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Randomized Control Trials

Consumption of peanut products improves memory and stress response in healthy adults from the ARISTOTLE study: A 6-month randomized controlled trial☆

Isabella Parilli-Moser [a, b, c], Inés Domínguez-López [a, b, c], Marta Trius-Soler [a, b, c], Magda Castellví [e], Beatriz Bosch [e], Sara Castro-Barquero [c, d], Ramón Estruch [c, d], Sara Hurtado-Barroso [a, b, c, **], Rosa M. Lamuela-Raventós [a, b, c, *]

[a] Department of Nutrition, Food Sciences and Gastronomy, XIA, School of Pharmacy and Food Sciences, University of Barcelona, 08028, Barcelona, Spain
[b] INSA-UB, Nutrition and Food Safety Research Institute, University of Barcelona, 08921, Santa Coloma de Gramanet, Spain
[c] CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, 28029, Madrid, Spain
[d] Department of Internal Medicine, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, 08036, Barcelona, Spain
[e] Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036, Barcelona, Spain

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SUMMARY

Background: Peanuts are rich in bioactive compounds that may have a positive impact on memory and stress response.
Objective: To evaluate the effect of regular consumption of peanut products on cognitive functions and stress response in healthy young adults.
Design: A three-arm parallel-group randomized controlled trial was conducted in 63 healthy young adults that consumed 25 g/day of skin roasted peanuts (SRP, n = 21), 32 g/d of peanut butter (PB, n = 23) or 32 g/d of a control butter made from peanut oil (free of phenolic compounds and fiber) (CB, n = 19) for six months. Polyphenol intake, cognitive functions, and anxiety and depression scores were evaluated using validated tests. Fecal short-chain fatty acids (SCFAs) and plasma and fecal fatty acids were assessed by chromatographic methods. Urinary cortisol was quantified by an enzymatic method.
Results: Comparing the two interventions with the control, a significant reduction in anxiety scores was observed in the SRP compared to the CB group. After the intervention, consumers of SRP and PB had an improved immediate memory ($p = 0.046$ and $p = 0.011$). Lower anxiety scores were associated with SRP and PB ($p < 0.001$ and $p = 0.002$, respectively) and lower depression scores with SRP, PB and CB ($p = 0.007$, $p = 0.003$ and $p = 0.032$, respectively). Memory functions and stress response were significantly correlated with polyphenol intake, fecal SCFAs, plasma and fecal very long chain saturated fatty acids (VLCSFAs).
Conclusions: Regular peanut and peanut butter consumption may enhance memory function and stress response in a healthy young population. These effects seem to be associated with the intake of peanut polyphenols, increased levels of fecal SCFAs, and unexpectedly, VLCSFAs, which were also present in the control product.

☆ Upon request, data described in the manuscript, code book, and analytic code will be made available.

* Corresponding author. Department of Nutrition, Food Sciences and Gastronomy, XIA, School of Pharmacy and Food Sciences, University of Barcelona, 08028, Barcelona, Spain.
** Corresponding author. Department of Nutrition, Food Sciences and Gastronomy, XIA, School of Pharmacy and Food Sciences, University of Barcelona, 08028, Barcelona, Spain.
E-mail addresses: iparillim@ub.edu (I. Parilli-Moser), idominguez@ub.edu (I. Domínguez-López), mtrius@ub.edu (M. Trius-Soler), sampol@clinic.cat (M. Castellví), beabc6@hotmail.com (B. Bosch), sara.castro@ub.edu (S. Castro-Barquero), restruch@clinic.cat (R. Estruch), sara.hurtado_17@ub.edu (S. Hurtado-Barroso), lamuela@ub.edu (R.M. Lamuela-Raventós).

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Abbreviations

BDNF	brain-derived neurotrophic factor
BMI	body mass index
CB	control butter
CRP	C-reactive protein
DPB	diastolic blood pressure
FAMEs	fatty acid methyl esters
FFQ	food frequency questionary
HADS-A	Hospital Anxiety and Depression Scale – anxiety
HADS-D	Hospital Anxiety and Depression Scale – depression
HDL-c	high density lipoprotein cholesterol
HS-GC-MS	headspace sampler connected to a gas chromatography – mass spectrometry analysis
LC-LTQ-Orbitrap MS	liquid chromatography coupled with linear ion trap quadrupole - Orbitrap mass spectrometry
LDL-c	low density lipoprotein cholesterol
LNS	Letter-number sequencing
MUFAs	monounsaturated fatty acids
PB	peanut butter
PUFAs	polyunsaturated fatty acids
SBP	systolic blood pressure
SCFAs	short chain fatty acid
SFAs	saturated fatty acids
SRP	skin roasted peanuts
TC	total cholesterol
TG	triglycerides
TMT	trail making test
VLCSFAs	very long chain saturated fatty acids
VPA	verbal paired association
WAIS	Wechsler Adult Intelligence Scale
WHR	waist-to-hip ratio
WMS	Wechsler Memory Scale

1. Introduction

The cultivation of peanuts is sustainable, and their consumption is increasing worldwide. Although botanically classified as legumes, they are commonly included in the group of nuts due to their similar nutritional composition [1]. Nuts are rich in unsaturated fatty acids, vitamins, minerals, fiber, and phytochemicals such as polyphenols. There is evidence indicating that nut consumption protects brain health and improves cognitive function, including memory and executive functions [[2],3]. A randomized crossover trial carried out by Barbour et al. showed an enhancement in cerebrovascular reactivity (defined as the change in cerebral blood flow in response to a vasodilatory or vasoconstrictive stimulus) and cognitive function in healthy overweight middle-aged adults consuming 56–84 g/day of high-oleic peanuts for 12 weeks [4]. Nuts seem to improve cognitive health due to their lipid profile and phytochemical content [3]. They may also have a beneficial effect on the gut microbiota, as they are rich in prebiotic fiber and polyphenols [5]. Systematic reviews have reported a relationship between the gut microbiota and the brain, and the role of diet in the microbiota-gut–brain axis is a growing field of research [6,7].

Although evidence is still limited, a recent systematic review and meta-analysis reported promising findings regarding the enhancement of brain health, including cognitive functions, in healthy young and middle-aged adults following polyphenol-rich interventions [8]. The beneficial effects of an early acute and chronic application of a low to high dose of phenolic components with high bioavailability rates (≥30%) were found to be more significant in the younger population [8]. Due to their very poor absorption, most polyphenols directly reach the colon, where they are metabolized by the microbiota [9]. There is strong evidence for the influence of polyphenols on gut microbiota composition and activity [10]. In addition, the metabolites produced by microbiota can modulate brain biochemistry by acting as neurotransmitters in the central nervous system [11]. Short-chain fatty acids (SCFAs), such as acetic, propionic, and butyric acids, the main metabolites produced by gut microbiota, seem to have effects against various diseases, including depression and neurodegenerative disease [12].

As there is insufficient evidence for the effects of peanut products on cognitive functions, we designed a trial to evaluate the impact of regular consumption of peanut products and their bioactive compounds on cognition and stress response, including anxiety and depression scores, in healthy young adults. The hypothesis of the study is that a daily intake of a portion of peanuts or peanut butter for 6 months will improve the cognitive and mood response of individuals due to prebiotic and postbiotic effects.

2. Material and methods

2.1. Study subjects

From the 90 healthy subjects who initially enrolled, 63 healthy participants (19 males and 44 females) aged between 18 and 33 years from the Food and Nutrition Torribera Campus of the University of Barcelona and surroundings completed the study (Supplemental Figure 1). The most effective recruitment strategies were flyer distribution and word of mouth. Participant exclusion criteria were the following: history of chronic diseases (cardiovascular diseases, cancer, diabetes, and others), peanut allergy or intolerance, body mass index (BMI) over 25 kg/m^2, active smoking, high alcohol consumption and other toxic habits.

After approval of the protocol by the Ethics Committee of Clinical Investigation of the University of Barcelona (Barcelona, Spain), the study was registered at https://register.clinicaltrials.gov (NCT04324749). Each participant signed an informed consent prior to the start of the trial, which was conducted according to the principles of the Declaration of Helsinki.

2.2. Study design

The ARISTOTLE study is a three-arm parallel-group randomized controlled trial (Fig. 1), performed between November 2019 and June 2020. The duration of the study was six months, extended to seven months in some cases due to the global COVID-19 pandemic. Randomization was performed, assigning the random numbers from random number tables to each subject at the moment of enrollment. The interventions were not blinded to the participants or researchers involved in the intervention, but remained blinded to the external analysts. After a two-week peanut-free run-in period, participants were randomly assigned to one of three interventions: 25 g/day of skin roasted peanuts (SRP) or 2 tablespoons (32 g)/day of peanut butter (PB) or 2 tablespoons (32 g)/day of a control butter (CB). SRP were produced in the USA and provided by Ferrer Segarra S.A. (Madrid, Spain). PB was manufactured by the Koeze Company (Michigan, USA). The non-commercial CB was designed and supplied by an external company named BDN Ingeniería de Alimentación S.L. (Barcelona, Spain). The CB was made with peanut oil and provided similar levels of energy (and a

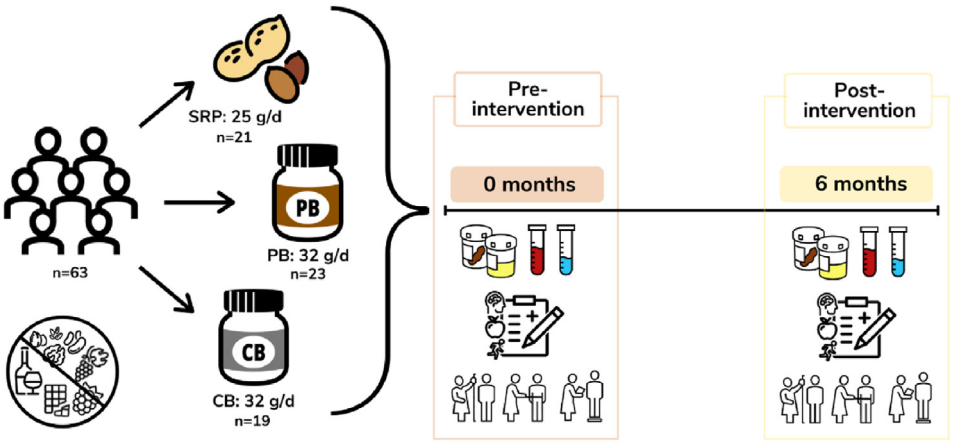

Fig. 1. Study design. Pre-intervention (0 months) is represented in orange and post-intervention (6 months) in yellow. SRP: skin roasted peanuts; PB: peanut butter; CB: control butter.

similar macronutrient composition) to the experimental interventions, but it was free of phenolic compounds and fiber. More details about the main polyphenols in the interventions are provided in Supplemental Table 1. Participants followed their habitual diet and consumed the test product at any time of the day. However, wine, grapes, dark chocolate (<70%) and berries were excluded from their diet because of their high contents of resveratrol, a phenolic compound also present in peanuts. Nuts were also removed due to a similar nutritional content to peanuts.

2.3. Sample collection

Biological samples (fasting blood, 24 h urine and feces) were collected at baseline and at 6 months of the intervention. In addition, a follow-up to monitor adherence to the intervention and to motivate the participants was done at 3 months (as this period coincided with the onset of the global COVID-19 pandemic, some visits were by phone or videocall). Fasting blood was drawn from the arm between 8:00 and 10:30 a.m. via venipuncture into tubes containing ethylenediaminetetraacetic acid (EDTA). Plasma and serum were separated after centrifugation at 1500*g* for 15 min at 4 °C and at 3000 g for 10 min at 4 °C, respectively. Subjects provided urine from 24 h before each visit. Fecal samples were drawn with the help of a stool collection kit at baseline and at the end of the study and stored immediately at −20 °C until the visit. All the samples were aliquoted and stored at −80 °C until SCFAs and VLCSFAs were analyzed, and aliquots of serum, plasma and urine samples were immediately sent to an external laboratory for biochemical analysis (Cerba Internacional, Barcelona, Spain).

2.4. Anthropometric and clinical measurements

Anthropometric measurements (height, weight, body fat, muscle mass, waist, and hip circumference) were collected in fasting conditions. Height was measured in the standing position using a portable stadiometer. Weight, body fat and muscle percentage were estimated using a tetrapolar OMRON BF511 bioelectrical device, with the participants wearing light clothes and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist and hip circumferences were measured using an inelastic flexible tape positioned equidistantly between the lowest rib and the iliac crest, and at the level of the widest circumference over the great trochanters, respectively. The waist-to-hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm).

Diastolic and systolic blood pressure, as well as heart rate, were measured in triplicate in the sitting position using a digital monitor OMRON M6. Biochemical markers in serum (glucose, lipid profile and C-reactive protein) and urine (cortisol) were measured in an external laboratory (Cerba internacional, Barcelona, Spain) using enzymatic methods.

2.5. Dietary and physical activity assessments

At baseline and at the end of the intervention, diet and physical activity were evaluated. A 151-item semi-quantitative food frequency questionnaire (FFQ) was administered by trained staff to quantify the usual food intake, estimated according to Spanish food composition tables [13]. Physical activity was assayed through a Spanish validated version of the Minnesota Leisure-Time Physical Activity Questionnaire [14,15]. Physical activity was measured as the metabolic equivalent of task per week (MET/week). To calculate these data, the following categories of physical activity were used: light (lower than or equal to 4 METs), moderate (4.5–5.5 METs), and heavy (greater than or equal to 6 METs).

2.6. Cognitive and mood assessment

At baseline and at the end of the study, trained personnel assessed the cognitive functions of participants, administrating in a standard order a broad range of validated neuropsychological tests and mood disorder questionnaires. These tests evaluated the three main cognitive domains: memory, executive function and processing speed. The Wechsler Memory Scale (WMS-IV) was used to test learning of verbal paired associates (immediate and delayed memory and recognition) [16,17]. The Wechsler Adult Intelligence Scale (WAIS) was used to measure working memory (Digit Span and Letter-Number Sequencing (LNS) by WAIS-III and WAIS-IV, respectively) and perceptual reasoning (matrix) (WAIS-IV), and the Trail Making Test (TMT) was used to measure cognitive flexibility and visual-motor processing speed [18–20] in a quiet room. Semantic and formal fluencies were tested according to the methodology described by Peña-Casanova et al. [21]. The Hospital Anxiety and Depression Scale (HADS), validated for the Spanish population was also used [22]. It consists of two subscales: HADS-A, designed to detect anxious states, and HADS-D, designed to detect

depressive states, higher scores indicating greater levels of anxiety or depression.

Due to the global COVID-19 pandemic, these assessments were performed by video call at the end of the study.

Participant raw test results were standardized to z-scores, and composite scores of different cognitive domains were calculated for each participant. A composite total verbal memory score was based on the combined z-scores of immediate and delayed memory and recognition. Similarly, a composite working memory score was calculated from combined z-scores of digit Span and LNS. A composite score was then obtained from verbal and working memory to provide a total memory score. A cognitive flexibility score was calculated from TMT-a and TMT-b z-scores. Also, a composite z-score of formal fluency was obtained from P, M and R fluency z-scores.

2.7. Determination of polyphenol intake

The intake of the polyphenols was estimated by multiplying polyphenol content in food by the daily consumption of each food from the 151-item FFQ, based on the phenol explorer database http://phenol-explorer.eu/ [23]. However, as the FFQ lacked a specific item for peanut products, the polyphenols of the test foods were quantified by liquid chromatography coupled with linear ion trap quadrupole Orbitrap - mass spectrometry and the data were added to the phenol intake calculated from the FFQ.

2.7.1. Extraction of polyphenols from test products

Resveratrol and *m*-coumaric, *o*-coumaric and *p*-coumaric acids were purchased from Sigma–Aldrich (St. Louis, MO, USA). Acetonitrile, water, formic acid, and ethanol were acquired from Merck (Darmstadt, Germany). Ultrapure water was obtained from a Milli-Q water purification system (Millipore Bedford, MA, USA). The extraction of polyphenols was performed following a previously reported procedure with minor modifications [24]. After homogenization of food samples using a blender, 0.5 g of each one was mixed with 5 mL of 80% ethanol in Milli-Q water (0.1% formic acid) and vortexed for 1 min. They were then sonicated in an ultrasound bath for 20 min and centrifuged at 4000 rpm for 20 min at 4 °C. The supernatant was collected in a tube and the extraction procedure was repeated. The supernatants were combined and evaporated under a nitrogen flow, and the residue was reconstituted with Mili-Q water (0.1% formic acid) up to 4 mL. The extract was filtered by a 0.45 μm PTFE filter into an insert-amber vial. Samples were stored at −20 °C until analysis by liquid chromatography coupled with linear ion trap quadrupole Orbitrap - mass spectrometry (LC-LTQ-Orbitrap MS).

2.7.2. LC-LTQ-Orbitrap-MS analyses

Liquid chromatography (LC) analysis was carried out in an Accela chromatograph (Thermo Scientific, Hemel Hempstead, UK) equipped with a quaternary pump, a photodiode array detector, and a thermostated autosampler. Chromatographic separation was performed using a Kinetex C18 column (2.1 × 150 mm, 3.5 μm) acquired from Waters (Milford, MA, USA). Gradient elution was performed with water/0.1% formic acid (solvent A) and acetonitrile/0.1% formic acid (solvent B) at a constant flow rate of 0.350 mL/min, and the injection volume was 10 μL. A non-linear gradient was used: 0 min, 5% B; 1 min, 5% B; 7 min, 45% B; 8.5 min, 80% B; 10.5 min, 80% B; 11 min, 5% B; 12 min, 5% B and the column was equilibrated for 5 min prior to each analysis. The LC system was coupled to an LTQ-Orbitrap Velos mass spectrometer (Thermo Scientific, Hemel Hempstead, UK) used for accurate mass measurements and equipped with an ESI source operated in negative mode. Operation parameters were as follows: source voltage, 4 kV; sheath gas, 20 a.u. (arbitrary units); auxiliary gas, 10 a.u; sweep gas, 2 a.u; and capillary temperature, 275 °C. Samples were analyzed in Fourier transformation mass spectrometry mode at a resolving power of 30000. Parent ions were fragmented by high-energy C-trap dissociation with normalized collision energy of 35 V and an activation time of 10 ms. The mass range in both modes was from *m/z* 100 to 2000. Instrument control and data acquisition were performed with Xcalibur 3.0 software (Thermo Fisher Scientific).

2.8. Quantification of short-chain fatty acids in feces

2.8.1. Extraction of short-chain fatty acids from feces

For the analysis and quantification of short-chain fatty acids (SCFAs), feces were acidified and homogenized with formic acid 1 M (500 mL/100 mg of feces). The slurry mixture (100 μL) was added with 20 μL of 2-ethylbutyric acid 0.85 mM (internal standard) into a headspace vial (Agilent, Santa Clara, CA, USA).

2.8.2. Chromatographic analysis

Chromatographic analysis of SCFAs was performed using a headspace sampler connected to a gas chromatography – mass spectrometry system (HS-GC-MS) based on a previously described method [25], using a TRACE GC Ultra system (Thermo Fisher Scientific), after incubating the samples for 20 min at 60 °C. The initial oven temperature was 80 °C, reaching a final temperature of 125 °C and 225 °C, with rates of 50 °C/min and 6 °C/min. The maximum temperature was 260 °C. An Agilent HP-FFAP column, 0.3 μm (25 m × 0.2 mm) was used to separate the compounds. A 1 mL volume of volatile analytes was injected with a flow rate of 10 mL/min. The carrier gas was helium at a constant flow rate of 1 mL/min. A blank sample (Milli-Q water) was injected between each sample to wash the injector and avoid interferences. Volatile Free Acid Mix 10 mM (Supelco, Bellefonte, PA, USA) containing acetic, propionic, isobutyric, butyric, isovaleric, valeric, isocaproic, caproic and heptanoic acids was used as a standard, and 2-ethylbutyric acid (Sigma–Aldrich, St. Louis, MO, USA) as the internal standard.

2.9. Quantification of fatty acids in plasma and feces

2.9.1. Sample preparation

Plasma and fecal fatty acids were determined by fast-gas chromatography with a previous derivatization to their corresponding fatty acid methyl esters (FAMEs), based on previously described methods for plasma [26] and feces [27]. Araquidic acid (C:20), behenic acid (C:22) and lignoceric acid (C:24), VLCSFAs found in peanuts and only a few other foods, were quantified as a biomarker of compliance for the three interventions. First, 20 μL and 40 μL of the internal standards, tridecanoic acid (C13:0) and henicosanoic acid (C21:0), purchased from Sigma–Aldrich (St. Louis, MO, USA), were added to 200 μL of plasma samples and 100 mg of fecal samples, respectively. 1 mL of sodium methylate (0.5% w/v), acquired from Sigma–Aldrich (St. Louis, MO, USA), was added and the mixture was heated to 100 °C for 15 min. After cooling, the samples were esterified at 100 °C for 15 min using 1 mL of boron trifluoride-methanol reagent (14% v/v), purchased from Sigma–Aldrich (St. Louis, MO, USA). Subsequently, the FAMEs were isolated by adding 1 mL n-hexane (Sigma–Aldrich, St. Louis, MO, USA). After shaking for 1 min, 1 mL of a saturated sodium chloride solution purchased from Panreac Quimica SLU (Barcelona, Spain) was added. Finally, the tubes were centrifuged for 10 min at 3000 rpm and after drying with anhydrous sodium sulphate (Scharlab, Barcelona, Spain), the clear n-hexane top layer was transferred into an automatic injector vial equipped with a volume adapter of 300 μL.

2.9.2. Chromatographic analysis

Chromatographic analysis was performed using a Shimadzu GC-2010 Gas Chromatograph (Shimadzu, Kyoto, Japan) equipped with a flame ionization detector and a Shimadzu AOC-20i Autoinjector. Separation of FAMEs was carried out on a capillary column (40 m × 0.18 mm i.d. x 0.1 μm film thickness), coated with an RTX-2330 stationary phase of 10% cyanopropyl phenyl - 90% byscyanopropyl polysiloxane from Restek (Bellefonte, USA).

Operating conditions were as follows: the split-splitness injector was used in split mode with a split ratio of 1:50. The injection volume of the sample was 1 μL. The injector and detector temperatures were kept at 250 °C and 300 °C, respectively. The temperature program was as follows: initial temperature 110 °C, increased at 52 °C/min to 195 °C, and held at this temperature for 6 min, and then increased at 25 °C/min until 230 °C and held for 6.5 min. Hydrogen was used as the carrier gas, at a constant pressure of 26 psi, which refers to a linear velocity of 40 cm/s at 110 °C. Data acquisition and processing were performed with the Shimadzu-Chemstation software for GC systems. Supelco 37 component FAMEs mix and PUFAs No.2 (Animal source), purchased from Merck (Darmstadt, Germany), were used for peak identification.

2.10. Statistical analyses

The sample size was calculated to ensure a significance level of 0.05 and statistical power of 80%, as well as 5% of loss for follow-up were included. Normality of distribution was assessed by the Shapiro–Wilk test. Non-parametric tests were used because of the small sample size (<30 in each group) and the non-normality of most of the variables. Differences between groups at baseline were tested by the chi-square test for categorical variables and the Kruskal Wallis test followed by Dunn's post hoc test for continuous variables. To evaluate any differences at the end of the study with respect to the baseline in each arm group, a Wilcoxon signed-rank test was used. Continuous variables were expressed as mean values with 95% confidence intervals (95% CI) and categorical variables as number (n) and proportion (%). Cognitive and mood responses were presented as z-scores (95% CI).

The effect of the interventions was estimated by performing a generalized estimating equation (GEE) on Poisson regression models for repeated measures. Analyses were adjusted for age and sex (model 1), plus level of education, physical activity and urinary cortisol (model 2). Spearman's coefficient was estimated to measure correlations between bioactive compounds of peanuts (polyphenol intake, fecal SCFAs and plasma and fecal VLCSFAs) and cognitive and mood measurements. Differences were considered significant when the p value was lower than 0.05. However, a corrected p value by multiple comparison was also considered in all analyses (p-*value* < 0.017). All statistical analyses were conducted using STATA software version 16.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Participant characteristics

Among the 90 healthy subjects who enrolled and were randomized to each arm, 63 (19 males and 44 females) completed the study. The 27 participants (30%) who left the study did so for a variety of reasons (Supplemental Figure 1). Dropouts were unevenly distributed among groups (30% SRP, 23% PB, and 36% CB), but no significant differences were observed between participants who withdrew and those who remained in the study. Supplemental Table 2 shows the baseline characteristics of the 63 participants who completed the study. Subjects had an average age of 22.71 ± 3.13 years; the average BMI was 22.3 ± 2.93 kg/m^2, and 36% had finished a 4-year college or graduate course. The mean of physical activity reported was higher than 4000 METs/week. At baseline, there were no statistical differences in measurements, except in the plasmatic high density lipoprotein cholesterol (HDL-c), the intake of *m*-coumaric and *p*-coumaric acids, and the fecal levels of isocaproic and heptanoic acids.

3.2. Anthropometric, clinical, and dietary changes during the interventions

Although a significant decrease of physical activity was reported in the SRP and CB groups at the end of the study compared to baseline ($p = 0.012$ and $p = 0.034$, respectively), no significant changes in body composition were observed (Table 1).

No statistical differences in nutrient intake between the groups were apparent (Table 2). Those in the SRP and PB groups had higher intakes of resveratrol, *p*-coumaric acid (p= <0.001 in both cases), as well as *m*-coumaric acid ($p = 0.029$ and $p = 0.002$, respectively) at the end of study compared to baseline. An increased intake of *o*-coumaric was observed only in the SRP group ($p = 0.002$). In contrast, a significant decrease in resveratrol ($p < 0.001$) and p-coumaric acid intake ($p = 0.016$) was observed in the CB group.

The volunteers reported their adherence to the intervention and they generally consumed the SRP, PB and CB in the morning. Although most of the participants tolerated the intervention well, some adverse effects were reported. Five individuals from the SRP group reported digestive symptoms, such as postprandial heaviness, bloating, flatulence, and heartburn. Three participants consuming PB or CB experienced stool softening and reduced constipation. Two participants reported sensitivity on the first days of consuming SRP or CB. However, none of these symptoms persisted throughout the study or led to withdrawal.

3.3. Cognition and stress response

Cognitive function as well as anxiety and depression scores are shown in Table 3. Comparing the two interventions with the control, a significant reduction of anxiety score was observed in the SRP compared to the CB group after full adjustment at 6 months ($p = 0.001$) (models of adjustment shown in Supplemental Table 3). However, no significant differences were found in the PB versus the CB group. A significant improvement was observed in immediate memory (learning of verbal paired associates) in the SRP ($p = 0.046$) and PB ($p = 0.011$) groups after the intervention. Also worthy of mention is that the control group showed an improvement in recognition ($p = 0.029$), unlike the SRP and PB groups. An enhancement in delayed memory, total verbal memory and total memory was also found in the PB group after the intervention compared to baseline ($p = 0.047$, $p = 0.004$ and $p = 0.015$, respectively). A lower anxiety score was found in SRP than in CB and PB consumers compared to baseline ($p < 0.001$ and $p = 0.016$, respectively), whereas a significant decrease in the depression score was observed for all three groups, SRP, PB and CB ($p = 0.007$, $p = 0.026$ and $p = 0.032$, respectively), compared to baseline.

Urinary cortisol levels decreased significantly in the SRP and PB group after the intervention compared to baseline ($p = 0.004$ and $p = 0.008$, respectively) (Fig. 2). However, no differences were found between the interventions and control group.

3.4. Short-chain fatty acids

As shown in Table 4, a significant increase in acetic acid, propionic acid, butyric acid, and the sum of the three SCFAs, was

Table 1
Anthropometric and clinical measurements in healthy adults during the ARISTOTLE study.

	SRP (n = 21)		p^1	PB (n = 23)		p^1	CB (n = 19)		p^1	p^2 SRP vs. CB	p^2 PB vs. CB
	Pre-intervention	Post-intervention		Pre-intervention	Post-intervention		Pre-intervention	Post-intervention			
Body composition											
Weight (kg)	63.26 (58.65, 67.86)	63.13 (58.17, 68.10)	0.850	60.10 (56.77, 63.44)	59.37 (55.95, 62.78)	0.742	63.78 (58.94, 68.62)	63.67 (58.39, 68.96)	0.930	0.891	0.832
BMI (kg/m^2)	22.12 (20.51, 23.72)	21.99 (20.42, 23.57)	0.940	22.19 (21.06, 23.31)	21.94 (20.77, 23.11)	0.835	22.59 (21.31, 23.88)	22.50 (21.09, 23.91)	0.895	0.949	0.905
Waist circumference (cm)	72.73 (68.96, 76.52)	71.81 (68.26, 75.35)	0.706	71.28 (68.89, 73.67)	70.24 (67.77, 72.70)	0.560	74.68 (71.80, 77.57)	73.84 (70.55, 77.14)	0.599	0.867	0.441
WHR	0.74 (0.71, 0.76)	0.73 (0.71, 0.76)	0.920	0.74 (0.72, 0.76)	0.73 (0.72, 0.75)	0.503	0.77 (0.74, 0.79)	0.76 (0.74, 0.79)	0.559	0.618	0.312
Body fat (%)	26.66 (22.99, 30.34)	26.16 (22.42, 29.90)	0.910	28.45 (25.04, 31.86)	27.77 (23.98, 31.58)	0.838	26.22 (22.37, 30.08)	25.66 (21.55, 29.77)	0.855	0.960	0.577
Visceral fat	4.19 (2.77, 5.61)	4.14 (2.89, 5.39)	0.867	3.96 (3.24, 4,68)	4.00 (3.24, 4.76)	0.880	4.47 (3.50, 5.44)	4.61 (3.45, 5.77)	0.938	0.900	0.992
Muscle mass (%)	32.09 (29.49, 34.69)	32.59 (29.80, 35.37)	0.782	31.04 (28.53, 33.55)	31.49 (3.24, 4.76)	0.725	33.29 (30.02, 36.56)	33.61 (30.22, 36.99)	0.879	0.779	0.880
Physical activity (mets/week)	4850 (3883, 5817)	3269 (2534, 4003)	**0.012**†	4703 (3674, 5733)	3736 (2941, 4530)	0.144	4607 (3774, 5440)	3330 (2374, 4287)	**0.034**	0.416	0.290
Blood pressure											
SBP (mmHg)	111 (108, 114)	111 (103, 120)	0.624	109 (105, 113)	106 (100, 113)	0.317	110 (104,116)	110 (102, 117)	0.715	0.962	0.843
DBP (mmHg)	72 (69.16, 76.10)	73 (68.18, 79.75)	0.734	72 (70.19, 75.54)	73 (69.80, 77.91)	0.886	70 (66.06, 74.47)	70 (64.68, 77.04)	0.693	0.802	0.713
Blood analytes											
Glucose (mmol/L)	4.54 (4.34, 4.74)	4.76 (4.62, 4.89)	0.087	4.59 (4.44, 4.74)	4.65 (4.53, 4.78)	0.875	4.47 (4.35, 4.58)	4.58 (4.45, 4.71)	0.238	0.252	0.407
TG (mmol/L)	0.71 (0.62, 0.80)	0.76 (0.66, 0.87)	0.876	0.85 (0.70, 1.00)	0.81 (0.69, 0.95)	0.505	0.80 (0.67, 0.92)	0.79 (0.67, 0.91)	0.594	0.525	0.979
TC (mmol/L)	4.33 (4.10, 4.57)	4.49 (4.17, 4.81)	0.498	4.60 (4.22, 4.98)	4.66 (4.25, 5.00)	0.975	4.09 (3.79, 4.40)	4.23 (3.91, 4.55)	0.807	0.870	0.839
LDL-c (mmol/L)	2.22 (2.04, 2.39)	2.45 (2.25, 2.65)	0.150	2.60 (2.30, 2.90)	2.80 (2.44, 3.09)	0.672	2.30 (2.06, 2.54)	2.49 (2.24, 2.74)	0.404	0.681	0.977
HDL-c (mmol/L)	1.75 (1.61, 1.89)	1.68 (1.54, 1.82)	0.519	1.69 (1.51, 1.86)	1.59 (1.45, 1.72)	0.740	1.50 (1.36, 1.65)	1.42 (1.32, 1.52)	0.629	0.952	0.930
CRP (mg/L)	0.71 (0.30, 1.11)	0.59 (0.19, 1.00)	0.726	1.09 (0.30, 1.88)	1.25 (−0.14, 2.58)	0.263	0.39 (−0.04, 0.84)	0.83 (−0.39, 2.06)	0.269	0.799	0.526

Data are expressed as mean (95% CI). SRP: skin roasted peanuts; PB: peanut butter; CB: control butter; BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; TC: Total cholesterol; LDL-c: low density lipoprotein cholesterol; HDL-c: high density lipoprotein cholesterol; CRP: C-reactive protein. $p < 0.050$ are statistically significant. p^1 refers to the difference between times in each arm and was calculated by Wilcoxon's test. p^2 refers to fully adjusted differences between SRP and PB vs. CB at 6 months and was calculated by a generalized estimating equation (GEE). $^\dagger p$ value by multiple comparison ($p < 0.017$).

Table 2
Dietary intake in healthy adults during the ARISTOTLE study.

	SRP (n = 21)		p^1	PB (n = 23)		p^1	CB (n = 19)		p^1	p^2 SRP vs. CB	p^2 PB vs. CB
	Pre-intervention	Post-intervention		Pre-intervention	Post-intervention		Pre-intervention	Post-intervention			
Nutritional intake											
Energy (kcal/day)	2770 (2500, 3041)	2663 (2435, 2890)	0.753	2705 (2445, 2966)	2668 (2461, 2875)	0.750	2596 (2366, 2827)	2640 (2484, 2797)	0.474	0.197	0.146
Carbohydrates (g/day)	257 (220, 294)	238 (209, 269)	0.443	241 (209, 273)	226 (203, 249)	0.462	246 (218, 275)	227 (204, 249)	0.373	0.613	0.962
Sugar	115 (100, 132)	101 (85.92, 116)	0.163	111 (96.49. 126)	95.69 (83.57, 107)	0.127	113 (94.11,133)	93.25 (79.52, 106)	0.118	0.166	0.748
Fiber	45.17 (35.18, 55.16)	43.80 (35.50, 52.09)	0.734	42.12 (35.79, 48.46)	40.56 (36.20, 44.92)	0.818	38.93 (31.67, 46.20)	34.97 (29.88, 40.05)	0.457	0.082	0.400
Protein (g/day)	103 (90.31, 117)	105 (93.70, 118)	0.753	110 (96.39, 123)	111 (101, 121)	0.974	107 (94.49, 121)	115 (103, 128)	0.194	0.532	0.106
Total fat (g/day)	144 (131, 157)	146 (134, 159)	0.642	141 (127, 157)	151 (138, 165)	0.386	129 (115, 143)	148 (137, 159)	0.084	0.090	0.130
SFAs	37.61 (33.07, 42.18)	36.76 (31.92, 41.58)	0.950	38.18 (33.41, 42.96)	37.28 (32.65, 41.90)	0.575	36.81 (30.53, 43.08)	38.04 (33.21, 42.87)	0.965	0.394	0.094
MUFAs	70.37 (63.03, 77.71)	67.76 (60.52,75.00)	0.811	69.06 (61.63, 76.49)	69.73 (62.83, 76.63)	0.957	59.46 (51.84, 67.08)	67.29 (60.24, 74.33)	0.088	0.100	0.130
PUFAs	25.91 (22.83, 28.99)	22.45 (20.26, 24.63)	0.076	23.99 (20.86, 27.13)	21.90 (19.79, 24.01)	0.318	23.59 (20.41, 26.77)	20.69 (18.48, 22.90)	0.140	0.715	0.881
Polyphenol intake											
Resveratrol (mg/day)	0.04 (0.03, 0.06)	0.08 (0.07. 0.08)	**<0.001**†	0.04 (0.03, 0.05)	0.09 (0.08, 0.09)	**<0.001**†	0.03 (0.02, 0.05)	0.01 (0.00, 0.01)	**<0.001**†	**<0.001**†	**<0.001**†
p-Coumaric acid (mg/day)	0.95 (0.76, 1.14)	6.81 (6.66, 6.96)	**<0.001**†	0.72 (0.57, 0.88)	13.44 (12.75, 14.12)	**<0.001**†	0.73 (0.54, 0.93)	0.43 (0.31, 0.56)	**0.016**†	**<0.001**†	**<0.001**†
m-Coumaric acid (mg/day)	0.83 (0.47, 1.19)	1.19 (0.86, 1.53)	**0.029**	0.64 (0.32, 0.96)	1.06 (0.74, 1.38)	**0.002**†	0.26 (0.11, 0.42)	0.28 (0.12, 0.44)	0.860	**0.003**†	**<0.001**†
o-Coumaric acid (mg/day)	0.51 (0.33, 0.69)	1.84 (1.07, 2.60)	**0.002**†	0.39 (0.22, 0.55)	0.40 (0.24, 0.56)	0.668	0.20 (0.11, 0.29)	0.18 (0.10, 0.27)	0.792	**<0.001**†	0.450

Data are expressed as mean (95% CI). CB: control butter; SRP: skin roasted peanuts; PB: peanut butter; SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids. $p < 0.050$ are statistically significant. p^1 refers to differences between times in each arm and was calculated by Wilcoxon's test. p^2 refers to fully adjusted differences between SRP and PB vs. CB at 6 months and was calculated by generalized estimating equation (GEE). $^\dagger p$ value by multiple comparison ($p < 0.017$).

Table 3
Cognitive measures in healthy adults during the ARISTOTLE study.

	SRP n = 21		P^1	PB n = 23		p^1	CB n = 19		p^1	p^2 SRP vs. CB	p^2 PB vs. CB
	Pre -intervention	Post-intervention		Pre -intervention	Post -intervention		Pre -intervention	Post -intervention			
Verbal memory											
Immediate memory - VPA1	−0.45 (−0.89, −0.01)	0.13 (−0.36, 0.61)	**0.046**	−0.17 (−0.54, 0.21)	0.44 (0.13, 0.74)	**0.011**†	−0.12 (−0.68, 0.43)	0.15 (−0.38, 0.68)	0.501	0.404	0.404
Delayed memory - VPA2	−0.26 (−0.81, 0.29)	0.24 (−0.42, 0.42)	0.476	−0.13 (−0.61, 0.33)	0.39 (0.12, 0.66)	**0.047**	−0.21 (−0.85, 0.43)	0.20 (−0.08, 0.47)	0.922	0.653	0.653
Recognition	−0.15 (−0.42, 0.42)	−0.07 (−0.50, 0.36)	0.739	0.16 (−0.15, 0.47)	0.35 (0.22, 0.48)	0.291	−0.73 (−1.55, 0.09)	0.18 (−0.16, 0.53)	**0.029**	0.063	0.063
Total verbal memory	−0.27 (−0.71, 0.16)	0.02 (−0.43, 0.47)	0.145	−0.05 (−0.43, 0.32)	0.45 (0.20, 0.71)	**0.004**†	−0.41 (−1.12, 0.30)	0.20 (−0.21, 0.62)	0.405	0.658	0.658
Working Memory											
Digit span	−0.09 (−0.56, 0.38)	0.14 (−0.38, 0.66)	0.545	−0.26 (−0.66, 0.14)	0.15 (−0.27, 0.58)	0.093	−0.02 (−0.49, 0.45)	0.09 (−0.38, 0.57)	0.597	0.969	0.969
LNS	−0.02 (−0.50, 0.46)	0.22 (−0.31, 0.76)	0.595	−0.32 (−0.62, 0.01)	0.06 (−0.37, 0.49)	0.329	−0.07 (−0.55, 0.40)	0.17 (−0.37, 0.72)	0.702	0.945	0.945
Total working memory	−0.05 (−0.54, 0.43)	0.20 (−0.32, 0.73)	0.513	−0.31 (−0.66, 0.04)	0.12 (−0.31, 0.55)	0.214	−0.07 (−0.54, 0.40)	0.14 (−0.38, 0.67)	0.635	0.921	0.921
Total memory	−0.23 (−0.69, 0.23)	0.12 (−0.41, 0.64)	0.346	−0.20 (−0.55, 0.15)	0.38 (0.09, 0.68)	**0.015**†	−0.34 (−0.98, 0.31)	0.23 (−0.24, 0.69)	0.229	0.753	0.753
Cognitive flexibility											
TMT-a	−0.02 (−0.44, 0.40)	−0.18 (−0.59, 0.23)	0.465	−0.06 (−0.42, 0.29)	−0.14 (−0.45, 0.18)	0.502	0.19 (−0.13, 0.51)	0.28 (−0.59, 1.16)	0.315	0.604	0.794
TMT-b	0.03 (−0.49, 0.55)	−0.35 (−0.86, 0.15)	0.203	0.19 (−0.22, 0.60)	−0.11 (−0.55, 0.34)	0.307	0.36 (−0.05, 0.77)	−0.11 (−0.53, 0.31)	0.068	0.589	0.394
Total cognitive flexibility	0.01 (−0.49, 0.50)	−0.32 (−0.84, 0.20)	0.204	0.07 (−0.31, 0.46)	−0.14 (−0.51, 0.21)	0.586	0.33 (−0.03, 0.68)	0.11 (−0.52, 0.74)	0.129	0.939	0.568
Perceptual Reasoning											
Matrix	0.12 (−0.33, 0.56)	0.22 (−0.31, 0.76)	0.620	−0.39 (−0.91, 0.13)	0.06 (−0.27, 0.38)	0.220	−0.16 (−0.56, 0.25)	0.19 (−0.25, 0.63)	0.100	0.523	0.783
Semantic fluency	0.19 (−0.29, 0.67)	−0.09 (−0.49, 0.31)	0.398	0.08 (−0.40, 0.56)	−0.15 (−0.51, 0.21)	0.644	0.10 (−0.43, 0.64)	−0.13 (−0.64, 0.38)	0.770	0.711	0.564
Formal fluency	−0.23 (−0.70, 0.24)	0.03 (−0.56, 0.62)	0.538	0.01 (−0.40, 0.43)	0.22 (−0.10, 0.55)	0.546	−0.08 (−0.53, 0.36)	0.02 (−0.48, 0.52)	0.651	0.542	0.790
HADS											
Anxiety	0.78 (0.48, 1.10)	−0.64 (−0.71, −0.20)	**<0.001**†	0.27 (−0.10, 0.64)	−0.49 (−0.73, −0.26)	**0.016**†	0.22 (−0.35, 0.80)	−0.12 (−0.70, 0.01)	0.241	**0.001**†	0.154
Depression	0.46 (−0.06, 0.99)	−0.45 (−0.97, −0.31)	**0.007**†	0.25 (−0.15, 0.66)	−0.47 (−0.73, −0.20)	**0.026**	0.58 (−0.06, 1.22)	−0.35 (−0.71, 0.47)	**0.032**	0.639	0.403

Data are expressed as z-score (95% CI). SRP: skin roasted peanuts; PB: peanut butter; CB: control butter; VPA1: Verbal paired associates 1; VPA2: Verbal paired associates; LNS: Letter-number sequence; TMT-a: Trial making test A; TMT-b: Trial making test B; HADS: Hospital anxiety and depression scale. $p < 0.05$ are statistically significant. p^1 refers to differences between times in each arm and was calculated by Wilcoxon's test. p^2 refers to fully adjusted differences between SRP and PB vs. CB at 6 months and was calculated by a generalized estimating equation (GEE). †p value by multiple comparison ($p < 0.017$).

observed after SRP ($p = 0.020$, $p = 0.046$, $p = 0.019$ and $p = 0.014$, respectively) and PB interventions ($p = 0.029$, $p = 0.042$, $p = 0.031$ and $p = 0.040$, respectively). Total SCFAs were also higher at the end of the study in the SRP group ($p = 0.012$). In addition, a significant increase of acetic acid was found in consumers of SRP and PB compared to CB ($p = 0.009$, $p = 0.041$ respectively), but after full adjustment only the main SCFAs and total SCFAs had significantly increased in the SRP versus the CB group ($p = 0.016$, $p = 0.007$ respectively) (models of adjustment in Supplemental Table 4).

3.5. Plasmatic and fecal fatty acids

Arachidic, behenic and lignoceric acids (the VLCSFAs used as biomarkers of peanut products) increased significantly in plasma after the SRP, PB and CB interventions compared to baseline ($p < 0.001$ in all cases) (Table 5). This increase was significantly higher in the groups consuming products with a buttered texture (PB and CB) rather than whole peanuts ($p = 0.005$), particularly regarding arachidic acid ($p = 0.046$). However, a lower amount of lignoceric acid was found in the SRP and PB versus CB groups after adjustment ($p = 0.022$ and p= <0.023, respectively) (models of adjustment shown in Supplemental Table 5). In feces, higher levels of total VLCSFAs and arachidic, behenic and lignoceric acids were observed in the SRP (p= <0.001 in all cases) and PB groups ($p = 0.009$, $p = 0.035$, $p = 0.011$ and $p = 0.005$, respectively) after 6 months compared to baseline. The differences between the three groups were significant, with the highest concentration of total VLCSFAs and arachidic, behenic and lignoceric acids associated with SRP, followed by PB and CB. After full adjustment, the SRP group presented significantly higher amounts of arachidic, behenic, lignoceric acids and total VLCSFAs in feces compared to the CB group ($p = 0.009$, $p = 0.002$, $p = 0.012$ and $p = 0.003$, respectively). No significant differences were observed for any of the other fatty acids from the lipid profile (data not shown).

3.6. Relationship between bioactive compounds and cognitive and stress response outcomes

In our original hypothesis, we proposed to assess the effect of polyphenols and SCFAs found in the administered products (SRP and PB). However, as changes in cognitive and stress response were observed in all three groups after the intervention, we decided to also evaluate VLCSFAs, present in each product, and thus verify if these fatty acids were exerting an unexpected effect. Table 6 shows

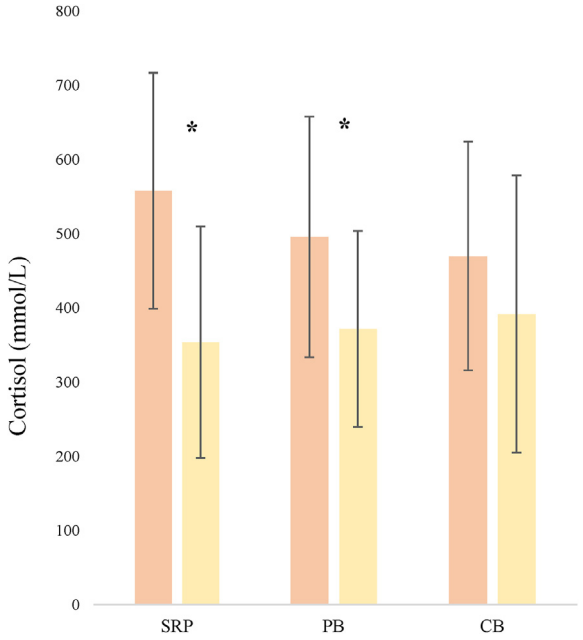

Fig. 2. Quantification of urinary cortisol, where pre-intervention levels are represented in orange and post-intervention levels in yellow. CB: control butter; SRP: skin roasted peanuts; PB: peanut butter. *p < 0.05 are statistically significant and were calculated by Wilcoxon's test.

the correlations between cognition and stress response (urinary cortisol, anxiety, and depression) and bioactive compounds (peanut polyphenol intake, fecal SCFAs and fecal and plasmatic VLCSFAs), based on the results obtained for all three groups (two interventions and the control). Regarding cognition, the improvement of total, verbal, immediate and delayed memory scores was directly correlated with the intake of polyphenols from peanuts (r = 0.19, $p = 0.030$; r = 0.18, $p = 0.034$; r = 0.18, $p = 0.039$ and r = 0.19, $p = 0.032$, respectively). An inverse correlation between cognitive flexibility and peanut polyphenols was also observed (r = −0.22, $p = 0.039$), which associates an improvement in processing speed with a higher intake of peanut polyphenols. Moreover, higher scores for total, verbal and immediate memory were associated with higher levels of VLCSFAs in plasma and feces (r = 0.18, $p = 0.045$; r = 0.20, $p = 0.025$; r = 0.20, $p = 0.024$ and r = 0.21, $p = 0.015$; r = 0.23, $p = 0.008$; r = 0.29, $p = 0.009$, respectively). In addition, urine cortisol levels decreased significantly with the increase of peanut polyphenol intake (r = −0.28, $p = 0.001$), plasmatic and fecal VLCSFAs (r = −0.30, $p = 0.014$ and r = −0.36, p= <0.001, respectively) and the total SCFAs in feces (r = −0.18, $p = 0.047$). Similarly, the anxiety score was inversely correlated with peanut polyphenol intake (r = −0.33, $p = 0.001$) and plasmatic and fecal VLCSFAs (r = −0.32, p= <0.001 and r = −0.20, $p = 0.029$, respectively), and the depression score was inversely correlated with peanut polyphenol intake (r = −0.22, $p = 0.005$), plasmatic VLCSFAs (r = −0.28, $p = 0.046$) and total SCFAs in feces (r = −0.18, $p = 0.045$).

4. Discussion

In this randomized clinical trial, a significant reduction in anxiety scores was observed in healthy young adults who consumed SRP daily for 6 months compared to those consuming CB, but no significant differences were found between PB and CB groups. Additionally, an improvement in memory function was

Table 4
Fecal short chain fatty acids in healthy adults during the ARISTOTLE study.

	SRP (n = 21)		p^1	PB (n = 23)		p^1	CB (n = 19)		p^1	p^2 SRP vs. CB	p^2 PB vs. CB
	Pre-intervention	Post-intervention		Pre-intervention	Post-intervention		Pre-intervention	Post-intervention			
Acetic acid	32.83 (26.25, 39.43)	51.07 (40.39, 61.75)	**0.020**	29.64 (25.17, 34.10)	39.15 (32.38, 45.92)	**0.029**	38.46 (29.86, 46.69)	37.18 (30.73, 43.65)	0.990	**0.009**†	**0.041**
Propionic acid	12.4 (9.02, 15.95)	16.99 (13.07, 20.92)	**0.046**	9.14 (7.05, 11.23)	12.95 (7.85, 18.05)	**0.042**	9.85 (7.56, 12.14)	10.84 (8.67, 13.02)	0.511	0.151	0.323
Isobutyric acid	1.36 (1.08, 1.63)	1.73 (0.71, 2.74)	0.772	1.34 (1.10, 1.57)	1.09 (0.90, 1.29)	0.144	1.55 (1.01, 2.10)	1.27 (0.94, 1.61)	0.609	0.860	0.746
Butyric acid	9.81 (6.60, 13.01)	13.84 (10.87, 16.83)	**0.019**	6.69 (4.79, 8.60)	10.71 (5.93, 15.51)	**0.031**	10.62 (7.31, 13.93)	10.80 (7.54, 14.08)	0.872	0.145	0.240
Isovaleric acid	1.78 (1.40, 2.17)	7.27 (3.07, 11.48)	0.076	1.80 (1.45, 2.14)	1.61 (1.41, 1.82)	0.621	2.21 (1.29, 3.11)	1.71 (1.21, 2.22)	0.630	**0.006**†	0.599
Valeric acid	1.65 (1.32, 1.97)	1.85 (1.21, 2.50)	0.929	1.64 (1.33, 1.94)	1.65 (1.24, 2.05)	0.742	1.67 (1.08, 2.26)	1.46 (1.12, 1.80)	0.804	0.384	0.709
Isocaproic acid	0.43 (0.31, 0.55)	0.43 (0.26, 0.60)	0.660	0.55 (0.51, 0.59)	0.52 (0.48, 0.56)	0.214	0.54 (0.47, 0.61)	0.50 (0.46, 0.55)	0.569	0.255	0.927
Caproic acid	0.84 (0.63, 1.05)	0.97 (0.62, 1.32)	0.909	0.86 (0.62, 1.10)	0.70 (0.60, 0.81)	0.717	0.82 (0.49, 1.13)	0.71 (0.55, 0.88)	0.942	0.262	0.727
Heptanoic acid	0.60 (0.47, 0.73)	0.63 (0.39, 0.86)	0.505	0.72 (0.66, 0.77)	0.66 (0.62, 0.69)	0.077	0.68 (0.60, 0.77)	0.65 (0.59, 0.71)	0.804	0.332	0.539
Main SCFAs	55.13 (43.14, 67.12)	81.91 (66.20, 97.63)	**0.014**†	45.47 (38.16, 52.77)	62.82 (47.60, 78.05)	**0.040**	58.73 (45.95, 71.52)	58.84 (48.92, 68.77)	0.942	**0.016**	0.068
Total SCFAs	61.78 (49.18, 74.38)	94.80 (75.44, 114)	**0.012**†	52.36 (44.63, 60.10)	69.05 (53.40, 84.71)	0.063	66.21 (52.35, 80.06)	65.16 (54.75, 75.57)	0.896	**0.007**†	0.080

Data are expressed as mean (95% CI) (mmol/kg). SRP: skin roasted peanuts; PB: peanut butter; CB: control butter; SCFAs: Short chain fatty acids; Main SCFAs: sum of acetic, propionic and butyric acids; Total SCFAs: sum of all SCFAs. $p < 0.05$ are statistically significant. p^1 refers to differences between times and was calculated by Wilcoxon's test. p^2 refers to fully adjusted differences between SRP and PB vs. CB at 6 months and was calculated by a generalized estimating equation (GEE). †p value by multiple comparison ($p < 0.017$).

Table 5
Plasmatic and fecal very long-chain saturated fatty acids in healthy adults during the ARISTOTLE study.

	SRP (n = 21)		p^1	PB (n = 23)		p^1	CB (n = 19)		p^1	p^2 *SRP vs. CB*	p^2 *PB vs. CB*
	Pre-intervention	Post-intervention		Pre-intervention	Post-intervention		Pre-intervention	Post-intervention			
VLCSFAs in plasma											
Arachidic acid	2.54 (1.94, 3.14)	3.06 (2.59, 3.53)	**0.048**	3.05 (2.62, 3.51)	4.23 (3.53, 4.93)	**0.012**†	2.60 (2.36, 2.84)	4.45 (3.37, 5.53)	**<0.001**†	**0.046**	0.291
Behenic Acid	2.09 (1.62, 2.56)	4.66 (3.89, 5.43)	**<0.001**†	2.63 (1.96, 3.30)	5.32 (4.65, 6.00)	**<0.001**†	3.10 (2.09, 4.11)	5.41 (4.76, 6.06)	**<0.001**†	0.766	0.751
Lignoceric acid	3.45 (3.10, 3.80)	9.28 (7.50, 11.07)	**<0.001**†	3.93 (2.97, 4.89)	11.18 (9.39, 12.96)	**<0.001**†	4.10 (3.35, 4.86)	14.46 (12.31, 16.62)	**<0.001**†	**0.022**	**0.023**
Total VLCSFAs	8.09 (6.93, 9.25)	17.00 (14.41, 19.59)	**<0.001**†	9.62 (8.08, 11.17)	20.73 (18.27, 23.20)	**<0.001**†	9.81 (0.20, 11.41)	24.33 (21.08, 27.57)	**<0.001**†	**0.005**†	0.089
VLCSFAs in feces											
Arachidic acid	31.45 (19.41, 43.49)	60.52 (43.74, 79.40)	**<0.001**†	25.30 (20.65, 29.94)	41.13 (31.33, 50.93)	**0.035**	24.95 (19.93, 29.96)	31.54 (17.70, 45.38)	0.569	**0.009**†	0.223
Behenic Acid	26.72 (14.45, 39.99)	75.46 (5.21, 94.05)	**<0.001**†	21.35 (16.36, 26.33)	42.18 (28.05, 56.30)	**0.011**†	22.42 (16.44, 28.40)	30.43 (15.04, 45.83)	0.826	**0.002**†	0.361
Lignoceric acid	24.81 (13.66, 35.97)	53.73 (41.23, 67.18)	**<0.001**†	21.39 (17.79, 24.99)	35.23 (27.34, 43.64)	**0.005**†	20.67 (15.84, 25.51)	27.21 (19.05, 35.36)	0.226	**0.012**†	0.288
Total VLCSFAs	82.99 (49.73, 116)	191 (145, 238)	**<0.001**†	68.04 (55.71, 80.37)	118 (88.94, 148)	**0.009**†	68.04 (53.37, 82.72)	89.18 (60.36, 118)	0.307	**0.003**	0.265

Data are expressed as mean (95% CI) (μg/mL for plasma μg/100 mg for feces). SRP: skin roasted peanuts; PB: peanut butter; CB: control butter; VLCSFAs: Very long-chain saturated fatty acids; Total VLCSFAs: sum of arachidic, behenic and lignoceric acids. $p < 0.05$ are statistically significant. p^1 refers to differences between times and was calculated by Wilcoxon's test. p^2 refers to fully adjusted differences between SRP and PB vs. CB at 6 months and was calculated by a generalized estimating equation (GEE). †p value by multiple comparison ($p < 0.017$).

observed in healthy young adults who consumed 25 g of SRP or 32 g of PB or 32 g of CB daily for 6 months compared to baseline. Specifically, subjects in the SRP and PB groups showed improvements in immediate memory, and those in the CB group in recognition memory. In particular, those consuming PB achieved significantly better results in overall memory domains, including delayed episodic recall and in both primary and working memory tests. Barbour et al. similarly reported an enhancement in cerebrovascular reactivity and cognitive function in healthy overweight middle-aged adults who consumed 56–84 g/day of high-oleic peanuts for 12 weeks [4]. In general, the inclusion of nuts in a healthy dietary pattern could be beneficial for cognitive function in adults [3], the effects being more significant in a population with a higher risk of cognitive decline [28]. A randomized controlled parallel clinical trial showed an enhancement of memory and executive functions in healthy adults aged 50–75 years consuming 84 g of almonds daily for six months [29]. Although Pribis et al. did not observe significant changes in non-verbal reasoning or memory, they reported a possible positive effect on verbal reasoning in a randomized controlled crossover study with college students consuming 60 g of walnuts for 8 weeks [30]. In the WAHA study of community-dwelling elderly men and women, carried out in two research centers (Loma Linda, CA, USA and Barcelona, Spain), a delay in cognitive decline was not observed after the intake of 30–60 g/day of walnuts for two years, but global cognition and perception scores improved in the Spanish cohort [31]. The more pronounced protective effect of the intervention on the latter group could be explained by a lower educational level and higher smoking rate of the participants, both associated with a higher risk of cognitive impairment. In the PREDIMED study, participants following a Mediterranean diet supplemented with 30 g of mixed nuts/day showed improvements in cognitive function, including memory domains [32,33] which was partially attributed to polyphenol consumption. After the current six-month intervention, the intake of polyphenols found in peanuts (coumaric acids and resveratrol) had increased in consumers of SRP and PB. Other dietary sources of resveratrol, such as wine, grapes, berries, and dark chocolate [34–36], were excluded from the habitual diet of participants for the duration of the trial.

In addition, anxiety scores had improved in the SRP and PB groups at the end of the study compared to the control, although the differences were significant only in the former. Lower depression scores were obtained after all three interventions. Similarly, Arab et al. reported lower depression scores among walnut consumers in the National Health and Nutrition Examination Survey [37]. However, the consumption of walnuts for 8 weeks, shorter than the period of the previous study, did not change the mood of college students [30]. Moreover, lower levels of cortisol in urine were observed after the SRP and PB interventions compared to baseline. Although depression and anxiety scores were not correlated with urinary cortisol in this study (data not shown), some authors have reported a direct association between mood states and cortisol [38,39]. Nevertheless, this relationship can be modified by various factors, including the influence of sex on the activity of the hypothalamic-pituitary–adrenal axis [40].

In the present study, we found that the polyphenols in peanuts are directly correlated with memory functions and inversely correlated with stress response (cortisol, anxiety, and depression levels). In agreement with these results, there is some evidence that resveratrol has a beneficial effect on cognition and mood [41–43], although its role in cognitive performance has not been conclusively defined [44–46]. Polyphenols may affect cognition and mood indirectly through interactions with the gut microbiota

Table 6
Correlations of cognitive function, mood and urinary cortisol measurements with plasma and fecal VLCSFAs, intake of peanut polyphenols, and total SCFAs in feces.

	Peanut polyphenol intake (n = 63)	Fecal total SCFAs (n = 63)	Plasma VLCSFAs (n = 63)	Fecal VLCSFAs (n = 63)
Immediate memory	0.18 (**0.039**)	0.03 (0.725)	0.20 (**0.024**)	0.29 (**0.009**)
Delayed memory	0.19 (**0.032**)	0.06 (0.480)	0.12 (0.057)	0.13 (0.133)
Recognition	0.17 (0.065)	0.05 (0.580)	0.11 (0.085)	0.11 (0.126)
Verbal memory	0.18 (**0.034**)	0.03 (0.726)	0.20 (**0.025**)	0.23 (**0.008**)
Working memory	0.13 (0.132)	0.11 (0.224)	0.01 (0.839)	0.12 (0.195)
Total memory	0.19 (**0.030**)	0.03 (0.966)	0.18 (**0.045**)	0.21 (**0.015**)
Cognitive flexibility	−0.22 (**0.013**)	0.06 (0.542)	−0.02 (0.749)	−0.08 (0.365)
Perceptual reasoning	0.07 (0.408)	0.05 (0.549)	0.05 (0.521)	0.06 (0.474)
Semantic fluency	0.01 (0.907)	0.16 (0.073)	−0.11 (0.215)	0.02 (0.781)
Formal fluency	0.129 (0.151)	−0.12 (0.197)	0.06 (0.492)	0.07 (0.460)
Cortisol	−0.28 (**0.001**)	−0.18 (**0.047**)	−0.30 (**0.014**)	−0.36 (**<0.001**)
Anxiety	−0.33 (**<0.001**)	−0.11 (0.211)	−0.32 (**<0.001**)	−0.20 (**0.029**)
Depression	−0.22 (**0.005**)	−0.18 (**0.045**)	−0.28 (**0.046**)	−0,04 (0.623)

Data are expressed as r coefficient (*p* value). Significant Spearman correlations p < 0.05. VLCSFAs: very long-chain saturated fatty acids. SCFAs: short-chain fatty acids.

and enhanced brain-derived neurotrophic factor (BDNF) expression [9,47,48] However, the findings of randomized trials evaluating the effects of acute and chronic polyphenol-rich interventions on cognition are mixed and controversial [8].

We found that higher concentrations of total SCFAs in feces were inversely related to the depression score and urinary cortisol levels. The main SCFAs (acetic, propionic, and butyric acids) were significantly higher after the SRP and PB interventions. Produced by the gut microbiota, the immunomodulatory and anti-inflammatory properties of these fatty acids have promising beneficial effects against depression and neurodegenerative disease [11,49,50]. Nut consumption (including walnuts, pistachios and almonds) may increase butyrate-producing bacteria in healthy adults [51–54], depending on the nut type and duration of the intervention [55]. In agreement with our results, Szczesniak et al. reported a slightly negative association of butyric acid with depression, whereas the concentration of isovaleric acid was directly correlated with cortisol and depression [56]. SCFAs may have an impact on the central nervous system by modulating energy metabolism, neuroinflammation, and blood–brain barrier permeability via their effects on receptors, transporters, and histone deacetylases. They can potentially increase BDNF levels in the prefrontal cortex by inhibiting-histone deacetylation [12].

Circulating VLCSFAs, biomarkers of peanut product consumption, increased after all three interventions, whereas the concentration of fecal VLCSFAs was higher in those consuming SRP or PB but not CB. Similar results for total fatty acids have been reported in other intervention studies with peanuts, fecal fat being significantly higher after whole peanut consumption [57]. This could be explained by the low efficiency of energy absorption from lipid-rich nuts due to poor bioaccessibilty [58,59]. Looking for an explanation for our results, we found that plasmatic and fecal VLCSFAs, present in the lipid fraction of all three products administered in the trial, were directly correlated with memory function and inversely correlated with stress response. These results may have contributed to the small differences observed between the interventions and the control. Research on the effect of these fatty acids on health is limited, but in agreement with our results, a higher level of plasma VLCSFAs in midlife participants in the Atherosclerosis Risk in Communities study was associated with a lower overall cognitive decline over a 20-year period [60].

Regarding physical activity, which is known to influence mental health [61,62], the participants in the ARISTOTLE study maintained a level of physical activity during the study considered optimal by health recommendations (3000–4000 METs/week) [63]. They reported a significant decrease in physical activity after the SRP and CB interventions compared to baseline, but this did not negatively impact on mental outcomes. Despite the decrease in physical activity and the daily consumption of peanuts, which have a high energetic value, no changes in total energy intake or body composition were observed at the end of the intervention. Similarly, Cleasson et al. did not find any changes in anthropometric measurements in a randomized controlled parallel trial carried out in healthy adults consuming 20 kcal/kg/day (~200 g/day) of peanuts for 14 days [64].The ARISTOTLE study is the first randomized controlled clinical trial in healthy young adults to evaluate the effect of daily consumption of peanut products and their bioactive compounds on cognition and stress response, also assessing the main metabolites produced by microbiota (SCFAs).

The strong points of the present study include the randomized and controlled design, the use of a broad battery of standardized cognitive tests, and the impactful results obtained in healthy young adults (most of them university students), despite three months of lockdown due to the COVID-19 pandemic. The main limitations of the study are the small sample size for each group, the lack of blinding, and the absence of a peanut-free product as a control. Although the sample size was calculated to ensure 80% of statistical power, this value decreased to 60% due to dropouts. This study provides promising results about the effect of peanut product consumption on cognition and mood, but the small sample size, the possible effect of VLCSFAs in the products consumed by each group, and lack of a peanut-free control could have contributed to the lack of differences observed between groups.

In conclusion, regular peanut and peanut butter consumption may enhance memory function and stress response in a healthy young population. These effects seem to be related to the intake of polyphenols found in peanuts, the increased level of fecal SCFAs, and plasma and fecal VLCSFAs associated with peanut consumption. Further well-designed clinical trials with peanut products, a larger sample size and longer follow-up should be conducted to confirm these findings.

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Author contributions

SH-B, MT-S, RE and RML-R designed the research. IP-M, ID-L, SC-B and SH-B: conducted the experiments and data collection. IP-M, ID-L, MC, BB and SH-B: analyzed the data. IP-M wrote the paper. SH-B and RML-R had primary responsibility for final content. All authors reviewed and approved the paper.

Conflict of interest

R.M.L-R reports receiving lecture fees from Cerveceros de España; and receiving lecture fees and travel support from Adventia. R.E reports personal fees, grants, and nonfinancial support from the California Walnut Commission and Alexion; personal fees and nonfinancial support from Danone; and nonfinancial support from the International Nut Council. Nevertheless, these foundations were not involved in the study design, the collection, analysis and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. The other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.09.020.

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