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The attention-enhancing effects of spearmint extract supplementation in healthy men and women: a randomized, double-blind, placebo-controlled, parallel trial

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ABSTRACT

Previous studies have demonstrated that chronic supplementation with a proprietary spearmint extract (PSE) can improve cognitive performance in individuals 50–70 years of age with age-related memory issues. In the present study, our hypothesis was that chronic supplementation of PSE would improve cognitive performance in young, active individuals. Using a randomized, double-blind, placebo-controlled, parallel design, healthy, recreationally active men and women ($N = 142$) received 900 mg of PSE or placebo (PLA) daily for 90 days. Cognition was assessed via cognitive test battery (CNS Vital Signs) that resulted in 10 cognitive domains. Sleep, mood, and quality of life were assessed via validated questionnaires. Measurements were evaluated on days 0, 7, 30, and 90 of supplementation. Significant ($P < .05$) treatment effects were observed for sustained attention, wherein PSE improved sustained attention vs PLA at day 30 (PSE: 33.3 ± 0.54 vs PLA: 31.2 ± 0.98 ; $P = .001$) and day 90 (PSE: 34.0 ± 0.44 vs PLA: 32.7 ± 0.75 ; $P = .007$). Significant ($P < .05$) treatment \times visit interactions were observed for complex attention, wherein PSE improved complex attention compared to PLA at day 7 (PSE: 8.0 ± 2.22 vs PLA: 7.6 ± 0.57 ; $P = .016$). Significant ($P < .05$) improvements were observed in 2 individual tests: the shifting attention test and the 4-part continuous performance test. No significant differences were observed in mood, sleep, or quality of life. The current study demonstrates

Abbreviations: BMI, body mass index; LSEQ, Leeds Sleep Evaluation Questionnaire; MMRM, mixed model of repeated measures; PLA, placebo; POMS, Profile of Mood States; PSE, proprietary spearmint extract; PSQI, Pittsburgh Sleep Quality Index.

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that chronic supplementation with 900 mg of PSE improves cognitive performance in a young, active population, further supporting PSE as an efficacious nootropic.

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1. Introduction

Cognition includes coordinated processes associated with attention, memory, perception and evaluation, reasoning, problem solving, and decision making [1]. Furthermore, disruption in the neural physiology supporting cognition can lead to impairment and ultimately cognitive dysfunction [2]. Consumption of certain nutrients has widely been accepted to influence brain structure and function [3–6]. Therefore, interest in herbal preparations as cognitive-enhancing agents, commonly called nootropics, is increasing with several promising compounds available [7,8], including spearmint [9].

Spearmint (*Mentha spicata*) is a member of the Lamiaceae (mint) family which comprises over 900 common species including sage (*Salvia officinalis*), rosemary (*Rosmarinus officinalis*), and lemon balm (*Melissa officinalis*). These plants are suggested to support cognitive performance which may be connected to their shared polyphenolic constituents [10–12]. Specifically, polyphenols contained within the aqueous extracts from the Lamiaceae family could mechanistically account for the reported benefits on cognitive performance [13,14]. Polyphenols found in aqueous extracts of spearmint such as salvianolic and rosmarinic acids have been shown to have antioxidant [15], anti-inflammatory [16,17], antiacetylcholinesterase [18,19], and neuroprotective [20–22] biological activity both *in vitro* and *in vivo*.

Previous work on the proprietary spearmint extract (PSE) used in the current trial demonstrated high levels of rosmarinic acid as well as other polyphenols such as salvianolic acid, lithospermic acid, and caftaric acid [13]. Efficacy of PSE was first evaluated *in vivo* using the senescence-accelerated mouse model. In this model of accelerated aging, spearmint extract supplementation at 16 and 32 mg/kg body weight (600–1200 mg equivalent for a 70-kg man) for 12 weeks resulted in improved learning and memory as evidenced by T-maze retention and novel object recognition tasks [23]. In an open-label supplementation trial, 900 mg PSE daily for 30 days improved scores in reasoning and attention compared to baseline in men and women 50–70 years of age with self-reported memory impairment [24]. A randomized, double-blind, placebo-controlled trial that evaluated the same spearmint extract in a similar population confirmed the cognitive benefits demonstrated in the open-label trial. Supplementation of PSE at 900 mg daily for 90 days resulted in improvements in quality of working memory and spatial working memory scores relative to placebo [9]. To investigate whether the improvements might translate to a younger population, a pilot study was completed in young, healthy men and women [25], wherein memory improvements were observed after acute supplementation with PSE.

In summary, the efficacy of PSE has been previously demonstrated in a mouse model of accelerated aging [23] and in humans 50–70 years of age with age-related memory issues [9] after acute and chronic supplementation. A pilot trial suggested that the cognitive benefits of acute supplementation extended to younger individuals. To determine if chronic supplementation

improved cognition in younger individuals, the objective of the present trial was to evaluate the effects of chronic supplementation of 900 mg of PSE on cognitive performance, sleep, mood, and quality of life in healthy, active adults, 18–50 years of age. Our hypothesis was that chronic supplementation of 900 mg of PSE would improve cognitive performance as measured by the CNS Vital Signs test battery.

2. Methods and materials

2.1. Study design

A randomized, double-blind, placebo-controlled, parallel design was implemented in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki [26], and the United States 21 Code of Federal Regulations [27]. A third-party, independent Institutional Review Board (Quorum Review IRB, Seattle, WA, USA) approved all study-related materials including the protocol and informed consent documents prior to initiation of the study. The trial was registered at clinicaltrials.gov as NCT02518165. The study included 1 screening visit; a baseline visit (day 0); and 3 treatment visits at days 7, 30, and 90 (Fig. 1). One hundred forty-two participants were randomized into PSE or placebo (PLA) groups in a staggered start design (1 week after screening visit). To generate a randomization schedule using block randomization, participants were stratified by sex and age into 4 groups: young (18–35 years)/male, older (36–50 years)/male, young/female, and older/female. The age strata were chosen from approximately 15-year intervals used in the literature [28] so that equal proportions of younger and older adults within the specified age range could be allocated to both groups. A random sequence of blinded treatments (A and B) was generated by the principal investigator using 37 blocks of 4 on a research randomizer Web site (www.randomizer.org). These blocks were applied to each stratum mentioned above as each previous block of 4 was filled by participants. Signed informed consent and authorization for use of protected health information were provided by the participants prior to implementing any protocol-specific procedures. Participants were informed of their right to withdraw from the study at any time. All blood was collected at a LabCorp facility (Laboratory Corporation of America, Burlington, NC, USA [29]), and all other measures were performed at the MusclePharm Sports Science Institute.

2.2. Participants

Generally healthy, recreationally active, men and women 18–50 years of age, with a minimum of a high school diploma, and with body mass index (BMI) between 18.5 and 29.9 kg/m² or 30.0–34.99 kg/m² with body fat <39% for women 18–39 years

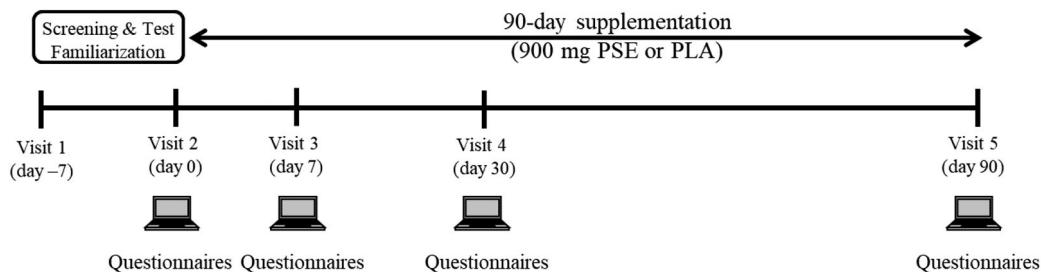


Fig. 1 – Study design overview. This double-blind, placebo-controlled, parallel study included 1 screening visit (day -7), a baseline visit (day 0), and 3 treatment visits (days 7, 30, and 90). Participants were randomly assigned 900 mg of PSE or PLA, which was consumed each day with breakfast over a 90-day treatment period. Participants completed the cognitive performance test battery during the screening visit (day -7) to familiarize the participants with the testing procedure. The following were completed on test visits: electronic cognitive performance test battery (CNS Vital Signs, Morrisville, NC, USA), electronic Profile of Moods State (days 0, 7, 30, and 90), electronic PSQI (days 0, 7, 30, and 90), LSEQ (days 7, 30, and 90), and Quality of Life Index (days 0, 30, and 90).

of age, <40% for women 40–50 years of age, <25% for men 18–39 years of age, or <28% for men 40–50 years of age were recruited for this study [30]. Participants were considered recreationally active if they completed ≥1 and ≤6 hours of moderate to vigorous physical activity per week as assessed by the New Zealand Physical Activity Questionnaire [31]. Eligible participants were willing to abstain from consuming caffeine-containing products for 10 hours, alcohol consumption and physical activity for 24 hours, and strenuous resistance exercise for 48 hours prior to and during all visits. Eligible participants were also willing to keep their hours of sleep consistent each night prior to all study visits and maintain their normal diet, exercise, and sleep regimens throughout the study. Exercise, sleep, and 3-day food logs were completed by participants throughout the trial to control for variability. In addition, participants completed a 24-hour diet record prior to the baseline (day 0) visit. The record was copied and returned to the participant for replication of meal consumption 24 hours prior to each remaining test visit. Fasted blood samples were also collected by venipuncture from eligible participants at days 0, 7, 30, and 90 for assessment of tolerability via complete blood count, lipid, and chemistry panels (LabCorp [29]).

Participants were deemed ineligible to participate based on the following exclusion criteria: uncontrolled hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg); history or presence of clinically important cardiac, renal, hepatic, endocrine (including type 1 or type 2 diabetes mellitus), pulmonary, biliary, gastrointestinal, pancreatic, or neurologic disorders (including sleep disorders, head injuries, Alzheimer disease, Parkinson disease, stroke, inflammatory brain disease); recent history or presence of cancer, except nonmelanoma skin cancer; history of or strong potential for alcohol (>14 servings per week) or substance abuse within 12 months of screening; history of depression within 24 months of screening; history of tobacco use within 6 months of screening; history of heavy caffeinated beverage consumption (>500 mg caffeine per day); an active infection; use of psychotropic medications within 4 weeks of screening; use of supplements known to improve cognitive function; allergies to ingredients in the test product or the snack provided; a sleep disorder or occupation where sleep

during the overnight hours is irregular; and pregnancy or the possibility of becoming pregnant throughout the study period.

2.3. Study product and treatment

PSE (Neumentix Phenolic Complex K110-42, containing a minimum 14.5% rosmarinic acid and a minimum 24% total phenolic content) was provided by Kemin Foods, LC (Des Moines, IA, USA) and was prepared as described [32,33]. PSE was packaged in 450-mg capsules by Five-Star Pharmacy (Clive, IA, USA). Participants were instructed to consume 2 capsules daily with breakfast equaling a daily total of 900 mg PSE or 0 mg (PLA, microcrystalline cellulose) PSE for 90 days. On visit days, capsules were consumed after testing to eliminate acute effects. Both types of capsules were produced by the same manufacturer to be identical in shape, size, and color and were sealed in identical bottles. All investigators involved in product dispensing, data collection, and analysis of outcomes were blinded in the following manner: PSE and PLA bottles were labeled "A" or "B" by unblinded individuals at Kemin Foods LC who were not involved in subject interaction or data assessment. All bottles were labeled according to the Good Clinical Practice Guideline of the International Conference on Harmonization. Compliance was calculated as a percentage of study product consumed according to the returned quantity of study product and a study product diary that participants completed daily. Adverse events were evaluated at each visit (Fig. 1).

2.4. Cognitive assessments

Cognitive performance was assessed using a computerized battery of tests (CNS Vital Signs Inc, Morrisville, NC, USA) which included finger tapping, symbol digit coding, Stroop, shifting attention, continuous performance, reasoning, 4-part continuous performance, and digit span and have been described elsewhere [34]. Briefly, the finger tapping test (test time = 2 minutes) is a commonly used test for motor speed. The symbol digit coding test (test time = 4 minutes) is derived from the Symbol Digit Modalities test and contributes to processing speed. The Stroop test (test time = 4–5 minutes) is well known and measures information processing via congruent and noncongruent

associations of color and word. The shifting attention test (test time = 2.5 minutes) measures participants' ability to shift from differing sets of instructions. The continuous performance test (test time = 5 minutes) is a measure of sustained attention. The reasoning test (test time = 3.5 minutes) involved visual analogies using symbols. The 4-part continuous performance test included 4 separate tests (total test time = 7 minutes) that range from measuring simple reaction time to working memory. The digit span test (test time = 3 minutes) was a working memory test where sequences of numbers were presented to be recalled, either forward or backward.

Scores from individual tasks were combined for cognitive domain scores consisting of psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, reasoning, sustained attention, working memory, simple attention, and motor speed (Fig. 2). The cognitive test battery had built in practice tests before each test (except for the continuous performance test) to help familiarize participants with the test protocol. During the familiarization visit, participants completed 1 “run-through” of the entire test battery to

allow for additional familiarization with the test protocol and to further reduce learning effects. All words, letters, and symbols in the test battery are autorandomized from a large bank of potential stimuli so that the tests were not repeated. The testing room was free of distraction and extraneous noise.

2.5. Sleep assessment

The Leeds Sleep Evaluation Questionnaire (LSEQ) was completed on paper and administered at days 7, 30, and 90. This questionnaire consisted of 10 separate 100-mm lines flanked by antonyms. Participants rated aspects of sleep by placing a mark on a horizontal line (50 mm is neutral). This subjective evaluation of sleep by the LSEQ results in 4 domains: ease of getting to sleep, quality of sleep, awakening from sleep, and behavior following wakefulness [35].

The Pittsburgh Sleep Quality Index (PSQI) was incorporated into the computerized test battery which included the cognitive tests and administered at days 0, 30, and 90. The questionnaire consisted of 9 questions inquiring about the participants' sleep habits in the last month [36]. The responses

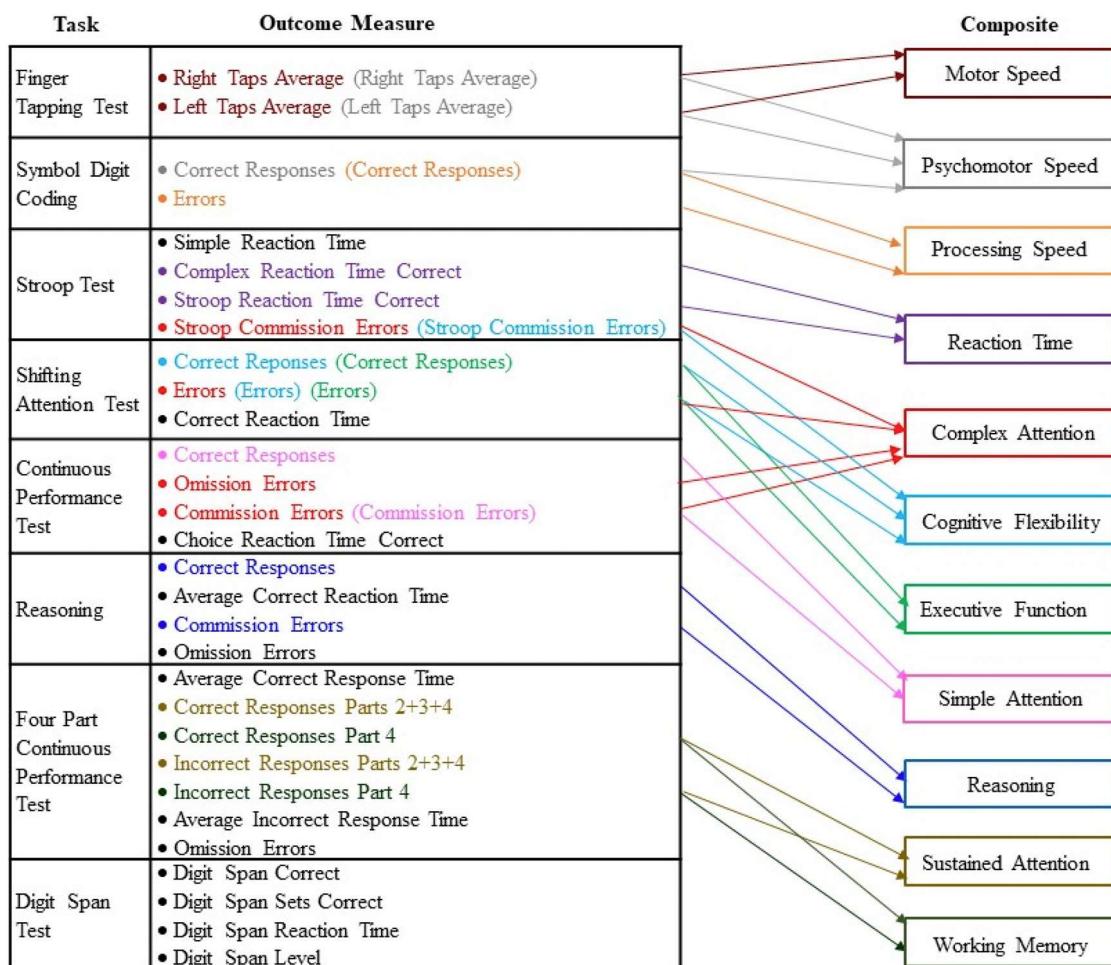


Fig. 2 – Cognitive performance assessments. The computerized cognitive performance test battery (CNS Vital Signs, Morrisville, NC, USA) [34] is summarized, indicating how tasks are separated into specific outcomes, and the outcome scores that contribute to each composite cognitive domain. Colors correspond with arrows and outlines of composite domains. The outcomes that are repeated contribute to more than 1 composite domain. Figure modified from Herrlinger et al [9] and reproduced with permission.

were used to calculate 8 component scores including duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency, overall sleep quality, the need for medications to sleep, and total PSQI score.

2.6. Mood assessments

The Profile of Mood States (POMS) Standard Form questionnaire was also incorporated into the computerized assessment system and administered at days 0, 7, 30, and 90 as described [37]. Participants were asked to rate how they have been feeling in the last week using 65 adjectives with a 5-point Likert scale as follows: not at all (0), a little (1), moderately (2), quite a bit (3), and extremely (4). Ratings were combined into 7 factor composites as recommended: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment, and friendliness. A score for total mood disturbance was also calculated by summing the raw scores for all composites except for the

vigor-activity score which was subtracted and friendliness which was excluded [37].

2.7. Quality of life assessment

Quality of life was assessed using the Ferrans and Powers Quality of Life Index questionnaire [38]. This questionnaire was administered on paper at days 0, 30, and 90. The questionnaire consists of 66 questions on the satisfaction and importance of various aspects of life. Responses to individual questions were then used to calculate domain scores including health, social, psychological, family, and total quality of life.

2.8. Exercise and food logs

To control for changes in exercise and diet, exercise and food logs were submitted throughout the study. These methods and data are described elsewhere [29]; briefly, exercise duration and type were logged daily. Three-day food logs were recorded throughout

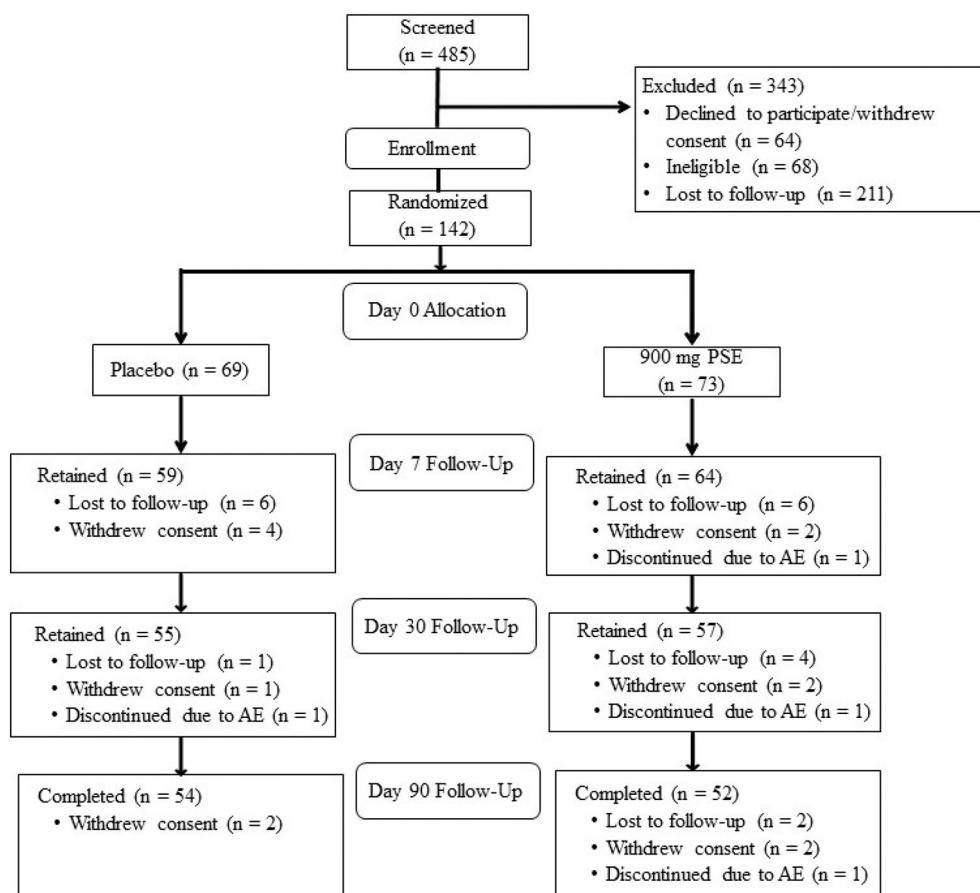


Fig. 3 – Study flow diagram. A total of 485 participants were screened. Healthy men and women were randomly assigned to 0 (PLA) or 900 mg/d of PSE (N = 142; PLA, n = 69; PSE, n = 73). A total of 54 and 52 participants completed the trial in the PLA and 900 mg/d PSE groups, respectively. In PLA, 1 participant discontinued because of acid reflux, which was deemed “likely” related to the intervention. Two participants withdrew from the study in the PSE group because of adverse events including pregnancy and headache and nausea resulting from a back injury which were deemed unrelated to the intervention. A third participant in the PSE group reported insomnia which was deemed unlikely related to the intervention. All available data were included in the intent-to-treat population. Abbreviation: AE, adverse event(s).

Table 1 – Baseline characteristics

Parameter	Overall (N = 142)	PLA (n = 69)	PSE (n = 73)	P value ^a
Sex				.600
Male	98 (69)	48 (70)	50 (69)	
Female	44 (31)	21 (30)	23 (31)	
Race				.110
White	122 (86)	55 (80)	67 (92)	
Black/African American	11 (8)	7 (10)	4 (5)	
Asian/Pacific Islander	9 (6)	7 (10)	2 (3)	
Age (y)	27.5 ± 0.7	27.9 ± 0.9	27.2 ± 0.9	.600
BMI (kg/m ²)	25.9 ± 0.3	25.8 ± 0.4	25.9 ± 0.4	.860
Sleep (h/d) ^b	7.2 ± 0.1	7.3 ± 0.1	7.2 ± 0.1	.820
Exercise (h/wk) ^b	3.8 ± 0.2	3.8 ± 0.2	3.7 ± 0.3	.660
New Zealand Physical Activity (h/wk) ^c	4.7 ± 1.3	5.0 ± 1.2	4.2 ± 1.4	.010

Data for sex and race presented as n (%). Data for age, BMI, sleep, exercise, and physical activity presented as means ± SEM.

^a P values for categorical variables were generated from Fisher exact test. P values for continuous variables were generated from the Student t test.

^b Data were obtained from study diary completed by participants between the screening (day -7) and baseline (day 0) visits.

^c The New Zealand Physical Activity Questionnaire was administered at screening (day -7) to assess activity level [31].

Table 2 – Cognitive domain scores before and after supplementation with the spearmint extract or placebo^a

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Psychomotor speed					
0	187.0 ± 2.66	195.9 ± 3.41		Txt P = .804	↓
7	187.3 ± 3.01	198.6 ± 3.27		Txt × visit	
30	190.0 ± 2.85	197.6 ± 3.71		P = .837	
90	191.5 ± 3.22	201.0 ± 4.17			
Reaction time					
0	653.26 ± 11.458	627.23 ± 8.710		Txt P = .884	↓
7	646.51 ± 14.409	622.23 ± 10.486		Txt × visit P = .920	
30	649.61 ± 12.341	634.25 ± 10.466			
90	641.97 ± 11.899	629.93 ± 11.849			
Complex attention					
0	7.0 ± 0.47	7.3 ± 0.50		Txt P = .431	↓
7	7.6 ± 0.57	6.1 ± 0.52 ^d		Txt × visit	
30	6.6 ± 0.54	6.6 ± 0.51		P = .022	
90	5.9 ± 0.60	6.3 ± 0.57			
Cognitive flexibility					
0	47.2 ± 1.01	48.2 ± 1.13		Txt P = .927	↑
7	47.6 ± 1.32	51.6 ± 0.96		Txt × visit	
30	48.7 ± 1.07	50.6 ± 1.08		P = .070	
90	50.8 ± 0.90	51.5 ± 1.02			
Processing speed					
0	66.7 ± 1.55	69.0 ± 1.83		Txt P = .438	↑
7	66.9 ± 1.77	70.9 ± 1.66		Txt × visit	
30	68.3 ± 1.81	71.4 ± 1.62		P = .325	
90	80.9 ± 10.65	72.6 ± 1.95			
Executive function					
0	48.9 ± 1.00	50.2 ± 1.09		Txt P = .862	↑
7	49.5 ± 1.34	53.3 ± 0.91		Txt × visit	
30	50.5 ± 1.01	52.5 ± 1.05		P = .182	
90	52.4 ± 0.88	53.2 ± 1.05			
Reasoning					
0	7.6 ± 0.47	6.6 ± 0.49		Txt P = .617	↑
7	8.4 ± 0.47	7.5 ± 0.45		Txt × visit	
30	8.5 ± 0.50	8.4 ± 0.55		P = .725	
90	9.1 ± 0.42	8.7 ± 0.43			
Working memory					

(continued on next page)

Table 2 (continued)

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Sustained attention	0	12.3 ± 0.43	11.9 ± 0.42	Txt P = .102	↑
	7	12.7 ± 0.40	12.6 ± 0.32	Txt × visit	
	30	12.3 ± 0.48	13.0 ± 0.38	P = .296	
	90	12.5 ± 0.50	13.3 ± 0.34		
	0	32.4 ± 0.64	30.6 ± 0.84	Txt P = .003	↑
	7	32.8 ± 0.58	32.6 ± 0.63	Txt × visit	
	30	31.2 ± 0.98	33.3 ± 0.54 ^e	P = .074	
	90	32.7 ± 0.75	34.0 ± 0.44 ^f		
Simple attention	0	38.8 ± 0.17	38.9 ± 0.18	Txt P = .525	↑
	7	38.8 ± 0.22	39.0 ± 0.18	Txt × visit	
	30	38.7 ± 0.26	39.1 ± 0.20	P = .994	
	90	38.8 ± 0.47	39.1 ± 0.27		
Motor speed	0	119.0 ± 1.86	125.9 ± 2.45	Txt P = .185	↑
	7	119.0 ± 2.15	125.8 ± 2.43	Txt × visit	
	30	119.3 ± 2.02	124.3 ± 3.05	P = .692	
	90	119.6 ± 2.25	126.0 ± 3.39		

PSE, n = 52–73; PLA, n = 54–69. Data presented as means ± SEM. Txt, treatment.

^a The CNS Vital Signs cognitive test battery [38] was administered at baseline (day 0) and after 7, 30, and 90 days of PSE (900 mg/d) or PLA supplementation. Participants were asked to perform various cognitive tasks while seated at a computer. Scores from various tests were combined to provide cognitive domain scores.

^b P values for the overall treatment effect were generated from an MMRM analysis of variance model based on the change from baseline.

^c The arrow notes the direction of change that suggests improvement in the associated outcome.

^d PSE vs PLA at day 7, P = .016.

^e PSE vs PLA at day 30, P = .001.

^f PSE vs PLA at day 90, P = .007.

the study to ensure that diets remained the same during the supplementation period.

2.9. Statistical analyses

A power analysis was conducted via GPower version 3.1.9.2 [39] to calculate sample size. An evaluable sample size of 53 participants per group was expected to provide 80% power (2-sided, $\alpha = .05$) to detect an 8% difference in number of hits in assessments of physical performance [29]. A sample of at least 69 participants per group was randomized to account for attrition and noncompliance (Fig. 3).

Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA) by independent, third-party statisticians (Summit Analytical, Denver, CO, USA). Analyses were completed on an intent-to-treat population which included all participants who were randomized into the study and consumed at least 1 dose of study product. A mixed model of repeated measures analysis (MMRM) was applied to variables with data collected across treatment groups and over time, which differed slightly depending on the assessment as described above. All MMRM models contained terms for treatment (active vs control), time, and the time × treatment interaction using change from baseline values. Baseline comparability of demographic variables, compliance, and adverse events was assessed by Fisher exact test. All tests of significance were completed at $\alpha = .05$, 2-tailed.

Data are presented as means ± SEM. No adjustments were made for multiple comparisons; however, it is important to note that although adjustment for multiple comparisons can result in type II error, the lack of adjustment for multiple comparisons can result in type I error.

3. Results

3.1. Participants

One hundred and forty-two individuals were randomized (PLA: n = 69; PSE: n = 73). Fifty-four and 52 participants completed the trial in the PLA and PSE treatment groups, respectively. The overall attrition rate was 25.4%, and there was not a difference in attrition between treatments or sexes ($P = .548$). Demographics are shown in Table 1. Baseline demographic characteristics were well-balanced between treatment groups. Exercise hours per week, as self-reported on the New Zealand Physical Activity Questionnaire, differed between treatment groups at the screening visit ($P = .01$); however, the comparison of the actual hours of exercise collected on study diaries during the week between screening and baseline visits (day 0) indicated no differences, and both groups were within the inclusion criteria of greater than 1 and less than 6 hours of exercise per week. Compliance was 95.4% and 96.8% in the PLA and PSE groups at day 90, respectively, with no difference between groups ($P = .328$).

3.2. Cognitive assessments

Data for cognitive domain outcomes are shown in Table 2. Significant ($P < .05$) treatment effects were observed for sustained attention (Fig. 4A), with pairwise comparisons indicating improvements for PSE vs PLA at day 30 and day 90. Significant ($P < .05$) treatment \times visit interactions were observed for complex attention (Fig. 4B), with pairwise comparisons indicating improvements for PSE compared to PLA at day 7. No other significant differences were observed among the cognitive domains at any other time points. Individual test scores are shown in Table 3. Significant ($P < .05$) improvements were observed in PSE vs PLA in the shifting attention test for reduction in errors (Fig. 4C) at day 7 and for reaction time of correct responses at day 7 and day 90. In part 4 of the 4-part continuous performance test, improvements were observed in PSE over PLA for correct responses (Fig. 4D) and for omission errors at day 30 and day 90. No other significant differences were observed among the cognitive test scores at any other individual time points.

3.3. Sleep, mood, and quality of life assessments

All data for sleep, mood, and quality of life assessments are shown in supplementary tables. Regarding sleep, there were no significant differences evident in any of the component or

domain scores from the LSEQ (Supplemental Table S1) and the PSQI questionnaires (Supplemental Table S2). No significant differences were identified for any of the mood domains assessed by the POMS questionnaire (Supplemental Table S3). Regarding quality of life, significant ($P = .036$) treatment effects were observed in the psychological and spiritual domain rating (Supplemental Table S4), with pairwise differences indicating a significant difference in PSE compared with PLA at day 90 (PSE: 24.8 ± 0.5 vs PLA: 25.0 ± 0.5 ; $P = .020$).

4. Discussion

In the present study, we formally accept our hypothesis that chronic consumption of a proprietary spearmint extract can sustainably improve cognitive performance in young, healthy adults. Supplementation with PSE evinced improvements in sustained attention at day 30, which were maintained for the duration of the study (day 90). Complex attention also increased at day 7 after supplementation. Scores in individual tests supported the results in attention, as improvements were observed for sections of the shifting attention test and the 4-part continuous performance test.

Regarding the 2 cognitive domains of sustained and complex attention, previously published literature supports

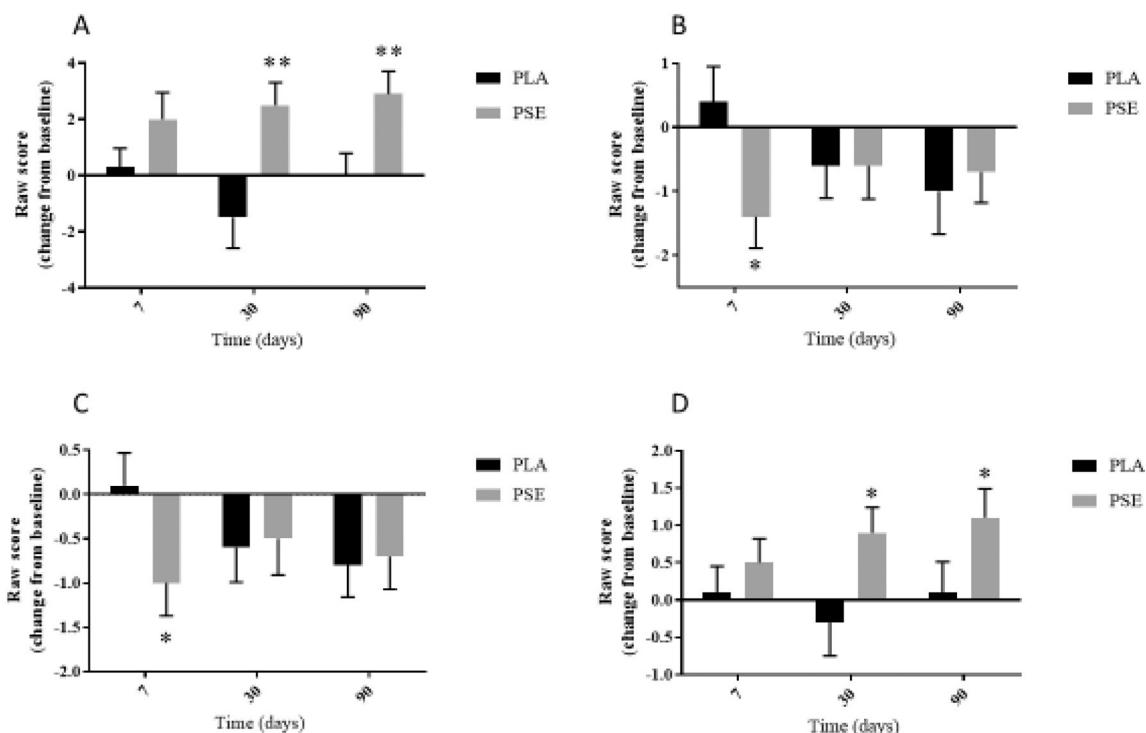


Fig. 4 – Domain scores and test scores after spearmint extract supplementation. A, Sustained attention: supplementation with PSE at 900 mg/d for 7, 30, and 90 days resulted in improved (overall treatment effect, $P = .003$) sustained attention vs PLA at day 30 ($P = .001$) and day 90 ($P = .007$). B, Complex attention: PSE at 900 mg/d improved (overall treatment \times visit interaction effect, $P = .020$) complex attention vs PLA at day 7 ($P = .017$). C, Shifting attention: PSE at 900 mg/d evinced less errors (overall treatment \times visit interaction, $P = .011$) vs PLA at day 7 ($P = .033$). D, Four-part continuous performance test: PSE at 900 mg/d improved (overall treatment effect, $P = .030$) correct responses vs PLA at day 30 ($P = .020$) and day 90 ($P = .029$). P values were generated from an MMRM analysis of variance model based on the change from baseline. Data are presented as change from baseline (day 0) means \pm SEM. PSE, n = 52–73; PLA, n = 54–69. * $P < .05$; ** $P < .01$.

Table 3 – Scores from individual cognitive tests before and after spearmint extract supplementation^a

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Finger tapping					
Right taps					
0	61.3 ± 1.03	65.0 ± 1.38		Txt P = .218	↑
7	62.2 ± 1.16	65.3 ± 1.33		Txt × visit	
30	61.7 ± 1.01	64.9 ± 1.64		P = .735	
90	62.2 ± 1.11	67.2 ± 1.77			
Left taps					
0	57.6 ± 0.96	60.0 ± 1.27		Txt P = .613	↑
7	56.8 ± 1.10	60.5 ± 1.23		Txt × visit P = .433	
30	57.6 ± 1.12	59.4 ± 1.58			
90	57.4 ± 1.30	59.9 ± 1.56			
Symbol digit coding					
Correct responses					
0	68.0 ± 1.56	70.8 ± 1.74		Txt P = .949	↑
7	68.8 ± 1.77	72.8 ± 1.62		Txt × visit	
30	70.2 ± 1.80	73.1 ± 1.62		P = .661	
90	72.1 ± 1.79	74.1 ± 1.93			
Errors					
0	1.5 ± 0.16	1.8 ± 0.23		Txt P = .101	↓
7	1.9 ± 0.24	1.9 ± 0.21		Txt × visit	
30	1.9 ± 0.21	1.7 ± 0.25		P = .376	
90	2.0 ± 0.24	1.6 ± 0.21			
Stroop test					
Simple reaction time (ms)					
0	324.0 ± 5.13	299.8 ± 3.30		Txt P = .049	↓
7	319.4 ± 5.85	308.6 ± 4.99		Txt × visit	
30	322.9 ± 4.87	309.2 ± 4.29		P = .926	
90	324.8 ± 10.48	307.4 ± 5.63			
Complex reaction time (ms)					
0	605.9 ± 9.55	573.0 ± 8.01		Txt P = .426	↓
7	597.9 ± 13.10	580.4 ± 10.19		Txt × visit	
30	598.8 ± 10.64	579.2 ± 9.44		P = .716	
90	586.6 ± 10.19	569.6 ± 9.50			
Stroop reaction time (ms)					
0	700.5 ± 15.26	672.7 ± 10.77		Txt P = .722	↓
7	694.9 ± 16.78	663.7 ± 12.20		Txt × visit	
30	700.1 ± 16.08	688.9 ± 13.79		P = .985	
90	697.0 ± 14.82	690.0 ± 16.01			
Stroop commission errors					
0	1.6 ± 0.17	1.9 ± 0.19		Txt P = .621	↓
7	1.9 ± 0.22	1.7 ± 0.17		Txt × visit	
30	1.8 ± 0.23	1.9 ± 0.20		P = .065	
90	1.6 ± 0.19	1.9 ± 0.22			
Shifting attention test					
Correct responses					
0	52.8 ± 0.79	54.4 ± 0.86		Txt P = .757	↑
7	53.9 ± 1.04	56.7 ± 0.71		Txt × visit	
30	54.1 ± 0.89	56.2 ± 0.82		P = .473	
90	55.5 ± 0.80	56.8 ± 0.81			
Errors					
0	4.0 ± 0.34	4.3 ± 0.33		Txt P = .615	↓
7	4.3 ± 0.40	3.4 ± 0.32 ^d		Txt × visit	
30	3.5 ± 0.27	3.7 ± 0.37		P = .011	
90	3.1 ± 0.25	3.5 ± 0.34			
Correct reaction time (ms)					
0	957.8 ± 16.70	910.4 ± 16.14		Txt P = .135	↓
7	923.2 ± 18.89	881.4 ± 14.26		Txt × visit	
30	939.7 ± 19.43	882.9 ± 14.17		P = .050	
90	910.1 ± 18.31	878.9 ± 14.23 ^e			
Continuous performance test					
Correct responses					
0	39.8 ± 0.06	39.7 ± 0.10		Txt P = .349	↑
7	39.7 ± 0.12	39.7 ± 0.11		Txt × visit	
30	39.5 ± 0.16	39.7 ± 0.10		P = .826	

Table 3 (continued)

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Omission errors	90	39.8 ± 0.06	39.8 ± 0.07		
	0	0.2 ± 0.06	0.3 ± 0.10	Txt P = .349	↓
	7	0.3 ± 0.12	0.3 ± 0.11	Txt × visit	
	30	0.5 ± 0.16	0.3 ± 0.10	P = .826	
	90	0.2 ± 0.06	0.2 ± 0.07		
Commission errors	0	1.0 ± 0.14	0.8 ± 0.12	Txt P = .971	↓
	7	0.9 ± 0.14	0.6 ± 0.11	Txt × visit	
	30	0.8 ± 0.19	0.6 ± 0.15	P = .998	
	90	1.0 ± 0.45	0.8 ± 0.23		
Choice reaction time correct (ms)	0	444.6 ± 5.18	434.5 ± 4.39	Txt P = .536	↓
	7	449.1 ± 6.51	436.8 ± 5.00	Txt × visit	
	30	455.0 ± 7.19	437.2 ± 4.46	P = .226	
	90	442.4 ± 5.43	433.1 ± 5.06		
Nonverbal reasoning test					
Correct responses	0	11.0 ± 0.24	10.6 ± 0.24	Txt P = .572	↑
	7	11.6 ± 0.24	11.1 ± 0.22	Txt × visit	
	30	11.5 ± 0.25	11.6 ± 0.27	P = .574	
	90	11.9 ± 0.21	11.7 ± 0.22		
Correct reaction time (ms)	0	4325.3 ± 122.54	4158.0 ± 103.44	Txt P = .543	↓
	7	4229.4 ± 116.75	4130.0 ± 107.12	Txt × visit	
	30	4046.0 ± 95.97	4061.0 ± 103.59	P = .594	
	90	4123.2 ± 130.78	3982.3 ± 109.8		
Commission errors	0	3.4 ± 0.24	4.0 ± 0.25	Txt P = .523	↓
	7	3.2 ± 0.24	3.6 ± 0.24	Txt × visit	
	30	3.0 ± 0.25	3.2 ± 0.29	P = .948	
	90	2.8 ± 0.21	3.0 ± 0.22		
Omission errors	0	0.6 ± 0.08	0.4 ± 0.06	Txt P = .658	↓
	7	0.2 ± 0.06	0.3 ± 0.07	Txt × visit	
	30	0.4 ± 0.09	0.3 ± 0.06	P = .044	
	90	0.3 ± 0.06	0.3 ± 0.06		
Digit span-forward					
Total digits correct	0	58.8 ± 2.54	62.6 ± 2.50	Txt P = .918	↑
	7	60.6 ± 3.19	63.5 ± 2.36	Txt × visit	
	30	57.7 ± 2.63	67.0 ± 2.94	P = .284	
	90	62.7 ± 3.08	67.2 ± 2.91		
Total digit sets correct	0	10.3 ± 0.27	10.8 ± 0.28	Txt P = .726	↑
	7	10.5 ± 0.33	11.0 ± 0.26	Txt × visit	
	30	10.3 ± 0.30	11.4 ± 0.31	P = .247	
	90	10.9 ± 0.36	11.4 ± 0.32		
Average reaction time (ms)	0	71 948.0 ± 3697.90	71 085.1 ± 3194.68	Txt P = .102	↓
	7	75 335.2 ± 7368.79	71 448.8 ± 2869.44	Txt × visit	
	30	64 717.9 ± 3665.90	75 903.1 ± 4065.86	P = .146	
	90	70 607.8 ± 4114.58	76 636.0 ± 5169.43		
Level achieved	0	5.9 ± 0.16	6.1 ± 0.16	Txt P = .790	↑
	7	6.0 ± 0.23	6.2 ± 0.15	Txt × visit	
	30	5.7 ± 0.18	6.3 ± 0.18	P = .337	
	90	6.1 ± 0.20	6.4 ± 0.18		
Digit span-backward					
Total digits correct	0	42.2 ± 2.69	46.3 ± 2.52	Txt P = .761	↑
	7	42.2 ± 3.10	50.8 ± 3.38	Txt × visit	
	30	49.7 ± 3.33	59.1 ± 4.15	P = .929	
	90	47.9 ± 3.27	56.1 ± 4.21		

(continued on next page)

Table 3 (continued)

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Total digit sets correct					
	0	8.0 ± 0.33	8.6 ± 0.32	Txt P = .672	↑
	7	8.0 ± 0.41	9.3 ± 0.43	Txt x visit	
	30	8.8 ± 0.38	10.3 ± 0.51	P = .540	
	90	8.6 ± 0.42	9.5 ± 0.49		
Average reaction time (ms)					
	0	82 308.5 ± 6186.81	104 043.1 ± 7973.46	Txt P = .777	↓
	7	79 560.3 ± 6608.83	106 336.2 ± 961.36	Txt x visit	
	30	97 494.3 ± 7862.80	119 730.6 ± 9673.06	P = .591	
	90	88 700.1 ± 6619.76	114 860.7 ± 9576.73		
Level achieved					
	0	4.7 ± 0.20	5.0 ± 0.19	Txt P = .901	↑
	7	4.6 ± 0.23	5.2 ± 0.25	Txt x visit	
	30	5.2 ± 0.24	5.8 ± 0.28	P = .659	
	90	5.1 ± 0.25	5.5 ± 0.28		
4-Part Continuous Performance Test – Part 1					
Correct response time (ms)					
	0	365.9 ± 14.64	335.1 ± 7.68	Txt P = .885	↓
	7	370.3 ± 15.64	350.3 ± 15.74	Txt x visit	
	30	378.2 ± 16.37	361.3 ± 15.19	P = .561	
	90	377.3 ± 17.39	339.8 ± 9.61		
4-Part Continuous Performance Test – Part 2					
Correct responses					
	0	5.8 ± 0.12	5.8 ± 0.13	Txt P = .697	↑
	7	5.9 ± 0.05	5.8 ± 0.11	Txt x visit	
	30	5.9 ± 0.08	5.8 ± 0.12	P = .505	
	90	5.9 ± 0.09	6.0 ± 0.00		
Correct response time (ms)					
	0	415.2 ± 7.93	386.7 ± 8.93	Txt P = .316	↓
	7	420.1 ± 8.44	400.2 ± 8.92	Txt x visit	
	30	421.8 ± 9.19	412.7 ± 6.50	P = .751	
	90	418.8 ± 9.46	409.6 ± 6.59		
Incorrect responses					
	0	0.7 ± 0.17	1.3 ± 0.41	Txt P = .051	↓
	7	0.7 ± 0.28	0.7 ± 0.29	Txt x visit	
	30	1.2 ± 0.46	0.6 ± 0.10	P = .655	
	90	0.6 ± 0.34	0.3 ± 0.08		
Incorrect response time (ms)					
	0	165.4 ± 25.81	171.5 ± 26.55	Txt P = .969	↓
	7	143.7 ± 31.68	123.0 ± 25.58	Txt x visit	
	30	191.4 ± 38.41	209.1 ± 35.65	P = .349	
	90	84.2 ± 22.02	130.5 ± 34.01		
Omission errors					
	0	0.2 ± 0.12	0.2 ± 0.13	Txt P = .697	↓
	7	0.1 ± 0.05	0.2 ± 0.11	Txt x visit	
	30	0.1 ± 0.08	0.2 ± 0.12	P = .505	
	90	0.1 ± 0.09	0.0 ± 0.00		
4-Part Continuous Performance Test – Part 3					
Correct responses					
	0	15.0 ± 0.26	15.0 ± 0.34	Txt P = .974	↑
	7	15.2 ± 0.17	15.4 ± 0.25	Txt x visit	
	30	15.0 ± 0.29	15.5 ± 0.11	P = .095	
	90	15.4 ± 0.19	15.0 ± 0.29		
Correct response time (ms)					
	0	509.3 ± 13.68	483.8 ± 12.63	Txt P = .503	↓
	7	500.0 ± 12.69	473.6 ± 9.04	Txt x visit	
	30	524.1 ± 14.07	495.2 ± 16.15	P = .790	
	90	502.1 ± 12.53	487.4 ± 10.52		
Incorrect responses					
	0	0.4 ± 0.10	0.5 ± 0.15	Txt P = .633	↓
	7	0.3 ± 0.07	0.4 ± 0.13	Txt x visit	
	30	0.8 ± 0.48	0.5 ± 0.12	P = .615	
	90	0.5 ± 0.23	0.4 ± 0.14		
Incorrect response time (ms)					
	0	227.6 ± 61.27	215.2 ± 53.85	Txt P = .885	↓

Table 3 (continued)

Domain	Day	PLA	PSE	P value ^b	Direction ^c
Omission errors	7	233.1 ± 60.61	237.7 ± 68.26	Txt × visit	
	30	192.4 ± 59.50	212.0 ± 58.35	P = .669	
	90	212.6 ± 70.59	164.9 ± 48.63		
4-Part continuous performance test—part 4	0	1.0 ± 0.26	1.0 ± 0.34	Txt P = .949	↓
	7	0.8 ± 0.17	0.6 ± 0.24	Txt × visit	
	30	1.0 ± 0.29	0.5 ± 0.11	P = .105	
	90	0.6 ± 0.19	1.0 ± 0.29		
Correct responses	0	13.7 ± 0.32	13.4 ± 0.30	Txt P = .030	↑
	7	13.8 ± 0.31	13.8 ± 0.28	Txt × visit	
	30	13.5 ± 0.39	14.2 ± 0.35 ^f	P = .221	
	90	13.8 ± 0.33	14.5 ± 0.25 ^g		
	0	615.2 ± 16.35	557.7 ± 12.89	Txt P = .095	↓
	7	589.1 ± 17.40	574.0 ± 13.86	Txt × visit	
	30	595.2 ± 22.73	580.1 ± 18.27	P = .689	
	90	594.6 ± 17.72	570.8 ± 15.31		
Incorrect responses	0	1.4 ± 0.21	1.5 ± 0.21	Txt P = .928	↓
	7	1.2 ± 0.15	1.2 ± 0.14	Txt × visit	
	30	1.2 ± 0.17	1.2 ± 0.16	P = .957	
	90	1.2 ± 0.24	1.1 ± 0.18		
Incorrect response time (ms)	0	521.0 ± 64.57	555.6 ± 51.55	Txt P = .767	↓
	7	567.9 ± 64.52	542.1 ± 51.99	Txt × visit	
	30	515.2 ± 55.25	515.6 ± 60.00	P = .974	
	90	519.9 ± 79.80	480.8 ± 72.20		
Omission errors	0	2.3 ± 0.32	2.6 ± 0.30	Txt P = .023	↓
	7	2.2 ± 0.31	2.2 ± 0.28	Txt × visit	
	30	2.5 ± 0.39	1.8 ± 0.35 ^h	P = .164	
	90	2.3 ± 0.34	1.5 ± 0.25 ⁱ		

PSE, n = 52–73; PLA, n = 54–69. Data presented as means ± standard error of the mean.

^a The CNS Vital Signs cognitive test battery [38] was administered at baseline (day 0) and after 7, 30, and 90 days of PSE (900 mg/d) or PLA supplementation. Participants were asked to perform various cognitive tasks while seated at a computer. Scores from various tests were combined to provide cognitive domain scores.

^b P values for the overall treatment effect were generated from an MMRM analysis of variance model based on the change from baseline.

^c The arrow notes the direction of change that suggests improvement in the associated outcome.

^d PSE vs PLA at day 7, P = .033.

^e PSE vs PLA at day 90, P = .045.

^f PSE vs PLA at day 30, P = .020.

^g PSE vs PLA at day 90, P = .029.

^h PSE vs PLA at day 30, P = .016.

ⁱ PSE vs PLA at day 90, P = .018.

that PSE can improve aspects of attention [24,25]. Consumption of PSE has been shown to improve attention and concentration when administered both acutely and chronically for 30 days in an open-label trial of older individuals with self-reported memory impairment [24]. Moreover, 3 small-scale studies in healthy men and women between the ages of 18 and 50 found trends for improvements in objective measures of attention as well as subjective reporting of increased feelings of alertness after acute supplementation with PSE [25]. In addition to the existing human clinical data, the polyphenol molecules contained in PSE have been shown to increase neurotransmitter levels in the brain related to attention [40,41]. Specifically, the polyphenols rosmarinic acid and salvianolic acid B have both been shown to inhibit the enzyme that breaks down acetylcholine in the brain [40,41]. In

an animal model, rosmarinic acid has been shown to increase levels of acetylcholine in the brain following acute administration [40]. Although the role of acetylcholine in learning and memory has been known for some time, more recent studies have revealed the additional function of acetylcholine for attention in both human and animal studies [42]. An increase in acetylcholine following long-term supplementation with PSE provides at least 1 potential mode of action for the attention improvements observed in the current study.

Sustained attention is an essential component of daily life and refers to the capacity to maintain focus on a specific item or task over an extended period of time [43]. Shortcomings in sustained attention can be as mundane as losing focus while reading and needing to read the paragraph again or as critical as failing to maintain attention while driving for long stretches of

time. Indeed, pilots were better at identifying systems failures toward the beginning of a flight simulation task than toward the end [44], and this reduction in sustained attention over time could have “real-world” consequences, such as more vehicle crashes. The inability to sustain attention also impacts performance on cognitive tasks related to learning and memory [45]. In the current study, daily supplementation with PSE led to an 11% increase in sustained attention performance at day 90 over baseline levels. In contrast, the individuals supplemented with PLA demonstrated a 0.9% increase in sustained attention following 90 days of supplementation. For comparison, a study investigating the effects of caffeine on sustained attention observed a 6.9% improvement after an acute administration of 60 mg caffeine in healthy young adults and a 0.6% increase for the placebo group [46]. Caffeine has been studied extensively for its potential benefits on attention and provides an ideal model for understanding the practical significance of an effect. However, most of the attentional benefits of caffeine have been observed on an acute time basis, and controversy exists as to the long-term, chronic benefits of caffeine administration on attention [47]. In contrast, the current study found that chronic daily supplementation of PSE led to significant improvements in sustained attention compared to PLA and that these benefits were still significant after 90 days of supplementation. It is also important to note that these gains are reflective of long-term supplementation because participants did not receive PSE supplementation immediately prior to testing on days 0, 7, 30, or 90, thus ruling out the possibility of acute effects on the day of testing.

Examining the individual tasks can shed additional light on the cognitive domains that are most affected by PSE supplementation. The shifting attention test errors were improved with short-term supplementation (day 7) and mirror the findings in complex attention. Shifting attention measures how an individual can multitask, or switch between tasks, effectively. Given the high demand for multitasking in today’s society, shifting attention is a cognitive area that has great relevance in quotidian life. Sustained attention is calculated from the correct responses on parts 2, 3, and 4 of the 4-part continuous performance test, with each test increasing in complexity. The score for correct responses during part 4 was significantly improved at days 30 and 90, suggesting that improvements in sustained attention after PSE supplementation may be even more significant as the complexity of the task increases.

Significant changes were not observed in sleep, mood states, or quality of life measures following consumption of PSE, suggesting that daily supplementation with spearmint does not disrupt these important aspects of life in a young, healthy, recreationally active population. Although a previous study showed that chronic supplementation of 900 mg of PSE for 90 days improved sleep parameters on the LSEQ and reduced the participants’ total mood disturbance and increased their vigor as measured by POMS [9], the population in that study was an older demographic aged 50 to 70 years. Sleep disruptions increase as age increases [48], resulting in declines in sleep quality and quantity and possibly making it easier to observe benefits from PSE supplementation. Similarly, exercise has been shown to improve sleep quality [49,50], mood [49,51,52], and quality of life [53,54], such that active individuals, as used in the current study, may already

exhibit high baseline values. Importantly, the current study demonstrated that these variables were not negatively impacted by the daily supplementation with PSE.

A major strength of the present study was its randomized, double-blind, placebo-controlled design. Another strength of the study was that supplementation did not occur in the morning prior to testing periods; therefore, any improvements are indicative of chronic supplementation with no confounding of acute supplementation. However, some limitations exist with the study. Many of the young individuals tested were in college, and their daily schedules and demands could vary based on time of year, class schedule, testing, and others. Measures were taken to address any fluctuations in schedule by containing each participant’s 3-month intervention period within a specific semester, by avoiding major holiday breaks, and by avoiding midterm and finals testing periods whenever possible. Also, changes in diet, sleep, and lifestyle were potentially confounding. As a result, participants were asked to maintain their habitual diet, sleep, and exercise regimen throughout the intervention period, and diet, sleep, and exercise were logged so that consistency could be confirmed.

In conclusion, chronic PSE supplementation improved scores in 2 domains of attention: complex and sustained. Benefits were also observed during 2 specific tests: the shifting attention test and the 4-part continuous performance test. The present study is the first time that improved attention has been demonstrated after chronic consumption of PSE in young, healthy individuals and provides further support to the body of evidence indicating that PSE is an efficacious nootropic.

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Supplemental materials

Supplemental materials to this article can be found online at <https://doi.org/10.1016/j.nutres.2018.11.012>.

REFERENCES

- [1] McIntosh AR. Towards a network theory of cognition. *Neural Netw* 2000;13:861–70.
- [2] Bennett IJ, Madden DJ. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. *Neuroscience* 2014;276:187–205.

- [3] Wainwright PE, Colombo J. Nutrition and the development of cognitive functions: interpretation of behavioral studies in animals and human infants. *Am J Clin Nutr* 2006;84:961–70.
- [4] Warnberg J, Gomez-Martinez S, Romeo J, Diaz LE, Marcos A. Nutrition, inflammation, and cognitive function. *Ann N Y Acad Sci* 2009;1153:164–75.
- [5] Renzi-Hammond LM, Bovier ER, Fletcher LM, Miller LS, Mewborn CM, Lindbergh CA, et al. Effects of a lutein and zeaxanthin intervention on cognitive function: a randomized, double-masked, placebo-controlled trial of younger healthy adults. *Nutrients* 2017;9:1246.
- [6] Lindbergh CA, Renzi-Hammond LM, Hammond BR, Terry DP, Mewborn CM, Puente AN, et al. Lutein and zeaxanthin influence brain function in older adults: a randomized controlled trial. *J Int Neuropsychol Soc* 2018;24:77–90.
- [7] Elsabagh S, Hartley DE, Ali O, Williamson EM, File SE. Differential cognitive effects of Ginkgo biloba after acute and chronic treatment in healthy young volunteers. *Psychopharmacology* 2005;179:437–46.
- [8] Kumar N, Abichandani LG, Thawani V, Gharpure KJ, Naidu MUR, Venkat Ramana G. Efficacy of standardized extract of Bacopa monnieri (Bacognize®) on cognitive functions of medical students: a six-week, randomized placebo-controlled trial. *Evid Based Complement Alternat Med* 2016;2016.
- [9] Herrlinger KA, Nieman KM, Sanoshy KD, Fonseca BA, Lasrado JA, Schild AL, et al. Spearmint extract improves working memory in men and women with age-associated memory impairment. *J Altern Complement Med* 2018;24:37–47.
- [10] Pengelly A, Snow J, Mills SY, Scholey A, Wesnes K, Butler LR. Short-term study on the effects of rosemary on cognitive function in an elderly population. *J Med Food* 2012;15:10–7.
- [11] Kennedy DO, Wake G, Savelev S, Tildesley NT, Perry EK, Wesnes KA, et al. Modulation of mood and cognitive performance following acute administration of single doses of *Melissa officinalis* (lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. *Neuropharmacology* 2003;28:1871–81.
- [12] Scholey AB, Tildesley NT, Ballard CG, Wesnes KA, Tasker A, Perry EK, et al. An extract of *Salvia* (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. *Psychopharmacology* 2008;198:127–39.
- [13] Cirlini M, Mena P, Tassotti M, Herrlinger KA, Nieman KM, Dall'Asta C, et al. Phenolic and volatile composition of a dry spearmint (*Mentha spicata* L.) extract. *Molecules* 2016;21.
- [14] del Bano MJ, Lorente J, Castillo J, Benavente-Garcia O, del Rio JA, Ortuno A, et al. Phenolic diterpenes, flavones, and rosmarinic acid distribution during the development of leaves, flowers, stems, and roots of *Rosmarinus officinalis*. Antioxidant activity. *J Agric Food Chem* 2003;51:4247–53.
- [15] Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. *Free Radic Res* 2006;40:223–31.
- [16] Da Silva S, Calgarotto A, Maso V, Damico D, Baldasso P, Veber C, et al. Molecular modeling and inhibition of phospholipase A 2 by polyhydroxy phenolic compounds. *Eur J Med Chem* 2009;44:312–21.
- [17] Rocha J, Eduardo-Figueira M, Barateiro A, Fernandes A, Brites D, Bronze R, et al. Anti-inflammatory effect of rosmarinic acid and an extract of *Rosmarinus officinalis* in rat models of local and systemic inflammation. *Basic Clin Pharmacol Toxicol* 2015;116:398–413.
- [18] Falé PL, Borges C, Madeira PJA, Ascensão L, Araújo MEM, Florêncio MH, et al. Rosmarinic acid, scutellarein 4'-methyl ether 7-O-glucuronide and (16S)-coleon E are the main compounds responsible for the antiacetylcholinesterase and antioxidant activity in herbal tea of *Plectranthus barbatus* ("falso boldo"). *Food Chem* 2009;114:798–805.
- [19] Mushtaq N, Schmatz R, Pereira LB, Ahmad M, Stefanello N, Vieira JM, et al. Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats. *Cell Biochem Funct* 2014;32:287–93.
- [20] Lee YW, Kim DH, Jeon SJ, Park SJ, Kim JM, Jung JM, et al. Neuroprotective effects of salvianolic acid B on an Abeta25–35 peptide-induced mouse model of Alzheimer's disease. *Eur J Pharmacol* 2013;704:70–7.
- [21] Fallarini S, Miglio G, Paoletti T, Minassi A, Amoruso A, Bardelli C, et al. Clovamide and rosmarinic acid induce neuroprotective effects in *in vitro* models of neuronal death. *Br J Pharmacol* 2009;157:1072–84.
- [22] Fonseca BA, Herrlinger KA. The effects of a proprietary spearmint extract on neurogenesis rates in rat hippocampal neurons. *Neurol 2015;84(14 Supplement):7–105.*
- [23] Farr SA, Niehoff ML, Ceddia MA, Herrlinger KA, Lewis BJ, Feng S, et al. Effect of botanical extracts containing carnosic acid or rosmarinic acid on learning and memory in SAMP8 mice. *Physiol Behav* 2016;165:328–38.
- [24] Nieman KM, Sanoshy KD, Bresciani L, Schild AL, Kelley KM, Lawless AL, et al. Tolerance, bioavailability, and potential cognitive health implications of a distinct aqueous spearmint extract. *Funct Foods Health Dis* 2015;5:165–87.
- [25] Herrlinger KA, Lewis BJ, Lasrado JA, Sanoshy KD, Baldwin JM, Mah E, et al. Acute effects of a proprietary spearmint extract on cognition in healthy men and women. *Soc Neurosci* 2016;88(27).
- [26] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA* 2013;310(20):2191.
- [27] U.S. Department of Health and Human Services FDA. 21CFR50: protection of human subjects. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>; 2013.
- [28] Sjöberg J, Halthur C, Kristinsson SY, Landgren O, Nygell UA, Dickman PW, et al. Progress in Hodgkin lymphoma: a population-based study on patients diagnosed in Sweden 1973–2009. *Blood* 2012;119:4:990–6.
- [29] Falcone PH, Tribby AC, Vogel RM, Joy JM, Moon JR, Slayton C, et al. Efficacy of a nootropic spearmint extract on reactive agility: a randomized, double-blind, placebo-controlled, parallel trial; 2018 [in press].
- [30] Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr* 2000;72:694–701.
- [31] Moy KL, Scragg RK, McLean G, Carr H. The New Zealand physical activity questionnaires: validation by heart-rate monitoring in a multiethnic population. *J Phys Act Health* 2008;5(Suppl. 1):S45–61.
- [32] Narasimhamoorthy B, Zhao LQ, Liu W, Yang W, Greaves JA. Differences in the chemotype of two native spearmint clonal lines selected for rosmarinic acid accumulation in comparison to commercially grown native spearmint. *Ind Crop Prod* 2015;63:87–91.
- [33] Lasrado JA, Trinker D, Ceddia MA, Herrlinger KA. The safety of a dry spearmint extract *in vitro* and *in vivo*. *Regul Toxicol Pharmacol* 2015;71:213–24.
- [34] Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol* 2006;21:623–43.
- [35] Tarrasch R, Laudon M, Zisapel N. Cross-cultural validation of the Leeds sleep evaluation questionnaire (LSEQ) in insomnia patients. *Hum Psychopharmacol* 2003;18:603–10.
- [36] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- [37] McNair DM, Lorr M, Dropelman LF. Profile of mood states. San Diego, CA: Educational and Industrial Testing Service, San Diego; 1992.

- [38] Ferrans CE, Powers MJ. Quality of life index: development and psychometric properties. *ANS Adv Nurs Sci* 1985;8:15–24.
- [39] Paul F, Erdfelder E, Lang A-G, Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.
- [40] Fale PL, Madeira PJ, Florencio MH, Ascensao L, Serralheiro ML. Function of Plectranthus barbatus herbal tea as neuronal acetylcholinesterase inhibitor. *Food Funct* 2011;2:130–6.
- [41] Yin G, Li YM, Wei W, Jiang SH, Du WH. Interactions of acetylcholinesterase with salvianolic acid B and rosmarinic acid from Salvia miltiorrhiza water extract investigated by NMR relaxation rate. *Chin Chem Lett* 2008;19:747–51.
- [42] Klinkenberg I, Sambeth A, Blokland A. Acetylcholine and attention. *Behav Brain Res* 2011;221:430–42.
- [43] Sarter M, Givens B, Bruno JP. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Res Rev* 2001;35:146–60.
- [44] Molloy R, Parasuraman R. Monitoring an automated system for a single failure: vigilance and task complexity effects. *Hum Factors* 1996;38:311–22.
- [45] O'Halloran L, Cao Z, Ruddy K, Jollans L, Albaugh MD, Aleni A, et al. Neural circuitry underlying sustained attention in healthy adolescents and in ADHD symptomatology. *NeuroImage* 2018;169:395–406.
- [46] Wilhelmus MM, Hay JL, Zuiker RG, Okkerse P, Perdrieu C, Sauser J, et al. Effects of a single, oral 60 mg caffeine dose on attention in healthy adult subjects. *J Psychopharmacol (Oxf)* 2017;31:222–32.
- [47] Judelson DA, Armstrong LE, Sokmen B, Roti MW, Casa DJ, Kellogg MD. Effect of chronic caffeine intake on choice reaction time, mood, and visual vigilance. *Physiol Behav* 2005;85:629–34.
- [48] Mander BA, Winer JR, Walker MP. Sleep and human aging. *Neuron* 2017;94:19–36.
- [49] Kovacevic A, Mavros Y, Heisz JJ, Fiatarone Singh MA. The effect of resistance exercise on sleep: a systematic review of randomized controlled trials. *Sleep Med Rev* 2018;39:52–68.
- [50] Lavretsky H, Abbott R. Community-based Acupunch exercise program improves physical health and quality of sleep in Taiwanese older adults. *Am J Geriatr Psychiatry* 2018;26.5: 521–2.
- [51] Stephens T. Physical activity and mental health in the United States and Canada: evidence from four population surveys. *Prev Med* 1988;17:35–47.
- [52] Michishita R, Jiang Y, Ariyoshi D, Yoshida M, Moriyama H, Yamato H. The practice of active rest by workplace units improves personal relationships, mental health, and physical activity among workers. *J Occup Health* 2017;59:122–30.
- [53] Izutsu K, Arima K, Abe Y, Okabe T, Tomita Y, Mizukami S, et al. Exercise intervention implemented by trained volunteers improves health-related quality of life among Japanese community-dwelling older females: an intervention study. *J Phys Ther Sci* 2017;29:2126–32.
- [54] Abd El-Kader SM, Al-Jiffri OH. Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with Alzheimer's disease. *Afr Health Sci* 2016;16:1045–55.