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RESEARCH ARTICLE

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Dietary intake of anthocyanins improves arterial stiffness, but not endothelial function, in volunteers with excess weight: A randomized clinical trial

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Abstract

Excess body weight has been associated with endothelial dysfunction and increased arterial stiffness. Foods rich in polyphenols and anthocyanins such as açaí-juçara (*Euterpe edulis Martius*) fruit may have protective vascular effects. Thus, we examined the effect of dietary intake of anthocyanins (açaí-juçara fruit) on endothelial function (flow-mediated dilation [FMD]) and arterial stiffness (pulse wave velocity [PWV]) in individuals with excess body weight. Fifty-five individuals with BMI ≥25 kg/m^2 were randomized into non-anthocyanin (N-ATH, $n = 25$) or anthocyanin (ATH, $n = 30$) intake groups. A 12-week individualized diet plan (20% reduction in total energy intake) was prescribed and included daily intake of açaí-juçara 200 g (anthocyanins 293.6 mg) in the ATH diet plan. We evaluated anthropometric and biochemical parameters, FMD, PWV, and peripheral vascular resistance (PVR). A GEE (Bonferroni post-hoc) was used ($p \leq 0.05$). No change in FMD was observed. However, PWV showed a reduction from baseline in the ATH ($p = 0.002$) and vs. N-ATH ($p = 0.036$). Both groups showed reduced peripheral vascular resistance (N-ATH, $p = 0.005$; ATH, $p = 0.040$) with no significant differences between them. In conclusion, dietary intake of anthocyanins proved effective in protecting against arterial stiffness (by PWV) in individuals with excess weight. PVR was reduced in both diet groups regardless of dietary intake of anthocyanins.

KEYWORDS
açaí fruit, arterial health, flow-mediated dilation, pulse wave velocity

1 | INTRODUCTION

Excess weight is a leading risk factor for chronic non-communicable diseases, mostly cardiovascular diseases (Pouwels et al., 2019). In 2016, 1.9 billion adults (39% of the world's adult population) were suffering from excess weight. Of these, 650 million (13%) were obese (WHO, 2020). Obesity and excess visceral fat are accompanied by hormonal changes, high level of inflammation, endothelial dysfunction, and increased arterial stiffness among other adverse health conditions (Seravalle & Grassi, 2017).

Endothelial function is a predictor of cardiovascular disease (Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015), further in population with excess weight (Engin, 2017). It is thus a potentially important therapeutic target in hypertension, pathogenesis of atherosclerosis, and others cardiovascular risk factors. Flow-mediated dilation (FMD) is a low-cost, non-invasive, accurate ultrasound technique widely used for measuring endothelial function (Matsuzawa et al., 2015). In turn, arterial stiffness assessed by pulse wave velocity (PWV) may detect middle layer changes which are strongly associated with vascular aging (Alvim, Santos, Bortolotto, Mill, & Pereira, 2017).

Also, it has been suggested that vascular dysfunction along with increased arterial stiffness may be associated with obesity and cardiovascular diseases (Ben-Shlomo et al., 2014; Ohkuma et al., 2017). Some studies have reported increased arterial stiffness in adults with obesity when compared with eutrophic individuals (Sutton-Tyrrell et al., 2001; Wildman, Mackey, Bostom, Thompson, & Sutton-Tyrrell, 2003).

Evidence shows that dietary changes with intake of foods with high contents of bioactive compounds, such as anthocyanins, can improve vascular wall health of the intima (endothelial function) (Alqurashi, Galante, Rowland, Spencer, & Commane, 2016; Curtis et al., 2019) and middle layer (arterial stiffness) (Jennings et al., 2012). *Açaí-juçara* (*Euterpe edulis Martius*) is a *fruit* native to the Atlantic Forest in Brazil especially rich in anthocyanins (Schulz, Borges, Gonzaga, Oliveira Costa, & Fett, 2016), and contains minerals (phosphorus, potassium, calcium, magnesium, sulfur, iron, manganese, copper, zinc, sodium, boron, and cobalt) as well as fibers and vitamins C, B1, and B2. It is though widely consumed due to its high content of antioxidants, in particular anthocyanins. Thus, dietary intake of açaí-juçara may help improve vascular health (endothelial function and/or arterial stiffness).

Indeed, Alqurashi et al. (2016) examined the acute effects of dietary intake of conventional açaí (*Euterpe oleracea*) on endothelial function (assessed by FMD), reporting an 1.4% increase in FMD within two hours of a single serving of açaí smoothie (Alqurashi et al., 2016). However, to the best of our knowledge, there is no study examining medium/long-term effects of daily intake of açaí-juçara on vascular health, particularly in a population with excess body weight who used to present vascular and arterial stiffness alterations. Thus, we aimed to examine the effect of dietary intake of anthocyanins (açaí-juçara fruit) on endothelial function, measured by FMD, and arterial stiffness, measured by PWV, in individuals with excess weight. We hypothesized that this amount of açaí-juçara, rich in anthocyanins, is enough to improve endothelial function and arterial stiffness in this population.

2 | MATERIALS AND METHODS

We conducted an evaluator-blinded, parallel-group clinical trial following the *CONSORT* guidelines and the Declaration of Helsinki. This study was approved by the local institutional review (ID number: 5483/18; Date: June 18, 2018) and registered on "ClinicalTrials.gov" (ID NCT04434534).

2.1 | Outcomes

Endothelial function (assessed by FMD) and arterial stiffness (assessed by PWV) were the study primary outcomes: anthropometric parameters (body mass, body mass index [BMI], and waist circumference); lipid profile (total cholesterol, low density lipoprotein cholesterol [LDL-c], high density lipoprotein cholesterol [HDL-c], and triglycerides); glucose disorders parameter (fasting blood glucose, and glycated hemoglobin [HbA1c]); liver function markers (aspartate transaminase [AST], and alanine amino transaminase [ALT]); hemodynamic parameters (peripheral systolic and diastolic blood pressure [SBP and DBP], central systolic and diastolic blood pressure [cSBP and cDBP], pulse pressure [PP], augmentation index corrected for heart rate of 75 bpm [Aix@75], and peripheral vascular resistance [PVR]).

2.2 | Participants

The study was conducted from June 2018 to March 2020 at Clinical Research Laboratory (ICFUC). Recruitment was through advertisements and postings in newspapers with large circulation, and social media.

2.2.1 | Inclusion criteria

The study participants were adults (16 males and 39 females) 30–50 years, with overweight (BMI ≥25 and < 30 kg/m^2) or class 1 obese (BMI ≥30 and < 35 kg/m^2) (WHO, 2020) and insufficient or low level of physical activity (IPAQ long version; www.minu.ki.se).

2.2.2 | Exclusion criteria

There were excluded volunteers with infectious and inflammatory diseases, diabetes mellitus, recent cardiovascular events (in the preceding 3 months), chronic kidney failure, statin use, history of malignancy or life expectancy <2 years, smoker or alcohol users.

2.3 | Sample size

The calculation of the sample size was based on data from the study by Fairlie-Jones, Davison, Fromentin, and Hill (2017). This meta-analysis showed, as a chronic effect of anthocyanins consumption on FMD, a standardized mean difference of 0.84 (95% CI: 0.55–1.12). Thus, for an effect size of 0.84 (standardized mean difference), a statistical power of 80%, and at 5% significance level, we estimated that a sample of 48 volunteers would be necessary. We added 10% to cover losses totaling "$n = 27$/group" (for a total of 54 volunteers). This calculation was made using the online version of PSS Health (Borges et al., 2020).

2.4 | Randomization

A blinded staff member conducted a simple procedure of randomization by computer-generating a random numerical list (www.randomization.com) to two groups (1: non-anthocyanin intake [N-ATH]; 2: anthocyanin intake [ATH]). The investigators and volunteers

were blinded to group allocation before the start of the intervention (second visit); the random allocation of participants was kept in an inaccessible place and researchers did not have a priori knowledge of the intervention assignment to each participant. The study evaluators were also blinded to the participants' group allocation to minimize potential measurement biases.

2.5 | Visit 1

The volunteers were invited to take part in the study in a brief phone call. On visit 1, we explained them the study objective and intervention. Those who agreed to participate signed an informed consent form. To confirm the volunteers' status of overweight or obesity, we performed anthropometric measurements and BMI was stratified according to the literature (WHO, 2020). We also measured waist circumference using a stretch-resistant tape, and it was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, as describe in World Health Organization (WHO, 2008).

Although the diet plan was prescribed as an individualized diet with a 20% reduction of total energy – see "Intervention (diet plans)" section – it was very important in our study to know the volunteers' eating habits. So, the study nutritionists (TOPA and FG) carried out a food survey with a 24-h dietary recall (24HR) and diet history to better understand their meal patterns (Table 1, "Baseline time points"). Based on their reports, we set up an individualized diet plan adjusted to their daily intake to ensure more adherence.

2.6 | Visit 2

On visit 2, the participants fasted for 12 h overnight and came, between 8 and 9 a.m., for blood collection (total cholesterol, HDL-c, LDL-c, triglycerides, fasting blood glucose, HbA1c, aspartate transaminase, and alanine amino transaminase) at Clinical Research Laboratory (ICFUC). After 15 min rest, FMD and PWV techniques were performed in the same laboratory.

2.7 | Visit 3

Based on information collected in an entry interview and 24-h food recall (visit 2), a diet plan was prepared and adjusted to individual routines. On visit 3, we explained the diet plan to the volunteers and all their questions were answered. They were strongly recommended not to include food supplements of any kind (macronutrients, vitamins, or antioxidants), as well as not to change the level/pattern of physical activity during the study. Those assigned to the ATH group received an amount of açaí-juçara enough for 15 days. Then they would return to our clinical research laboratory (ICFUC) and get more fruit enough for another 15 days.

2.8 | Intervention (diet plans)

All volunteers (N-ATH and ATH groups) were prescribed individualized diets with 20% reduction in total energy value containing

TABLE 1 Nutritional patterns in 24-h dietary recall

	Baseline		Week 6		Post-intervention				
	N-ATH	ATH	N-ATH	ATH	N-ATH	ATH	*p*-value (group)	*p*-value (time)	*p*-value (interaction)
Total calories (kcal)	2,170 ± 435	1986 ± 211	1830 ± 353[a]	1,650 ± 253[a]	1,683 ± 253[a,b]	1,589 ± 237[a]	0.073	<0.001	0.262
Carbohydrates (g)	259 ± 84	231 ± 43	217 ± 71[a]	202 ± 45[a]	190 ± 56[a,b]	180 ± 41[a,b]	0.329	<0.001	0.093
Lipids (g)	84 ± 19	87 ± 38*	66 ± 13[a]	54 ± 13*[,a]	63 ± 13[a,b]	54 ± 14*[,a]	0.014	<0.001	0.523
Proteins (g)	95 ± 26	93 ± 30	92 ± 25	88 ± 30*	89 ± 27	92 ± 34	0.911	0.012	0.278
Fibers (g)	18 ± 7	17 ± 7	19 ± 6	20 ± 7	19 ± 5	21 ± 5	0.561	0.053	0.375
Saturated fat (g)	30 ± 8	26 ± 11*	26 ± 7[a]	21 ± 6*[,a]	24 ± 6[a,b]	20 ± 5*[,a]	0.013	<0.001	0.039
Monounsaturated fat (g)	24 ± 10	19 ± 13*	23 ± 9	17 ± 4*	21 ± 7[a]	18 ± 2*	0.005	0.217	0.067
Polyunsaturated fat (g)	9 ± 6	10 ± 10	10 ± 4	10 ± 5	11 ± 4	11 ± 4	0.892	0.090	0.629
Sodium (mg)	2,190 ± 1,040	2,267 ± 1,103	1818 ± 692[a]	2,173 ± 578[a]	1702 ± 542[a,b]	2035 ± 371[a]	0.185	<0.001	0.967
Calcium (mg)	569 ± 290	563 ± 267	562 ± 157	594 ± 160	641 ± 130[b]	661 ± 207[b]	0.518	<0.001	0.879
Iron (mg)	14 ± 5	11 ± 5	15 ± 4	13 ± 5	16 ± 4[a]	15 ± 4[a]	0.216	<0.001	0.904
Magnesium (mg)	234 ± 68	226 ± 91	254 ± 64	227 ± 70	288 ± 62	254 ± 64	0.247	0.001	0.571
Potassium (mg)	2,092 ± 573	2,279 ± 1,070	2,132 ± 550	2,249 ± 747	2,528 ± 551	2,421 ± 518	0.726	0.050	0.384
Vitamin A (mcg)	241 ± 154	265 ± 184	209 ± 172	283 ± 268	317 ± 268	277 ± 231	0.673	0.397	0.411
Vitamin C (mg)	72 ± 63	75 ± 58	86 ± 72	85 ± 52	108 ± 66	101 ± 52	0.961	0.021	0.790
Vitamin E (mg)	8.2 ± 6.6	9.5 ± 7.2	9.3 ± 5.0	10.9 ± 8.7	9.0 ± 3.1	8.2 ± 2.8	0.701	0.341	0.552

Abbreviations: ATH, anthocyanin intake; N-ATH: non-anthocyanin intake.

Note: Data described as mean ± standard deviation. Intention-to-treat approach and generalized estimating equations (GEE) followed by Bonferroni were used to test for differences ($p \le 0.05$). *$p \le 0.05$ vs. N-ATH group at the same time point; [a]$p \le 0.05$ vs. baseline; [b]$p \le 0.05$ vs. week 6.

55–60% carbohydrates, 15–20% protein, and 20–30% fat. Meal plans were developed by a nutritionist (TOPA) using a nutrition software (DietBox). In addition to a 20% reduction of total energy and macronutrient intake as described above, diet plans were designed based on information collected during Visit 1, including meal times, commonly consumed foods, household measures used, knowledge about industrial packaging, and food preparation techniques, among others. All plans were quite similar, except for daily intake of açaí-juçara 200 g in the ATH group (Table S1). Açaí-juçara pulp from a single batch was supplied by the study team (to ensure similar characteristics). The pulp chemical composition was as follows: anthocyanins 293.6 mg per 200 g; and total polyphenols 1,370 mg per 200 g. Thus, the daily amount of anthocyanins in our intervention is in accordance with the literature (Curtis et al., 2019; Fairlie-Jones et al., 2017; Park, Choi, & Lee, 2021). We also emphasize that there was no co-intervention.

2.9 | Patient compliance

Two nutritionists (TOPA and FG) contacted volunteers by phone on a biweekly basis to discuss their diet. They also were asked to attend face-to-face consultations every 3 weeks and could reach out the site staff through email or WhatsApp for any queries. The nutritionists cleared up any doubts about food consumption in their diet plans and stressed out the importance of adhering to the study procedures, recommendations and proposed interventions as detailed at the study entry as well as not adding any food supplements (macronutrients, vitamins, or antioxidants) and not engaging in any exercise programs during the study.

2.10 | Flow-mediated dilation of the brachial artery

We used a high-resolution Doppler ultrasound system (Esaote MyLab™ 70 XVision; Genoa, Italy) for non-invasive assessment of endothelial function. A high-frequency transducer (7–12 MHz) was used to acquire longitudinal images of the brachial artery walls according to Thijssen et al. (2011). Real-time Doppler ultrasound images were recorded and stored into an USB video card (EasyCAPture; China) connected to a computer for offline data analysis using an edge-detection and wall-tracking software program (Cardiovasculare Suit™; Pisa, Italy). Baseline video signals were recorded for 1 min. A rapid deflation cuff (Incoterm™ EC500; Porto Alegre, Brazil) was placed around the forearm 5 cm distal to the antecubital fossa and the forearm cuff was inflated to 200 mmHg for five minutes. Images were recorded for three minutes after cuff deflation. Blood flow was calculated at 30 Hz from the synchronized brachial artery diameter and blood flow velocity data. FMD was calculated as the percentage change in peak diameter after cuff deflation from baseline. FMD measurements were performed on visit 2 and at the end of the intervention period (12 weeks).

2.11 | Central blood pressure parameters

Pulse wave velocity (PWV), pulse pressure (PP), central (cSBP/cDBP) and peripheral (SBP/DBP) blood pressure, and peripheral vascular resistance (PVR) were assessed using a validated oscillometric Mobil-O-Graph 24hPWAMonitor® device (IEM GmbH, Stolberg, Germany) (Hametner et al., 2013; Trachet et al., 2010) at Clinical Research Laboratory (ICFUC). With the cuff placed around the participant's arm, three automated readings were made at intervals of 3 min. Arterial stiffness, measured by PWV, was estimates were derived from in-built ARCSolver algorithms. All analyses were performed on visit 2 and at the end of the intervention period (12 weeks).

2.12 | Statistical analysis

A Shapiro–Wilk test was used to confirm that all variables were normally distributed. Data were described as mean ± SD and/or confidence intervals (95% CI).

We used an intention-to-treat approach to the analysis and the differences were tested by generalized estimating equations (GEE) with two factors (groups and time; group x time interaction), and Bonferroni post-hoc. In a further analysis, we used Student's *t*-test to compare two independent samples and evaluate potential differences for mean differences (Δ). Also, we applied Pearson correlation as follows: none (≤0.29); weak (0.30–0.49); moderate (0.50–0.69), strong (0.70–0.79), and very strong (≥0.80), and we calculated Cohen's d effect size for FMD and PWV (baseline vs. post-intervention): none (≤0.19); small (0.20–0.49); moderate (0.50–0.79); and large (≥0.80). Lastly, we performed an analysis of covariance adjusted for the variables that showed baseline differences between the groups to control for confounders.

Data were analyzed using SPSS version 24, with $p \leq 0.05$ for all tests.

3 | RESULTS

Seventy-three volunteers with excess body weight were eligible to take part in our study. The study was conducted between June 2018 and March 2020 (recruitment and follow-up). Of these, 72 were randomly assigned to the study groups. Randomization and group allocation was not affected by any changes due to potential food intolerance or adverse events of the intervention (200 g/day of açaí-juçara). Thus, 55 volunteers (N-ATH, $n = 25$; ATH, $n = 30$) completed the 12-week dietary intervention (Figure 1). Their mean age was 38.8 ± 6.4 years. Also, all subjects reported insufficient or low level of physical activity as measured by the IPAQ, totaling 378 minutes. week^{-1} (~1,687 kcal.week^{-1}) at work, at home and during leisure time.

Table 2 shows anthropometric characteristics, lipid profile, fasting blood glucose, glycated hemoglobin and markers of liver function of

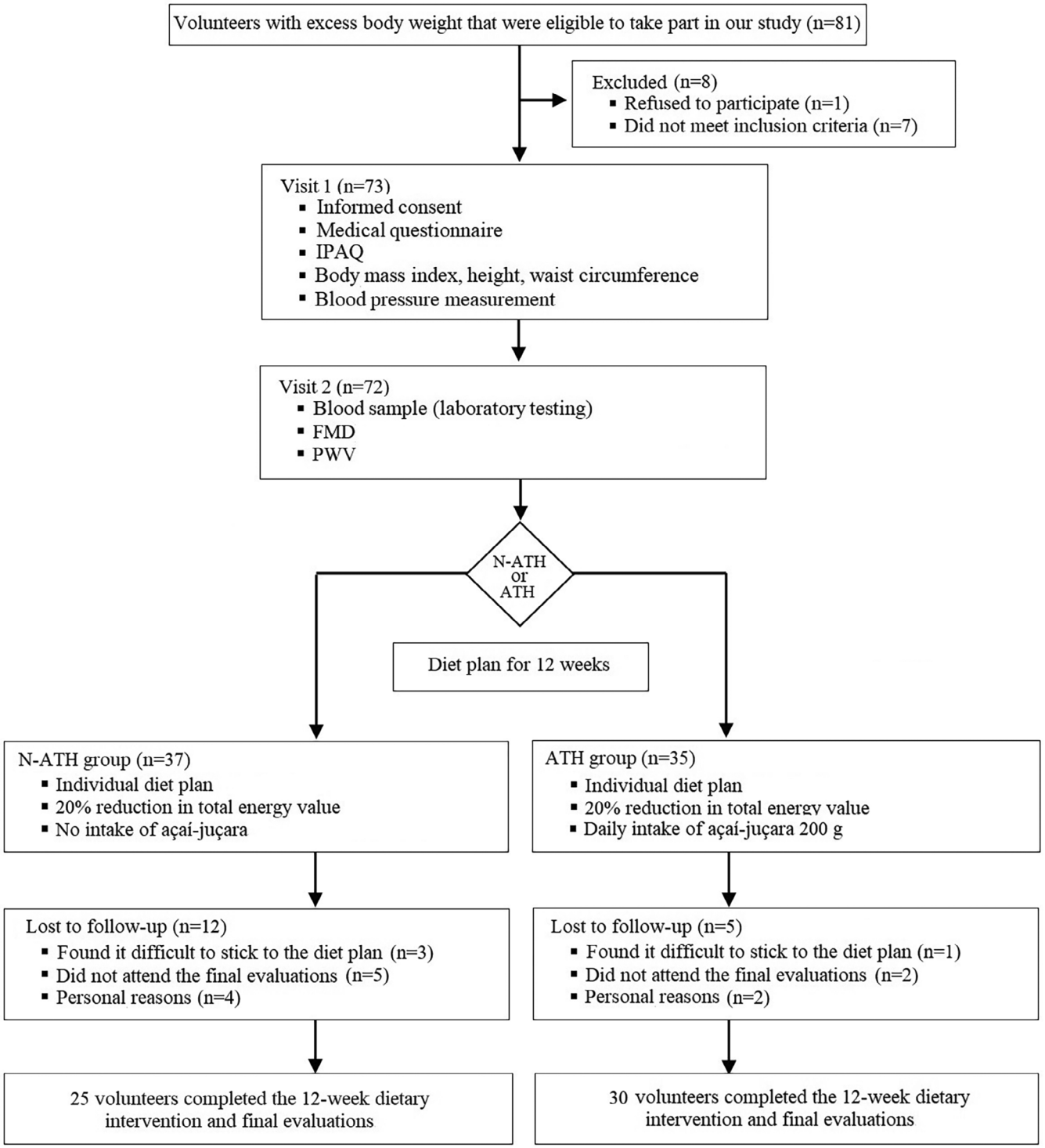

FIGURE 1 Study design. ATH, anthocyanin intake group; FMD, flow-mediated dilation; N-ATH, non-anthocyanin intake group; PWV, pulse wave velocity.

the study participants. After intervention period, both groups showed a reduction in total body weight, BMI and waist circumference measures from baseline (N-ATH and ATH, $p < 0.001$ for all comparisons) with no difference between them. Lipid profile, fasting blood glucose, glycated hemoglobin, and markers of liver function did not show any relevant changes post-intervention.

Peripheral and central blood pressures, and FMD are summarized in Table 3. There were no significant changes throughout the study (between groups and/or times) in resting artery diameter (pre-cuff occlusion), peak artery diameter (hyperemia after cuff release) and FMD. Also, pulse pressure was reduced only in the ATH group (baseline vs. post-intervention, $p = 0.002$) and lower when compared to

TABLE 2 Anthropometric parameters, lipid profile, and liver function markers of the study participants

	N-ATH ($n = 25$)			ATH ($n = 30$)						
	Baseline	Post-intervention	Δ	Baseline	Post-intervention	Δ	*p*-value (group)	*p*-value (time)	*p*-value (interaction)	Difference for mean difference (Δ)
Body mass (kg) (95% CI)	85.8 ± 15.0 (80.0; 91.5)	82.9 ± 14.6[a] (77.2; 88.3)	−2.9 (−4.3; −1.7)	87.3 ± 15.2 (82.0; 92.5)	83.8 ± 14.5[a] (78.8; 88.9)	−3.5 (−4.4; −2.4)	0.742	<0.001	0.602	0.678
BMI (kg/m^2) (95%CI)	32.7 ± 4.7 (30.5; 34.1)	31.1 ± 4.8[a] (29.3; 33.0)	−1.1 (−1.6; −0.7)	31.3 ± 3.9 (29.9; 32.7)	30.0 ± 3.8[a] (28.7; 31.3)	−1.3 (−1.7; −0.9)	0.358	<0.001	0.651	0.624
Waist circumference (cm) (95%CI)	99.8 ± 10.8 (95.6; 104.0)	95.6 ± 11.8[a] (91.1; 100.1)	−4.2 (−6.5; −1.9)	100.5 ± 9.6 (97.2; 103.8)	95.3 ± 8.3[a] (92.5; 98.2)	−5.2 (−7.0; −3.4)	0.937	<0.001	0.501	0.526
Total cholesterol (mg/dL) (95%CI)	187 ± 42 (170; 203)	184 ± 28 (173; 196)	−3 (−12; 8)	201 ± 38 (187; 215)	198 ± 35 (185; 211)	−3 (−12; 6)	0.133	0.463	0.921	0.723
LDL-c (mg/dL) (95% CI)	110 ± 35 (97; 123)	117 ± 28 (105; 128)	7 (−16; 3)	123 ± 34 (110; 135)	119 ± 28 (109; 130)	−3 (−12; 6)	0.355	0.618	0.144	0.128
Triglycerides (mg/dL) (95%CI)	105 ± 53 (82; 128)	92 ± 35 (79; 106)	−38 (−85; 9)	132 ± 83 (103; 161)	135 ± 84 (105; 165)	3 (−9; 15)	0.301	0.154	0.100	0.101
HDL-c (mg/dL) (95% CI)	50 ± 13 (45; 55)	49 ± 8 (46; 52)	−1 (−4; 1)	52 ± 15 (46; 57)	52 ± 14 (47; 57)	0 (−2; 3)	0.431	0.498	0.330	0.327
Fasting blood glucose (mg/dL) (95%CI)	94 ± 7 (91; 97)	92 ± 7 (89; 95)	−2 (−5; 1)	90 ± 7* (87; 93)	89 ± 7 (87; 92)	1 (−2; 2)	0.040	0.210	0.408	0.424
HbA1c (%) (95%CI)	5.5 ± 0.3 (5.4; 5.6)	5.6 ± 0.3 (5.5; 5.7)	0.1 (−0.4; 0.2)	5.3 ± 0.4 (5.2; 5.5)	5.5 ± 0.5 (5.3; 5.7)	0.2 (0.0; 0.3)	0.158	0.071	0.346	0.365
AST (μ/L) (95%CI)	18.8 ± 5.4 (16.7; 20.8)	18.5 ± 5.2 (16.5; 20.5)	−0.3 (−2.2; 1.8)	19.1 ± 6.6 (16.8; 21.4)	19.2 ± 6.2 (17.0; 21.4)	0.1 (−2.1; 2.4)	0.698	0.938	0.815	0.831
ALT (μ/L) (95%CI)	22.4 ± 10.5 (18.3; 26.4)	22.2 ± 10.9 (18.0; 26.4)	−0.2 (−3.2; 2.9)	22.0 ± 13.6 (17.3; 26.8)	20.9 ± 11.7 (16.8; 25.0)	−1.1 (−5.4; 3.2)	0.770	0.632	0.719	0.705

Note: Data described as mean ± standard deviation and 95% confidence interval (95%CI). Intention-to-treat approach and generalized estimating equations (GEE) followed by Bonferroni were used to test for differences ($p \leq 0.05$). *$p \leq 0.05$ vs. N-ATH group at the same time point; [a]$p \leq 0.05$ vs. baseline. Difference for mean difference (Δ) was tested by Student's *t*-test comparing two independent samples (N-ATH vs. ATH).

Abbreviations: LT, alanine amino transaminase; AST, aspartate transaminase; ATH, anthocyanin intake; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; N-ATH, non-anthocyanin intake.

TABLE 3 Peripheral and central blood pressure, and flow-mediated dilation measurements

	N-ATH ($n = 25$)			ATH ($n = 30$)			*p*-value (group)	*p*-value (time)	*p*-value (interaction)	Difference for mean difference (Δ)
	Baseline	Post-intervention	Δ	Baseline	Post-intervention	Δ				
SBP (mmHg) (95%CI)	123 ± 13 (117; 127)	122 ± 13 (116; 127)	−1 (−4; 3)	12 0 ± 12 (116; 124)	117 ± 8 (114; 120)	−3 (−6; 1)	0.255	0.215	0.346	0.372
DBP (mmHg) (95%CI)	77 ± 8 (74; 80)	78 ± 9 (75; 81)	1 (−3; 2)	77 ± 10 (73; 80)	78 ± 8 (75; 81)	1 (−1; 4)	0.891	0.251	0.674	0.609
Resting artery diameter (mm) (95%CI)	3.78 ± 0.86 (3.43; 4.08)	3.74 ± 0.17 (3.40; 4.08)	−0.04 (−0.23; 0.21)	3.76 ± 0.90 (3.44; 4.09)	3.69 ± 0.70 (3.46; 4.10)	0.07 (−0.24; 0.27)	0.917	0.972	0.877	0.905
Peak artery diameter (mm) (95%CI)	4.07 ± 1.02 (3.64; 4.46)	4.03 ± 0.17 (3.70; 4.35)	−0.04 (−0.24; 0.20)	4.04 ± 0.90 (3.71; 4.38)	4.00 ± 0.70 (3.78; 4.38)	0.04 (−0.23; 0.30)	0.919	0.943	0.737	0.936
FMD (%) (95%CI)	7.9 ± 16.0 (1.5; 14.3)	9.2 ± 10.0 (5.1; 13.2)	1.3 (−6.5; 9.0)	7.1 ± 5.1 (5.1; 9.0)	9.1 ± 7.1 (6.1; 11.6)	2.0 (−1.6; 5.2)	0.773	0.484	0.908	0.445
cSBP (mmHg) (95%CI)	125 ± 13 (120; 130)	125 ± 14 (120; 131)	0 (−3; 4)	121 ± 12 (117; 125)	120 ± 8 (117; 123)	−1 (−4; 2)	0.110	0.796	0.521	0.556
cDBP (mmHg) (95%CI)	79 ± 8 (75; 82)	79 ± 9 (76; 83)	0 (−2; 3)	78 ± 10 (74; 81)	79 ± 8 (76; 82)	1 (−1; 4)	0.779	0.280	0.702	0.634
Pulse pressure (mmHg) (95%CI)	44.3 ± 9.4 (40.5; 48.1)	43.8 ± 9.3 (40.0; 47.6)	−0.5 (−3.2; 2.2)	44.0 ± 11.0 (40.0; 48.2)	39.5 ± 6.6*a (36.9; 42.0)	−4.8 (−7.9; −1.7)	0.273	0.011	0.042	0.050**
Aix@75 (%) (95%CI)	16.8 ± 11.1 (12.2; 21.4)	16.9 ± 8.6 (13.3; 20.4)	0.1 (−3.0; 3.1)	19.6 ± 7.9 (16.5; 22.6)	16.0 ± 8.6 (12.7; 19.3)	−3.7 (−7.9; −0.3)	0.675	0.123	0.107	0.115

Note: Data described as mean ± standard deviation and 95% confidence interval (95%CI). Intention-to-treat approach and generalized estimating equations (GEE) followed by Bonferroni were used to test for differences, $^{*}p \leq 0.05$ vs. N-ATH group at the same time point; $^{a}p \leq 0.05$ vs. baseline. The difference for mean difference (Δ) was tested using Student's *t*-test to compare two independent samples (N-ATH vs. ATH). $^{**}p \leq 0.05$ vs. N-ATH group.

Abbreviations: Aix, augmentation index corrected for a heart rate of 75 bpm; ATH, anthocyanin intake; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; FMD, flow-mediated dilation; N-ATH, non-anthocyanin intake; SBP, systolic blood pressure.

the N-ATH (Δ4.3 mmHg; $p = 0.036$). Any difference for mean difference was assessed and the result was also confirmed (Table 3). ATH group showed a reduction in PWV from baseline (Δ−0.60 m/s; effect size of 1.20) as well as N-ATH group (Δ−0.30 m/s and effect size of 0.35). Also, PWV was reduced in the ATH compared to the N-ATH group (Δ−0.52 m/s) (Figure 2a). Peripheral vascular resistance (PVR) was reduced in both groups from baseline, but with no significant difference between them (Figure 2b).

We found a strong correlation between PWV and age ($r = 0.779$; $p < 0.001$), but a weak correlation between PWV and waist circumference ($r = 0.316$; $p = 0.001$). Pulse pressure showed a weak correlation with total body weight ($r = 0.460$; $p < 0.001$).

Finally, we performed an analysis adjusted for the variables (saturated and monounsaturated fat) that showed baseline differences between the groups (Table 1) for controlling for potential confounders. There was no influence of lipids on FMD, PWV, PVR, or PP.

4 | DISCUSSION

The main finding of our study was that daily intake of açaí-juçara 200 g (containing anthocyanins 293.6 mg and total polyphenols 1,370 mg) for 12 weeks improved arterial stiffness by decreasing PWV and PVR. There was no statistically significant change in FMD throughout the study for both groups. Also, both N-ATH and ATH groups showed a reduction in total body weight, BMI, and waist circumference measures. Thus, our hypothesis of improvements in endothelial function (FMD) and arterial stiffness (PWV) in response to medium/long-term daily intake of anthocyanins (by açaí-juçara) is partially confirmed.

Our results are clinically important because a 1% increase in FMD is associated with a 4% reduction in cardiovascular risk in healthy and asymptomatic adults (Ras, Streppel, Draijer, & Zock, 2013) and in individuals with increased cardiovascular risk, such as those with excess weight, the risk reduction may be greater as a 1% increase in FMD is associated with a 13% reduction in cardiovascular risk (Inaba, Chen, & Bergmann, 2010). Thus, even with no statistically significant changes in FMD, there was a Δ2% improvement (absolute value) in the ATH group (based on 70% statistical power). Besides, PWV and PVR are linked to major cardiovascular outcomes and other cardiovascular risk factors such as obesity (Ohkuma et al., 2017).

Evidence shows PWV is a predictor of adverse cardiovascular events (Ben-Shlomo et al., 2014). An 1 m/s increase in PWV is associated with a 12% increase in cardiovascular risk (Ohkuma et al., 2017). Progressive damage of the arterial wall leads to greater stiffness and, consequently, decreased vascular distensibility. Decreased vascular distensibility leads to increased pulse pressure that may increase the risk for developing cardiovascular diseases such as atherosclerosis and acute myocardial infarction (Ben-Shlomo et al., 2014). We found a 0.6 m/s decrease in PWV in the ATH group (based on 99% statistical power), which further supports the clinical importance of our dietary intervention. Increased *inflammation* in the *adipose tissue* of individuals with obesity contributes to increased arterial stiffness and increased

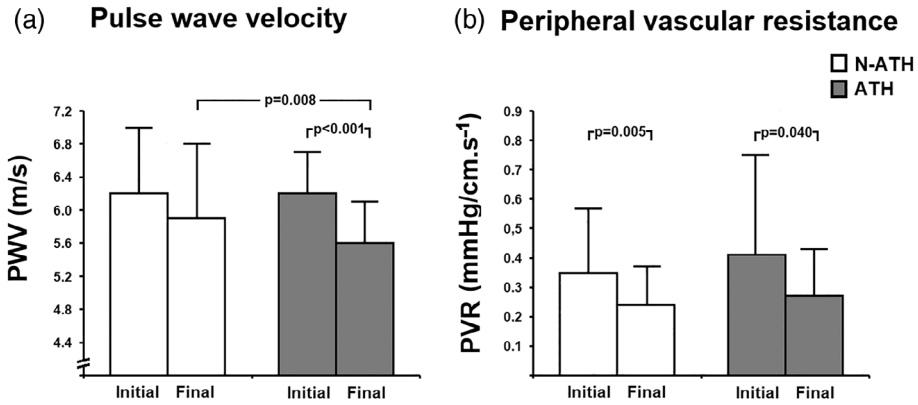

FIGURE 2 Pulse wave velocity (Panel A) and peripheral vascular resistance (Panel B). N-ATH: non-anthocyanin intake ($n = 25$); ATH: anthocyanin intake ($n = 30$). Data described as mean ± standard deviation. Generalized estimating equations (GEE) followed by Bonferroni was used to test for differences ($p \leq 0.05$)

blood pressure regardless of age (Nowak, Rossman, Chonchol, & Seals, 2018). Dietary changes may reduce arterial stiffness, assessed by PWV (Crichton, Elias, Dore, Abhayaratna, & Robbins, 2012), as seen in our study. This was demonstrated by a weak correlation between PWV and waist circumference and total body weight. However, we believe that, rather than changes in body composition, improvements in dietary quality throughout the study (reduction in total lipids and saturated fat; see Table 1) favored positive changes in PWV and PVR. In other words, improvements in the nutritional quality of foods may have a cardioprotective effect associated with PWV and PVR.

Studies with foods rich in phenolic acids, especially the flavonoid subclass, such as anthocyanins, have demonstrated vascular protection and increased arterial compliance (Curtis et al., 2019; Jennings et al., 2012). Our results demonstrated that daily intake of açaí-juçara 200 g can improve vascular response and arterial distensibility through a significant reduction in pulse pressure and PWV. A review of two cross-sectional studies and 12 randomized clinical trials examining the relationship between arterial stiffness and flavonoid intake reported that anthocyanins together with isoflavones and cocoa-derived flavonoids proved to be the most effective in improving arterial stiffness assessed by PWV (Fairlie-Jones et al., 2017). Our findings are in line with the literature as açaí-juçara high content of anthocyanins and polyphenols apparently lead to a decrease in PWV.

PVR was reduced in both groups from baseline with no significant difference between them. It should be noted that both the N-ATH and ATH groups followed low-calorie diet plans, an intervention aimed at weight loss, improving nutrition and macronutrient balance and reducing consumption of saturated fat, sodium, and processed foods. PVR favorable results were likely related to body weight loss and improved nutritional quality of foods consumed as reported in the literature (West et al., 2010). PVR changes have a direct impact on blood pressure levels as increased PVR leads to hemodynamic overload (AlGhatrif, Wang, Fedorova, Bagrov, & Lakatta, 2017). Thus, similar interventions may help decrease PVR by reducing pressure overload in the cardiovascular system and have clinically meaningful benefits.

Endothelial dysfunction is a well-established response in individuals with hypertension (Higashi, Kihara, & Noma, 2012) and to a lesser extent in those with obesity (Engin, 2017). Despite their excess weight, the volunteers in our sample showed normal blood pressure levels (Table 3). Thus, our finding of non-significant change of FMD measurements may be due to the fact that the volunteers in our sample did not have hypertension. Also, improvements in FMD can lower the risk of fatal and non-fatal cardiovascular events. Although the effect on endothelial function assessed by FMD was not statistically significant in our study, a small increase in FMD (1%) is associated with a 13% reduction in cardiovascular risk including in individuals with excess weight (Inaba et al., 2010). Thus, our findings on endothelial function can be interpreted positively as there was a Δ2% increase in FMD in the ATH group (based on 70% statistical power), when compared to the N-ATH group. In line with our findings, van Mierlo, Zock, van der Knaap, and Draijer (2010) found no improvement in FMD in response to polyphenol intake in healthy men. While our samples had different characteristics, we agree on the clinical importance of our results. Few studies have explored the mechanisms involved in the long-term effects of anthocyanin-rich foods on FMD. However, up-regulation of endothelial nitric oxide synthase (eNOS) (which is important for NO synthesis) (da Costa et al., 2012), increase in total antioxidant capacity, reduced activation of endothelial cells via vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (de Liz et al., 2020; Monteiro et al., 2020) are believed to be the most important ones. As a result, there is likely a reduction in circulating endothelial microvesicles (markers of endothelial cell injury) (Horn et al., 2014) and an increase in the number of progenitor cells circulating in the peripheral blood (Aleksinskaya et al., 2013), which may increase the number of progenitor endothelial cells (replacing damaged endothelial cells) (Asahara et al., 1997). Among the factors mentioned to produce improvements in FMD, an increase in NO viability along with the elastin content and a reduction in diastolic blood pressure are potential mechanisms involved in the reduction of arterial stiffness following the consumption of polyphenol-rich diets (De Bruyne et al., 2019). However, these mechanisms need to be explored further in other studies of açaí-juçara.

As for anthropometric parameters, we found a reduction in total body weight, BMI, and waist circumference measures in both the N-ATH and ATH groups from baseline with no difference between the groups. Improvements in anthropometric parameters in individuals

with excess weight, as seen in our study, can have cardiovascular benefits (Jenkins et al., 2017). Interestingly, the consumption of açaí-juçara did not lead to reduction of obesity criteria (Table 2). We believe that, in our study, the mechanisms for reducing BMI, total body weight and waist circumference were not associated with increased intake of foods rich in anthocyanins and polyphenols. A meta-analysis conducted by Park et al. (2021) examined the effects of anthocyanin supplementation on reduction of obesity criteria with no concomitant dietary intervention. The authors found a modest reduction in BMI (0.36 kg/m^2; 95% CI −0.58 to −0.13) including in individuals with diabetes mellitus, non-obesity, overweight, obesity, dyslipidemia, and cardiovascular disease. However, when they analyzed only individuals with obesity, as in our sample, anthocyanin supplementation was not effective in reducing BMI (Park et al., 2021), which is consistent with our findings. In addition, there was no change in total body weight or waist circumference regardless of baseline BMI classification. Our results and Park et al. findings (2021) show that anthocyanin intake alone does not seem to reduce classic obesity criteria (BMI, total body weight and waist circumference), suggesting that caloric restriction and quality foods are more important factors for weight reduction than these criteria.

It is noteworthy that there were no adverse effects or events in our study, particularly in the ATH group. Pure açaí-juçara pulp taste is bitter and unpleasant, so it was taken mixed with sweet fruit juice with a high glycemic load —the extra calories from the juice were included in the diet plan. The glycemic load indicates how much foods raise blood glucose levels after eating and increased glucose and/or glycated hemoglobin levels would be expected by the end of the intervention. However, this assumption was not verified. In addition, complaints of gastric discomfort and/or abnormal liver function were expected in our sample especially among those who have never tried açaí pulp, but they were not verified either.

Our study has some limitations. *Oxidative stress and inflammation*: Though not an objective of our study, an examination of oxidative stress and inflammation would have added value to our results. *Intervention*: It proved difficult for some participants to follow a low-calorie healthy diet and keep healthy habits as they were used to eating fast-food meals. Some also reported difficulty taking açaí drink during winter time. To ensure its nutritional properties frozen fruit pulp must be consumed before complete meltdown with no heating treatment. *Sample size*: The estimated sample size was 54 volunteers (27 per group) with FMD parameter as the outcome. Since FMD technique entails real-time Doppler ultrasound imaging recordings, some images are not suitable and are not analyzed, though this does not occur in the assessment of PWV. Thus, a common practice of our group is to include more individuals in addition to the sample size. However, one group can be larger than others due to dropouts, losses of imaging recordings etc. In our study, there were 25 volunteers in the N-ATH group and 30 in the ATH group. We expected to achieve a sample size of 27 individuals per group, so we recalculated the statistical power reaching 70% for FMD and 99% for PWV (both variables of interest in the study objective). Thus, despite this size difference between the two groups, they were considered adequate for our analyses and did not affect the results.

In conclusion, dietary intake of anthocyanins and polyphenols in açaí-juçara fruit (293.6 mg anthocyanins and 1,370 mg total polyphenols) proved effective in protecting against arterial stiffness, but it had no additional benefit of weight loss in individuals with excess weight. Peripheral vascular resistance was reduced in both diet groups regardless of dietary intake of anthocyanins. In addition, there was no statistically significant change in FMD throughout the study for both groups. However, our results may suggest a clinically relevant in FMD parameters (>1% in the ATH group) that they should be addressed in future studies. It should be stressed that our study focused on individuals with overweight and obesity and our results cannot be generalized to other populations.

We encourage that new evidence-based nutritional approaches including fresh or minimally processed foods, such as açaí-juçara, might be an alternative to be developed. Dietary intake of foods rich in anthocyanins and polyphenols could be further examined for their health benefits including cardiovascular risk reduction.

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CONFLICT OF INTEREST

The authors declare that no competing interest.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material.

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