPSS) and statistical significance was set at $p < 0.05$.

ETHICS AND DISSEMINATION

This study has been granted ethical approval by the University of Central Lancashire Health Research Ethics Committee (ref: HEALTH 0016) and formally registered as a trial (NCT04177238). Any required alterations to the experimental protocol will be sent for re-review/approval by the research ethics committee and amended at the trial registry. Participants who express a desire to see a summary of the trial findings will be provided with such information when the data have been analysed. Dissemination of the study findings from this investigation will be through publication in a leading peer-reviewed journal, and presentation at both national and international scientific conferences.

CONCLUSIONS AND LIMITATIONS

This protocol paper describes a placebo-controlled experiment to investigate the impact of Montmorency tart cherry and blueberry juice on the underlying causes of cardiometabolic disease and its associated comorbidities. Cardiometabolic conditions are a leading cause of global mortality and healthcare expenditure. This study suggests that anthocyanin-rich fruit supplementation may play a prophylactic role in healthy individuals.The trial protocol described in this work has limitations, as do all research protocols. To begin, in order to reduce both inter and intra-subject variability, the proposed strategy will have participants fast overnight. Data collection may not capture the whole vasomodulatory effect of experimental supplementation. Participants will receive storage and ingestion instructions, and compliance with each intervention group will be monitored by returning any unused supplements. However, it's impossible to predict how people stored or consumed their supplements. Blood pressure will be measured using standard techniques recommended by the European Society of Hypertension. Continuous blood pressure monitoring for 24 hours may be more effective and typical of daily life, while also reducing the risk of white-coat hypertension. Supplementing with anthocyanin-rich foods like Montmorency tart cherries or blueberries may improve cardiometabolic health by improving anti-inflammatory, antioxidant, and nitric oxide levels. Due to time and expense constraints, the proposed inquiry will not focus on pathophysiological biomarkers. As a result, the mechanisms behind any changes in cardiometabolic measures will remain unknown. Better understanding of the impact of anthocyanin-rich supplements on cardiovascular and metabolic health suggests that they can be more effectively used to improve cardiometabolic health throughout life. Future research should focus on the mechanisms of Montmorency tart cherry and blueberry supplementation, outside the scope of this study design.

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