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Consumption of peanut products enhances the production of microbial phenolic metabolites related with memory and stress response: Results from the ARISTOTLE trial

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ABSTRACT

Based on evidence demonstrating that gut microbiota can metabolize dietary polyphenols to more readily absorbable phenolic acids, this study aimed to evaluate the association of urinary microbial phenolic metabolites (MPMs) related to peanut intake with memory function and stress response. A total of 63 healthy young adults from a randomized controlled trial completed the intervention, consuming 25 g of skin roasted peanuts, 32 g of peanut butter, or 32 g of a control butter daily for six months. Cognition and mood were assessed using validated tests. Urinary cortisol was quantified by an enzymatic method and MPMs were analyzed by liquid chromatography coupled to mass spectrometry. Lignans and hydroxybenzoic acids with significantly higher post-intervention levels were correlated with improved cognition and mood in peanut product consumers. These findings suggest that peanut and peanut butter consumption may contribute to the production of MPMs involved in the improvement of memory.

1. Introduction

Nut consumption has been shown to be beneficial for cognitive function in adults (Pribis et al., 2012; Rakic et al., 2021; Sala-Vila et al., 2020; Theodore et al., 2021). Peanuts, although they are in fact legumes, are nutritionally grouped with tree nuts due to their similar characteristics, and are a source of monounsaturated fat, folate, vitamin E, magnesium, potassium, arginine, fiber, and polyphenols (Barbour et al., 2017; Theodore et al., 2021). Among these natural compounds, polyphenols have attracted attention for their association with improved cognitive status (Caruso et al., 2022). They have been reported to protect neurons from free radicals and other reactive oxygen species, and to slow cognitive decline (Gervasi et al., 2021). Their effect on brain health could also be mediated by the microbiota-gut-brain axis, a system that acts bidirectionally, synchronizing the intestine with the central nervous system, and modifying the behavior and immune homeostasis of the brain (Businaro et al., 2021; Filosa et al., 2018).

The gut microbiota is a complex and diverse community of microorganisms, including bacteria, viruses, and fungi, that resides in the gastrointestinal tract, particularly in the large intestine or colon (Marchesi & Ravel, 2015). These microbial species coexist in a symbiotic relationship with the host and play a crucial role in various physiological processes, such as digestion and absorption of nutrients, production of beneficial metabolites (Barko et al., 2018; Sekirov et al., 2010), modulation of the immune system, protection against pathogens (Lynch & Pedersen, 2016), and even influencing brain processes and behavior (Morais et al., 2021). The application of metabolomics approaches has greatly advanced our understanding of the mechanisms linking the gut microbiota composition and its activity to health and disease phenotypes (Thursby & Juge, 2017). Since then, current research suggests that diet has a large effect on gut microbiota, opening up promising avenues of research in areas such as nutrition, disease prevention, and personalized medicine (van Duynhoven et al., 2011).

The relationship between diet and the microbiota has been described

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in two ways. Firstly, certain foods components can have a prebiotic effect, meaning they can modulate the composition of the gut microbiota (Queipo-Ortuño et al., 2012; Tzounis et al., 2011). Secondly, microbiota can behave as a metabolic entity, producing metabolites derived from food consumption (Cuciniello et al., 2023; Rinninella et al., 2019). In accordance, most dietary polyphenols arrive intact at the colon, where, in addition to exerting a prebiotic action (Rodríguez-Daza et al., 2021), they are metabolized by gut bacteria (Laveriano-Santos et al., 2022). The biotransformation of polyphenols by the intestinal microbiota gives rise to more simple components known as microbial phenolic metabolites (MPMs) (Laveriano-Santos et al., 2022; Marhuenda-Muñoz et al., 2019), which can cross the blood–brain barrier, reach brain cells, and have a neuroprotective effect (Figueira et al., 2017). Enterolignans such as enterodiol and enterolactone are major microbial end metabolites derived from lignans present in whole grains, nuts, and legumes, including peanuts (Rodríguez-García et al., 2019). Hydroxybenzoic acids are the most prevalent microbial metabolites formed in the gut from phenolic compounds, both flavonoids and nonflavonoids (Plamada & Vodnar, 2022), and urolithins are the main microbial metabolites produced after the intake of ellagitannins in berries and nuts (Lamuel-Raventos & Onge, 2017; Marhuenda-Muñoz et al., 2019).

An improvement of memory function and stress response was previously observed in participants in the ARISTOTLE trial (Parilli-Moser et al., 2021). This result was attributed to the polyphenols from peanuts products, but we assessed polyphenols' intake and did not consider the ability of gut microbiota to metabolize dietary polyphenols into phenolic metabolites that are more easily absorbed. To address this gap, the aim of the present study was to evaluate the potential of gut microbiota to produce MPMs accurately identified by liquid chromatography coupled to mass spectrometry, after an intervention with peanut products and determine whether these microbiota-derived metabolites are also associated with the previously observed improvements in memory function and stress response.

2. Material and methods

2.1. Experimental design and study population

The study conducted was a randomized controlled trial designed to assess the impact of daily peanut and peanut butter intake on the gut microbiota-brain axis, previously described (Parilli-Moser et al., 2021). From the 90 healthy subjects who initially enrolled, 63 healthy participants (19 males and 44 females) aged between 18 and 33 years completed the study. The healthy status of each participant was validated by the following criteria: 1) absence of chronic diseases (cardiovascular diseases, cancer, diabetes, and others), peanut allergy or intolerance, 2) not being overweight or obese, 3) active smokers and high alcohol consumers were excluded. Participants were randomly assigned to a study group after a run-in period of 15 days (without consumption of peanut products). A simple randomization was performed using computer-generated random numbers. A random number and group were assigned to each subject at the moment of enrollment purely by chance. One group consumed 25 g/day of skin-roasted peanuts (SRP), and the two others consumed two tablespoons (32 g)/day of peanut butter (PB), or two tablespoons (32 g)/day of a control butter (CB) based on peanut oil and free of fiber and polyphenols, for 6 months. During the intervention, participants were not allowed to consume wine, grapes, dark chocolate (>70% cocoa), berries, and nuts or probiotics, prebiotics, and antibiotics with potential effects on the gut microbiota. As the intervention was dietary, it was blinded to the laboratory personnel and technicians but not to the participants or researchers.

2.2. Ethical statement

All the participant signed an informed consent and were able to withdraw from the study at any time without giving a reason. The products tested were safe for consumption. The study protocol was approved by the Bioethics Commission of the University of Barcelona (Institutional Review Board: IRB 00003099), the clinical trial was registered at https://register.clinicaltrials.gov (NCT04324749), and all procedures were carried out in compliance with the principles outlined in the Declaration of Helsinki.

2.3. Covariate assessment

Covariate data were collected by professional staff members using general questionnaires about socio-demographic variables (i.e., sex, age, level of education), physical activity, and dietary intake. Physical activity was assessed using a Spanish-validated version of the Minnesota Leisure-Time Physical Activity Questionnaire, measured as the metabolic equivalent of task-minutes per week (MET/week) (Elosua et al., 1994, 2000). Dietary intake was quantified using a validated semi-quantitative 151-item food frequency questionnaire (Juton et al., 2021). Trained staff obtained anthropometric measurements and biological samples in fasting conditions. Height was measured in the standing position using a portable stadiometer. Weight and body fat were measured using a tetrapolar OMRON BF511 bioelectrical device, with the participants wearing light clothes and no shoes. BMI was calculated as weight divided by height squared (kg/m^2). The waist circumference was measured using an inelastic flexible tape positioned at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Blood samples were collected via venipuncture in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 3000 g for 10 min at 4 °C to separate the serum. 24 h-urine was provided by participants. All measurements were carried out at baseline and at the end of the study. Aliquots were stored at −80 °C until analysis. Biochemical markers in serum (lipid profile) and urine (cortisol) were measured in an external laboratory (Cerba internacional, Barcelona, Spain) using enzymatic methods.

2.4. Microbial phenolic metabolite analysis

2.4.1. Standards and reagents

Phenolic standards were purchased from Sigma-Aldrich (St. Louis, MO, USA), Santa Cruz (Santa Cruz Biotechnology, Santa Cruz, CA), and Fluka (St. Louis, MO, USA). The reagents were supplied by Panreac Química S.A. (Barcelona, Spain), and ultrapure water (Milli-Q) was generated by a Millipore system (Bedford, MA, USA).

2.4.2. Extraction and analysis of urine samples

Urine samples were extracted by an SPE using a Waters Oasis HLB 96-well plate 30 μm (Waters Oasis, Milford, MA, USA) previously described and analyzed by liquid chromatography coupled with linear trap quadrupole Orbitrap high-resolution mass spectrometry (LC-LTQ-Orbitrap-HRMS) (Thermo Scientific, Hemel Hempstead, UK) equipped with electrospray ionization and working in negative mode, as described elsewhere (Laveriano-Santos et al., 2022; Parilli-Moser et al., 2023). Chromatographic separation was performed using a Kinetex F5 100A column (50 × 4.6 mm × 2.6 μm) from Phenomenex (Torrance, CA, USA). The gradient elution was performed with two mobile phases, A: water (0.05% formic acid) and B: acetonitrile (0.05% formic acid) and the flow rate was set at 0.5 mL/min and the injection volume was 5 μL.

2.4.3. Identification and quantification of MPMs

The identification and quantification of MPMs was performed using Trace Finder software version 4.1 (Thermo Fisher Scientific, San Jose, CA). The glucuronidated and sulfated MPMs were quantified with their respective aglycone equivalents due to the unavailability of standards. Values below the limit of detection were replaced by values corresponding to one-half the limit of detection, and values below the limit of quantitation were replaced by the midpoint between the limit of detection and the limit of quantitation.

2.5. Cognitive and mood assessment

At baseline and at the end of the study, trained personnel assessed cognitive functions of the participants by administering a broad range of validated neuropsychological tests and mood disorder questionnaires in a standard order. The Wechsler Memory Scale (WMS-IV) was used to assess immediate and delayed memory and recognition (Khalil et al., 2020; Wechsler, 1945). The Wechsler Adult Intelligence Scale (WAIS-III and IV) was used to measure working memory. Digit Span and Letter-Number Sequencing (LNS) and the Trail Making Test (TMT) were used to measure cognitive flexibility and visual-motor processing speed (Peña-Casanova et al., 2009; Wechsler, 2008; Wechsler D, 1997). The Hospital Anxiety and Depression Scale (HADS) validated for the Spanish population was also used (Herrero et al., 2003). This consists of two subscales: HADS-A, designed to detect anxious states, and HADS-D, designed to detect depressive states, with higher scores indicating greater levels of anxiety or depression. Participant raw test results were standardized to z-scores, and composite scores of different cognitive domains were calculated for each participant. A composite score for verbal memory 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 measurements to provide a total memory score. Also, a cognitive flexibility score was calculated from TMT-a and TMT-b z-scores.

2.6. Statistical analyses

The normality of distribution was assessed using the Shapiro–Wilk test. Given the small sample size in each group and the non-normal distribution of variables, non-parametric tests were used. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables as number (n) and proportion (%). Participant characteristics between the intervention groups at baseline were compared using the chi-square test for categorical variables and the Kruskal–Wallis test with Dunn's post-hoc test for continuous variables. To evaluate changes from baseline to the end of the study within each study group, the Wilcoxon signed-rank test was employed. The effect of the interventions was estimated using generalized estimating equation on Poisson regression models for repeated measures, incorporating an identity link function, autoregressive correlation, and robust standard error parameters due to the low number of clusters and the nature of the variables, and the analyses were adjusted for confounders. Additionally, Spearman's correlation coefficient was calculated to evaluate the associations between MPMs and cognitive and mood outcomes. Statistical analyses were performed using the Stata statistical software package version 16.0 (StataCorp, College Station, TX, USA). Statistical significance was considered when the *p*-value was lower than 0.050.

3. Results

3.1. Participant characteristics

Table 1 summarizes the participants' general characteristics at the beginning of the study. The average age was 22.71 ± 3.13 years, with approximately 70% being female. About 46% of the participants had completed a four-year degree program. The average BMI was 22.3 ± 2.93 kg/m^2 indicating a healthy body weight and the mean physical activity level exceeded 4000 MET/week. At baseline, no significant differences were found between groups, except for the level of plasmatic high density lipoprotein cholesterol (HDL-c) ($p = 0.006$). As shown in **Supplementary Table 1**, physical activity significantly decreased at the end of the intervention in the SRP and CB groups compared to baseline ($p = 0.012$ and $p = 0.034$, respectively). However, no significant changes were observed in body composition and clinical parameters. Besides the administered products, dietary parameters were also

Table 1
General characteristics of the study population at baseline.

	SRP (n = 21)	PB (n = 23)	CB (n = 19)	*p-value*
Female, n (%)	14 (66)	18 (78)	12 (63)	0.528
Age (years)	22.28 ± 3.20	23.43 ± 2.90	22.42 ± 3.29	0.247
Educational level, n (%)				0.512
University students	11 (52%)	11 (48%)	12 (63%)	
Graduated	10 (48%)	12 (52%)	7 (37%)	
Physical activity (MET/week)	4850 ± 2124	4703 ± 2381	4607 ± 1728	0.954
Anthropometric measurements				
Weight (kg)	63.26 ± 10.12	60.10 ± 7.72	63.78 ± 10.04	0.412
BMI (kg/m^2)	22.12 ± 3.52	22.19 ± 2.60	22.59 ± 2.67	0.679
Waist circumference (cm)	72.73 ± 8.31	71.28 ± 5.53	74.68 ± 5.99	0.228
Waist to hip ratio	0.74 ± 0.06	0.74 ± 0.05	0.77 ± 0.05	0.130
Body fat (%)	26.66 ± 8.07	28.45 ± 7.88	26.22 ± 7.99	0.628
Lipid profile				
TG (mmol/L)	0.71 ± 0.20	0.85 ± 0.35	0.80 ± 0.25	0.341
TC (mmol/L)	4.33 ± 0.52	4.60 ± 0.88	4.09 ± 0.64	0.137
LDL-c (mmol/L)	2.22 ± 0.39	2.60 ± 0.69	2.30 ± 0.50	0.142
HDL-c (mmol/L)	1.75 ± 0.30^b	1.59 ± 0.53^{ab}	1.50 ± 0.30^a	**0.006**
Dietary intake				
Energy (kcal/day)	2770 ± 594	2705 ± 602	2596 ± 478	0.588
Carbohydrates (g/day)	257 ± 80.73	241 ± 73.92	247 ± 59.49	0.867
Sugar (g/day)	116 ± 34.83	112 ± 35.04	114 ± 41.02	0.906
Fiber (g/day)	45.17 ± 21.95	42.12 ± 14.65	38.93 ± 15.07	0.768
Protein (g/day)	104 ± 29.47	110 ± 31.86	108 ± 27.51	0.598
Total fat (g/day)	145 ± 29.17	142 ± 35.35	130 ± 28.96	0.249
SFAs (g/day)	37.61 ± 10.00	38.18 ± 11.04	36.81 ± 13.02	0.871
MUFAs (g/day)	70.37 ± 16.12	69.06 ± 17.17	59.46 ± 15.87	0.093
PUFAs (g/day)	25.91 ± 6.76	23.99 ± 7.25	23.59 ± 6.59	0.541
Lignans (mg/day)	5.39 ± 6.74	3.85 ± 2.89	4.82 ± 6.08	0.792
Hydroxybenzoic acids (mg/day)	13.39 ± 7.97	10.92 ± 5.60	8.90 ± 6.02	0.097
Hydroxycoumarins (mg/day)	0.05 ± 0.05	0.05 ± 0.06	0.03 ± 0.05	0.333
Urinary microbial phenolic metabolites				
Lignans (mg/day)	26.63 ± 12.05	27.18 ± 7.19	29.01 ± 15.26	0.140
Hydroxybenzoic acids (mg/day)	56.05 ± 24.91	67.74 ± 59.66	71.71 ± 49.26	0.755
Hydroxycoumarins (mg/day)	7.99 ± 5.93	7.26 ± 4.17	7.25 ± 5.84	0.732

Data are expressed as mean ± SD. SRP: Skin roasted peanuts; PB: Peanut butter; CB: Control butter; MET/week: metabolic equivalent of task-minutes per week. BMI: Body mass index; TG: Triglyceride; TC: Total cholesterol; LDL-c: LDL-cholesterol; HDL-c: HDL-cholesterol; SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids. p column refers to differences between groups at baseline. P-values < 0.05 are statistically significant and were calculated by the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables.

monitored during the six-month intervention to determine any differences in dietary habits that could potentially influence MPM excretion. No differences were observed between groups in nutrient and food intake at the end of the intervention. A significant reduction in nut, wine, and cocoa intake was observed after six months compared to baseline in all groups ($p < 0.001$) in accordance with the request not to consume these products, due to their richness in polyphenols also found in peanuts or a similar lipid composition (Table S1).

3.2. Changes in microbial phenolic metabolites following the intervention

Table 2 provides the differences in MPM concentrations observed at the end of the intervention. After adjustment for sex and age, there was a trend to higher lignan and hydroxybenzoic acid excretion after consumption of SRP ($p = 0.084$ and $p = 0.020$, respectively) and PB ($p = 0.038$ and $p = 0.086$, respectively) compared with the control butter. Levels of urinary enterolignans were significantly higher in the SRP group (enterodiol glucuronide, $p = 0.012$; enterolactone $p = 0.032$; enterolactone glucuronide, $p = 0.042$; and enterolactone sulfate, $p = 0.009$) and the PB group (enterodiol glucuronide, $p = 0.042$, and enterolactone glucuronide, $p = 0.022$) after 6 months of intervention compared to baseline. Similarly, the SRP and PB groups showed significantly higher levels of enterodiol glucuronide ($p = 0.018$ and $p = 0.031$, respectively) and enterolactone glucuronide ($p = 0.045$ and $p = 0.032$, respectively) compared to the control group after adjustment. Regarding hydroxybenzoic acids, SRP and PB groups excreted higher levels of 3-hydroxybenzoic acid ($p < 0.001$ and $p < 0.001$), 4-hydroxybenzoic acid ($p = 0.046$ and $p = 0.009$), hydroxybenzoic acid glucuronide ($p = 0.012$ and $p < 0.001$), hydroxybenzoic acid sulfate ($p < 0.001$ and $p = 0.005$), protocatechuic acid sulfate ($p < 0.001$ and $p = 0.004$), syringic acid ($p = 0.001$ and $p = 0.004$), syringic acid sulfate ($p < 0.001$ and $p < 0.001$), and total hydroxybenzoic acids ($p = 0.076$ and $p = 0.018$) after six months compared to baseline. In addition, higher concentrations of 3-hydroxybenzoic acid ($p = 0.002$), vanillic acid sulfate ($p = 0.048$), and syringic acid sulfate ($p = 0.041$) were observed after the SRP versus CB intervention. A trend to higher concentrations of hydroxybenzoic acids ($p = 0.086$) was found in the PB compared to the CB group, with particularly significant increases of 3-hydroxybenzoic acid ($p < 0.001$), hydroxybenzoic acid sulfate ($p = 0.004$), vanillic acid sulfate ($p = 0.006$), and syringic acid glucuronide II ($p = 0.023$).

3.3. Impact of the intervention on cognitive and mood outcomes

Results regarding memory as well as anxiety and depression scores are shown in Table 3. After the six-month intervention, a significant improvement was observed in total verbal memory and total memory in the PB group compared to baseline ($p = 0.011$ and $p = 0.006$, respectively). Moreover, a lower anxiety score was found in SRP and PB consumers compared to baseline ($p < 0.001$ and $p = 0.003$, respectively), whereas a significant decrease in the depression score was observed for all three groups, SRP, PB and CB ($p = 0.007$, $p = 0.004$ and $p = 0.032$, respectively). Comparing peanut interventions with the control group, a significant reduction in the anxiety score was observed in the SRP compared to the CB group at six months after full adjustment ($p = 0.001$). In addition, urinary cortisol levels decreased significantly in the SRP and PB groups after the intervention compared to baseline ($p = 0.004$ and $p = 0.008$, respectively), but no differences were found between them and the control group.

Table 2
Post-intervention differences in microbial phenolic metabolite concentrations in urine of healthy young adults from the ARISTOTLE study, after adjustment for sex and age.

	SRP (n = 21) Post-intervention - Baseline	p^1	**PB (n = 23) Post-intervention - Baseline**	p^1	**CB (n = 19) Post-intervention - Baseline**	p^1	p^2 ***SRP vs. CB***	p^2 ***PB vs. CB***
Lignans	7.55 ± 17.29	0.121	9.45 ± 16.18	0.331	−0.69 ± 11.30	0.951	0.084	**0.038**
Enterodiol	−0.77 ± 10.01	0.685	0.28 ± 6.22	0.986	−0.38 ± 6.85	0.970	0.836	0.824
Enterodiol glucuronide	1.21 ± 2.50	**0.012**	1.92 ± 5.07	**0.042**	−0.81 ± 3.30	0.954	**0.018**	**0.031**
Enterodiol sulfate	0.12 ± 0.33	0.178	0.00 ± 0.12	0.621	−0.02 ± 0.62	0.293	0.373	0.901
Enterolactone	0.79 ± 2.78	**0.032**	0.13 ± 0.27	0.209	0.06 ± 0.21	0.868	0.206	0.545
Enterolactone glucuronide	6.90 ± 10.69	**0.042**	7.17 ± 8.87	**0.022**	1.39 ± 6.64	0.506	**0.045**	**0.032**
Enterolactone diglucuronide	−0.01 ± 0.05	0.571	−0.01 ± 0.04	0.621	0.02 ± 0.04	0.280	0.100	0.054
Enterolactone sulfate	0.04 ± 0.06	**0.009**	0.02 ± 0.05	0.218	−0.01 ± 0.07	0.823	**0.020**	0.086
Hydroxybenzoic acids	20.82 ± 32.50	0.076	32.74 ± 52.28	**0.018**	−0.19 ± 47.14	0.872	0.169	0.059
3- Hydroxybenzoic acid	3.35 ± 5.51	**<0.001**	3.83 ± 3.54	**<0.001**	−0.31 ± 2.50	0.385	**0.002**	**<0.001**
4-Hydroxybenzoic acid	0.44 ± 1.41	**0.046**	0.32 ± 0.77	**0.009**	0.27 ± 1.21	0.300	0.631	0.914
Hydroxybenzoic acid glucuronide	0.33 ± 0.67	**0.012**	0.25 ± 0.39	**<0.001**	0.19 ± 1.70	0.937	0.832	0.958
Hydroxybenzoic acid sulfate	3.18 ± 5.65	**<0.001**	7.12 ± 7.66	**0.005**	0.91 ± 4.66	0.908	0.090	**0.004**
Protocatechuic acid	−0.02 ± 1.18	0.636	−0.36 ± 2.25	0.449	0.62 ± 2.99	0.931	0.331	0.335
Protocatechuic acid glucuronide I	0.35 ± 1.11	0.485	0.41 ± 1.90	0.917	−0.05 ± 0.54	0.452	0.157	0.291
Protocatechuic acid glucuronide II	−0.05 ± 0.18	0.138	0.04 ± 0.34	0.977	−0.00 ± 0.16	0.988	0.083	0.921
Protocatechuic acid sulfate	1.16 ± 1.24	**<0.001**	1.97 ± 2.21	**0.004**	1.02 ± 3.95	0.096	0.354	0.885
Vanillic acid	−1.46 ± 4.89	0.469	−3.48 ± 15.03	0.991	0.81 ± 13.11	0.773	0.079	0.177
Vanillic acid glucuronide I	−0.91 ± 4.34	0.396	−0.15 ± 13.49	0.382	−0.06 ± 16.77	0.931	0.146	0.515
Vanillic acid glucuronide II	0.70 ± 7.18	0.842	7.77 ± 19.86	0.248	2.21 ± 14.96	0.773	0.112	0.976
Vanillic acid sulfate	3.05 ± 20.19	0.579	6.17 ± 12.85	0.157	−6.26 ± 15.12	0.123	**0.048**	**0.006**
Syringic acid	1.3 ± 2.45	**0.001**	0.83 ± 1.17	**0.004**	0.13 ± 3.06	0.402	0.083	0.149
Syringic acid glucuronide I	1.20 ± 3.14	0.396	1.15 ± 2.62	0.094	0.30 ± 0.68	0.751	0.267	0.165
Syringic acid glucuronide II	0.40 ± 3.09	0.584	0.94 ± 3.12	0.179	−3.30 ± 6.92	0.065	0.052	**0.023**
Syringic acid sulfate	7.75 ± 9.71	**<0.001**	5.92 ± 9.41	**<0.001**	2.34 ± 11.18	0.544	**0.041**	0.208
Hydroxycoumarins	4.78 ± 14.63	0.909	5.40 ± 11.96	0.132	4.23 ± 20.96	0.879	0.791	0.694
Urolithin A	−0.64 ± 1.58	0.146	−0.30 ± 1.74	0.503	−0.12 ± 0.42	0.960	0.123	0.572
Urolithin A glucuronide	5.27 ± 14.48	0.636	2.48 ± 11.65	0.129	4.29 ± 21.20	0.875	0.768	0.720
Urolithin A sulfate	0.09 ± 0.25	0.070	0.10 ± 0.36	0.412	0.02 ± 0.29	0.746	0.268	0.466
Urolithin B	0.05 ± 0.51	0.372	0.17 ± 0.80	0.875	0.02 ± 0.07	0.321	0.807	0.425

Data on changes (post-intervention value minus the baseline value) are expressed as mean (mg/day) ± SD. SRP: Skin roasted peanuts; PB: Peanut butter, CB: Control butter. p^1 refers to the difference between times in each arm and was calculated by Wilcoxon's test. p^2 refers to differences adjusted by age and sex between SRP and PB *vs.* CB at 6 months and was calculated by a generalized estimating equation. *p*-values < 0.05 were considered significant.

Table 3
Cognitive measurements and urinary cortisol levels of healthy young adults from 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			
Total memory	125 ± 15.47	132 ± 17.03	0.158	126 ± 11.97	136 ± 10.49	**0.006**	127 ± 17.61	133 ± 15.36	0.229	0.753	0.524
Verbal memory	92.09 ± 11.19	98.00 ± 12.06	0.062	94.77 ± 10.28	101.77 ± 7.95	**0.011**	94.79 ± 13.93	98.73 ± 11.78	0.491	0.658	0.485
Working memory	33.14 ± 6.75	34.76 ± 7.35	0.480	31.45 ± 5.37	34.41 ± 6.41	0.151	33.05 ± 6.06	34.39 ± 6.72	0.645	0.921	0.632
Cognitive flexibility	79.19 ± 26.84	70.62 ± 27.54	0.190	81.55 ± 22.24	74.95 ± 21.43	0.451	87.21 ± 18.73	79.22 ± 24.44	0.149	0.939	0.568
HADS											
Anxiety	8.48 ± 2.73	2.76 ± 2.89	**<0.001**	6.38 ± 3.43	3.38 ± 2.16	**0.003**	6.21 ± 4.76	4.84 ± 4.87	0.241	**0.001**	0.154
Depression	6.76 ± 4.46	3.23 ± 2.16	**0.007**	6.00 ± 3.56	3.19 ± 2.38	**0.004**	7.21 ± 5.11	3.63 ± 2.81	**0.032**	0.639	0.403
Cortisol (mmol/L)	558 ± 132	354 ± 132	**0.004**	489 ± 154	377 ± 191	**0.008**	470 ± 159	392 ± 157	0.145	0.068	0.584

Data are expressed as mean ± SD. SRP: Skin roasted peanuts; PB: Peanut butter; CB: Control butter; HADS: Hospital anxiety and depression scale. p^1 refers to the difference between times in each arm and was calculated by Wilcoxon's test. p^2 refers to differences full adjusted by age, sex, level of education and physical activity between SRP and PB *vs.* CB at 6 months and was calculated by a generalized estimating equation. *p*-values < 0.05 were considered significant.

3.4. Relationship between MPMs and cognitive and mood outcomes

The relationship between MPMs and cognitive and mood outcomes are shown in Fig. 1. We found that the improvement of total memory scores was directly correlated with the excretion of some MPMs: enterodiol sulfate (r = 0.26, $p = 0.005$), enterolactone (r = 0.25, $p = 0.006$), total hydroxybenzoic acids (r = 0.23, $p = 0.013$), 3-hydroxybenzoic acid (r = 0.31, $p < 0.001$), 4-hydroxybenzoic acid (r = 0.27, $p = 0.003$), hydroxybenzoic acid sulfate (r = 0.23, $p = 0.015$), vanillic acid sulfate (r = 0.26, $p = 0.005$), and syringic acid sulfate (r = 0.24, $p = 0.009$). Similarly, total verbal memory was associated with higher levels of total lignans (r = 0.20, $p = 0.033$), enterodiol sulfate (r = 0.28, $p = 0.002$), enterolactone (r = 0.25, $p = 0.006$), total hydroxybenzoic acids (r = 0.21, $p = 0.020$), 3-hydroxybenzoic acid (r = 0.26, $p = 0.004$), hydroxybenzoic acid sulfate (r = 0.20, $p = 0.027$), protocatechuic acid sulfate (r = 0.20, $p = 0.039$), vanillic acid sulfate (r = 0.24, $p = 0.010$) and syringic acid sulfate (r = 0.22, $p = 0.020$). While working memory score was related to higher levels of enterolactone (r = 0.19, $p = 0.042$), total hydroxybenzoic acids (r = 0.20, $p = 0.027$), 3- hydroxybenzoic acid (r = 0.28, $p = 0.002$), 4-hydroxybenzoic acid (r = 0.26, $p = 0.004$), hydroxybenzoic acid sulfate (r = 0.21, $p = 0.021$), protocatechuic acid glucuronide II (r = 0.21, $p = 0.026$), and vanillic acid sulfate (r = 0.25, $p = 0.006$). In addition, cognitive flexibility was inversely and significantly correlated with total hydroxybenzoic acids (r = -0.19, $p = 0.037$), 3-hydroxybenzoic acid (r = -0.28, $p = 0.003$), 4-hydroxybenzoic acid (r = -0.37, $p < 0.001$), hydroxybenzoic acid sulfate (r = -0.20, $p = 0.032$), protocatechuic acid sulfate (r = -0.25, $p = 0.008$), vanillic acid sulfate (r = -0.25, $p = 0.006$), and syringic acid sulfate (r = -0.22, $p = 0.017$).

Regarding anxiety, an inverse correlation with 3-hydroxybenzoic acid (r = -0.31, $p = 0.001$), hydroxybenzoic acid sulfate (r = -0.21, $p = 0.024$), protocatechuic acid sulfate (r = -0.35, $p < 0.001$), and syringic acid sulfate (r = -0.30, $p = 0.001$) was observed. A decrease in the depression score was significantly correlated with higher levels of 3-hydroxybenzoic acid (r = -0.26, $p = 0.004$), 4-hydroxybenzoic acid (r = -0.21, $p = 0.021$), protocatechuic acid sulfate (r = -0.19, $p = 0.049$), syringic acid glucuronide I (r = -0.36, $p = 0.005$), and syringic acid sulfate (r = -0.27, $p = 0.003$). Moreover, cortisol levels were also inversely and significantly correlated to protocatechuic acid sulfate (r = -0.20, $p = 0.034$) and syringic acid sulfate (r = -0.25, $p = 0.014$).

4. Discussion

Higher urinary excretion of enterolignans (enterodiol and enterolactone) and hydroxybenzoic acids was observed after SRP and PB consumption in healthy young adults from the ARISTOTLE trial. Additionally, the increase of these MPMs in urine after the peanut interventions was associated with an improvement in memory and stress response.

Both peanuts as peanut butter contain lignans, being enterolactone and enterodiol first detectable compounds in human biological fluids after lignan-rich food intake (Rodríguez-García et al., 2019). Better memory scores were significantly correlated with a higher concentration of urinary lignans after SRP and PB consumption, particularly enterolactone, whose production increased after the SPR intervention compared to baseline. Lignan bioavailability is highly dependent on gut microbiota metabolism. The microbial generation of enterolactone through the dehydrogenation of enterodiol is of particular interest, as this metabolite is more strongly associated with health benefits than enterodiol (Brito & Zang, 2019; Johnson et al., 2019). Notably, the participants tended to excrete more enterolactone than enterodiol after the peanut and peanut butter interventions. In a previous study, a higher intake of dietary lignans was associated with a lower decline in global cognitive function, memory function, and speed of cognitive processes in a middle-aged cohort (43–70 years) in the Netherlands, who were followed up after 5 years (Nooyens et al., 2015). Similarly, a study carried out in healthy women aged 42 to 52 years in the US showed that the consumption of lignans had beneficial effects on verbal memory (Greendale et al., 2012). A higher intake of total lignans was also associated with lower odds of cognitive impairment in a cohort of older Italian individuals (Giampieri et al., 2022). In a study with Argentinian postpartum women, an increase of lignan consumption was associated with cognitive improvement in all memory domains (Miranda et al., 2021). However, no differences in cognition were observed in a randomized placebo-controlled clinical trial with older healthy adults (60–80 years) who consumed a flaxseed lignan-enriched complex (~38% secoisolariciresinol diglucoside) for 24 weeks (Di et al., 2017).

Although the role of lignans in human cognitive function requires further research, it has been suggested that their consumption mitigates age-related decline of brain function via anti-oxidative activity (Shimoyoshi et al., 2019; Yan et al., 2016). Besides the anti-oxidative and anti-inflammatory effects of lignans on neurons, both *in vivo* and *in vitro* studies have reported their potential role in neuroprotection and cognitive function (An et al., 2020; Han et al., 2022; Shimoyoshi et al., 2019; Yan et al., 2016).

The major hydroxybenzoic acids identified after peanut consumption (3-hydroxybenzoic acid, hydroxybenzoic acid sulfate, vanillic acid sulfate, and syringic acid sulfate) were correlated with improvements in memory, anxiety, and depression measured by validated neuropsychological tests and mood disorder questionnaires. In addition, the higher concentrations of protocatechuic acid sulfate and syringic acid sulfate

Fig. 1. Heatmap of correlations between microbial phenolic metabolites and cognitive and mood outcomes. The value of the correlation coefficient (r) ranging from −1 to 1 is expressed in green and yellow, respectively, in the bar on the right. *: refers to significant Spearman correlations $p < 0.005$.

excreted after SRP and PB interventions were associated with a lower cortisol level in urine. In agreement with our findings, an observational study also reported a positive, but weaker, correlation between total hydroxybenzoic acid intake and long-term memory and learning in a cohort of Argentinian postpartum women (Miranda et al., 2021). Moreover, *in vitro* and *in vivo* studies have shown that 3-hydroxybenzoic acid significantly contributes to protection against Alzheimer's and Parkinson's disease, as it can reach and accumulate in the brain, where it exerts neuroprotective effects (D. Wang et al., 2015; J. Wang et al., 2010). Similarly, protocatechuic acid is associated with neuroprotective and pro-cognitive effects, which are still under investigation (Kakkar & Bais, 2014; Krzysztoforska, Mirowska-Guzel, et al., 2019). In a rat model of memory impairment induced by D-galactose, protocatechuic acid was found to restore brain serotonergic and dopaminergic turnover and to improve memory, suggesting that its long-term administration could potentially reverse the detrimental changes associated with cognitive deficiencies (Krzysztoforska, Piechal, et al., 2019). Similarly, Song et al. reported that protocateuchuic acid was able to improve learning and memory performance in a mouse model (Song et al., 2014). In another study, protocatechuic acid was found to prevent stress in mice by modulating the antioxidant defense system and reducing oxidative damage in the cerebral cortex and hippocampus, suggesting that it could exert antidepressant-like effects (Thakare et al., 2017). Previous research has also reported neuroprotective effects of vanillic acid, including a beneficial impact on memory, as well as anti-inflammatory and antioxidant effects that down-regulate neuroinflammatory processes (Amin et al., 2017; Singh et al., 2015). Moreover, after identifying neuroprotective and memory-enhancing properties of syringic acid, Ogut *et al.* reported that its administration for two months led to an increase in recognition and short-term memory in Wistar rats through the activation of dopaminergic receptors or pathways during the learning process (Ogut et al., 2019, 2022).

In line with the present results, a randomized crossover study found an improvement in cerebrovascular reactivity and cognitive function in

healthy overweight middle-aged adults consuming 56–84 g/day of skin unsalted high oleic peanuts daily for 12 weeks (Barbour et al., 2017). These effects have been partially attributed to the phenolic content of peanuts, although evidence is still limited. Studies have previously indicated that polyphenol-enriched diets may improve cognition and reduce the risk of developing neurodegenerative diseases (Ammar et al., 2020; Caruso et al., 2022; Valls-Pedret et al., 2012). However, a recent randomized controlled study involving healthy young adult women found a significant improvement on processing speed but no effect on depression, anxiety, or stress scores after 12 week consuming roasted peanuts (Reeder et al., 2022). It should be noted that the peanuts used in their study lacked skins, which contain fewer polyphenol compounds compared to peanut products that contain skin, such as the food products used in the ARISTOTLE study (Francisco & Resurreccion, 2009; Sobolev & Cole, 1999).

The maintenance of a healthy gut microbiota is recognized as crucial for protecting normal brain function (Ley et al., 2008). While the exact mechanisms underlying the interaction between the gut microbiota and brain remain to be fully determined, there are several potential pathways through which the gut microbiota can influence brain function (Borre et al., 2014). One pathway involves the production and release of neurotransmitters like serotonin and dopamine by the gut microbiota. These neurotransmitters can travel through the bloodstream or along the vagus nerve, reaching the brain and affecting neuronal function (Bonaz et al., 2017). Studies have shown that treatments with prebiotics and probiotics can alter the composition of the gut microbiota and increase levels of tryptophan, a serotonin precursor, in the brains of animal models with depression and chronic stress (Desbonnet et al., 2008; O'Mahony et al., 2015). Additionally, microorganisms from the gut microbiota can influence brain processes by modulating the immune system and releasing cytokines, which are signaling molecules involved in immune response and inflammation. Pathogenic microorganisms release metabolites and microbiota-derived molecules that activates cytokines in the host, leading to inflammation in the central nervous system and contributing to the development of brain disorders depression anxiety and Alzheimer's diseases. (Zhu et al., 2020). Furthermore, gut microbiota plays a role in metabolizing various nutrients and compounds found in the diet, produncing metabolites that can affect the brain. For instance, short-chain fatty acids such as acetate, butyrate, lactate, and propionate, produced by certain gut bacteria are believed to be crucial in the gut–brain axis (Dalile et al., 2019; Mirzaei et al., 2021; Silva et al., 2020).

To our knowledge, the present study is the first to analyze urinary MPMs after peanut consumption and associate them with cognitive and mood outcomes. Dietary polyphenols can influence the composition of the gut microbial community and, conversely, phenolic metabolism and bioavailability depend on the microbiota and associated enzymatic transformations (Filosa et al., 2018). The extensive metabolism that polyphenols undergo in the gut microbiota suggests that the resulting metabolites such as the MPMs may play a significant role in the health effects attributed to dietary polyphenols. Nevertheless, further research is needed to fully understand the molecular mechanisms that link these phenolic metabolites to cognitive health. Various mechanisms may be involved, including the inhibition of enzymes that form reactive oxygen species, the modulation of transcription factors that regulate inflammatory and oxidative pathways, or indirect enhancement of brain function by improving cerebral blood flow (Castelli et al., 2018; de Vries et al., 2022; Sarubbo et al., 2018). Furthermore, polyphenols could influence cognitive and mood health through their interactions with the gut microbiota leading to increased expression of brain-derived neurotrophic factor (Egan et al., 2003; Hosein et al., 2018; Scalbert et al., 2002).

The present study provides valuable insights to understand the role of microbial phenolic metabolites in the gut-brain axis. The results found are encouraging, but further research is needed to establish evidence-based recommendations for the use peanut products in dietary strategies aimed to improve memory and mental health. The study of the gut-brain axis is a promising field, but there is still much to uncover. Most of the existing literature focuses on animal models, highlighting the need for continued research, particularly using human models, to obtain more meaningful conclusions. Additionally, it is important to interpret the results of this study while considering its limitations. Firstly, the sample sizes per group were small. Secondly, there are a potential source of bias due to the lack of blinding and the absence of a peanut-free product as a control. Thirdly, molecular mechanisms clarifying the observed correlations are not include in the article, therefore causality could not be determined. However, despite these limitations, the study has several strengths, including the randomized and controlled design; the use of biological samples; the administration of a broad battery of standardized cognitive tests; and the use of a precise method based on liquid chromatography coupled to mass spectrometry to quantify urinary MPMs, which have been scarcely studied in human samples until now.

5. Conclusion

The findings from the present study indicate that consuming peanuts and peanut butter may contribute to the production of MPMs which could be involved in the improvement of memory function and the maintenance of healthy levels of anxiety and depression in healthy young adults. However, to confirm these results, more clinical trials with peanut products should be conducted, with larger sample sizes and longer follow-up periods.

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Author contributions

S.H.-B., and R.M.L.-R. were responsible for the design of the study. I. P.-M. and S.H.-B. conducted the study and participated in data collection. I.D.-L., I.P.-M. and A.V.-Q. performed the chemical analysis and data processing. I.P.-M. and R.L.-S.: statistical analysis and writing - original draft preparation. I.D.-L., S.H.-B., A.V.-Q., and R.M.L.-R. writing-review and editing. R.M.L.-R. had primary responsibility for the final content. All authors have read and agreed to the published version of the manuscript.

Ethical statement

All the participant signed an informed consent and were able to withdraw from the study at any time without giving a reason. The products tested were safe for consumption. The study protocol was approved by the Bioethics Commission of the University of Barcelona (Institutional Review Board: IRB 00003099), the clinical trial was registered at https://register.clinicaltrials.gov (NCT04324749), and all procedures were carried out in compliance with the principles outlined in the Declaration of Helsinki.

Disclosure of interest

R.M.L-R reports receiving lecture fees from Cerveceros de España and receiving lecture fees and travel support from Adventia and Idilia Foods SL. Nevertheless, these foundations were not involved in the study design, the collection, analysis and interpretation of data. The other authors declare no conflict of interest.

CRediT authorship contribution statement

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López: Investigation, Data curation. **Anna Vallverdú-Queralt:** Writing – review & editing, Investigation, Data curation. **Sara Hurtado-Barroso:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rosa M Lamuela-Raventós:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

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Data availability

Data will be made available on request.

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Data described in the manuscript, code book, and analytic code will be available upon request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2023.105746.

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