JOURNAL OF INTEGRATIVE AND COMPLEMENTARY MEDICINE
Volume 00, Number 00, 2023, pp. 000–000

DOI: 10.1089/jicm.2022.0543

JICM

A Randomized, Placebo-Controlled Clinical Trial of a Novel Dietary Supplement (Braini) on Standardized CNS Vital Signs Cognitive Performance Parameters in Adults

Amy Joy Lanou, PhD,[1] Aubrey C. Mast, MPH,[1] Benjamin D. Hill, PhD,[2] Sung-Su Kim, PhD,[3] and Patrick Hanaway, MD[4]

Abstract

Objective: To test the effectiveness of a novel dietary supplement as a support for cognitive function in healthy younger and older adults

Design: A double-blind, randomized, placebo-controlled trial of the dietary supplement, Braini® in two age cohorts with 60 participants: 31 healthy younger adults (18–30 years) and 29 healthy older adults (55–80 years).

Intervention: A 28-day intervention of a dietary supplement (active or placebo) taken daily with cognitive assessment using CNS Vital Signs computer-based testing at day 0 and 28. Participants were asked to fill out a daily survey regarding compliance with supplement protocol, changes in health, adherence to the protocol, and reported side effects. CNS Vital Signs provides aged normed aggregated outcome measures for Processing Speed, Psychomotor Speed, Reaction Time, Cognitive Flexibility, Executive Function, and Motor Speed.

Results: Significant improvements in performance were found for two CNS Vital Signs domains, Cognitive Flexibility ($p = 0.048$), and Executive Function ($p = 0.025$) in the treated younger adults ($n = 12$) compared with the placebo group ($n = 19$) at day 28 compared with baseline. The Shifting Attention Test Reaction Time (SAT-RT), a measure of shifting attention correct response reaction time, showed significant improvement at 28 days in those taking Braini in both younger ($p = 0.004$) and older adult cohorts ($p = 0.05$) with an average improvement over the control subjects of 44%. No serious side effects were reported.

Conclusions: The dietary formulation, Braini, safely and significantly improved cognitive flexibility and executive function in younger adults and trended positively in older adults in this study that was stopped prematurely due to pandemic restrictions. Scores on SAT-RT significantly improved in both younger and older adults. Further studies are needed to confirm that Braini reliably improves cognitive function in additional CNS domains in healthy adults (Clinicaltrials.gov under registration number: NCT04025255).

Keywords: cognitive flexibility, executive function, dietary supplement, Peptylin, Braini

[1]Department of Health and Wellness, University of North Carolina Asheville, Asheville, North Carolina, USA.
[2]Department of Psychology, University of South Alabama, Mobile, Alabama, USA.
[3]Precision Medicision Research Center, Gyeonggi-do, Korea.
[4]Family to Family, Asheville, North Carolina, USA.

Introduction

The number of people affected by cognitive decline continues to rise as the U.S. population ages and this decline can be seen as early as age 45.[1] Optimizing cognitive function performance in the areas of psychomotor speed, reaction time, cognitive flexibility, executive function, processing speed, and motor speed during adulthood is a key mechanism to combat cognitive decline as one reaches older adulthood.[2–6]

Human clinical studies in Korea have demonstrated that orally ingested active silk fibroin peptide, exclusively licensed in North America as Peptylin®, improves memory and cognitive performance scores up to 30%–40% in young and older cohorts in 30-day trials.[7–17] Although the exact mechanism of action for these clinical improvements has not been elucidated, active acetylcholinesterase inhibition, Peptylin's potent antioxidant activity, enhanced synaptogenesis, and down-regulated amyloid beta aggregation are likely mechanisms.[10,13,17] Significantly, the synergistic effect of the patented Braini formulation demonstrated superior benefits.[18]

Peptylin was developed under the leadership of Dr. Sung-Su Kim and is one of the important ingredients of the Braini® formulation. In 2018, Famenity received a US FDA New Dietary Ingredient Notification (NDIN) for Peptylin. Sustained memory enhancement from daily intake, with overall safety and tolerability, are the hallmarks of ingested Peptylin in Korea. In 2020, Braini received a US FDA NDIN 1137.

Braini is a proprietary nutraceutical formulation designed to support neural cell viability, signaling efficiency, and protection from pro-inflammatory and oxidative stressors.[7–17] Braini contains refined *Buglossoides arvensis* seed oil. This dietary oil is unique among the plant-based omega fatty acid rich plant-derived oils for having the highest combined omega-3 alpha linolenic acid (ALA, c18:3, n-3), stearidonic acid (SDA, c18:4, n-3), and gamma-linolenic acid (GLA, c:18:3, n-6) content. Licensed exclusively to Braini LLC as Neurxcel®, this oil has EU Novel Food status as of 2015 and Canadian Novel Foods status as of 2020.

The other active ingredient in the Braini formulation is North American wild blueberry (*Vaccinium corymbosum*) powder (minimum 12% anthocyanins). Wild blueberry is a common food ingredient and has been shown to support cognitive function in previous studies.[19–22]

Several clinical trials have studied these separate nutraceutical ingredients for improved memory enhancement and cognitive performance. Of those conducted, all formulations were well tolerated by participants.[18,23–27] Clinical trials using these key ingredients individually (Peptylin, Neurxcel and wild blueberry) have measured the effects of these active ingredients and have been shown to support anti-inflammatory, neuro-protective and cognitive performance benefits.[28–30]

The Braini formulation is novel and harnesses synergistic effects. *In vitro* cell challenge assays of the active constituents in Braini were performed to assess cell viability and anti-oxidant activity. Braini showed significant improvement in cell viability and inhibition of reactive oxygen species. These unpublished results (from Dr. E. Hernandez at Innoprot S.L.) highlight a possible mechanism for the support of cognitive function tested in this study and are the subject of patent and a pending patent application.[18,31]

Based on existing science supporting the neuroprotective role of Peptylin, the Braini formulation may be an effective dietary supplement for improving cognitive function and preventing cognitive decline stemming from oxidative challenges. Oxidative challenges are commonly associated with neurotransmitter viability and performance, which can lead to dementia and Alzheimer's disease.[28] The Braini formulation shows promise as a natural therapeutic candidate to slow or prevent damaging neurophysiologic effects.

The purpose of this randomized double-blinded, placebo-controlled study with two age cohorts was to determine whether the novel dietary supplement formulation of Braini, when orally ingested as directed, demonstrates improvements in standardized cognitive performance tests compared with a control population in both younger and older adults with normal cognitive function.

Materials and Methods

Participants

Cohort A participants ($n = 38$) were younger adults (18–30 years), and Cohort B participants ($n = 36$) were older adults (55–80 years). The trial was conducted on a university campus in a quiet office area. It was stopped early due to the coronavirus pandemic when the university campus was closed to visitors. A sample size of 50 in each cohort was determined by a power calculation. The planned subject enrollment was modified due to campus closures.

Study eligibility required participants to: (1) continue with their current diet and refrain from taking any new nutritional or herbal supplements; (2) have English language proficiency; (3) not be clinically diagnosed with Alzheimer's disease, stroke, Parkinson's, or dementia; (4) not have active fibromyalgia, multiple sclerosis, seizures/epilepsy, or other known diseases that may affect memory or cognition; (5) not have taken prescription drugs to support memory/prevent cognitive decline in the past 180 days nor to treat other diseases referenced earlier in criterion number 4; (6) not have taken dietary supplements that include wild blueberry extract, Neurxcel, or silk protein peptide in the past 90 days; (7) not have taken any medicines that are stimulants; (8) not have GI disorders known to impair absorption of nutrients; (9) not have traumatic brain injury in their personal history; (10) not be participating in another clinical trial; (11) not be pregnant; and (12) have a current Montreal Cognitive Assessment (MoCA) score of >21.

Standard protocol, recruitment, and informed consent

Informed consent was obtained from all participants, and methods were carried out in accordance with protocols approved by the University of North Carolina Asheville (UNCA) Institutional Review Board. Participants were recruited from the UNCA, from the Osher Lifelong Learning Institute (OLLI) at UNC Asheville, and from the surrounding area from November 2019 through February 2020. Participants were offered $50 for study completion, and month supply of the Braini dietary supplement was offered at the conclusion of the study to participants who were allocated to the placebo control group.

Study design

A randomized, double-blinded, placebo-controlled dietary supplement study with younger and older adult cohorts comparing Braini dietary supplement and a placebo was conducted between November 2019 and April 2020. Interested individuals were screened for eligibility by phone. If eligible and still interested, participants reviewed and signed a detailed informed consent form, completed a demographics and health behaviors questionnaire, a health history form, and the MoCA Test intake questionnaire.

When cleared for participation, they did a practice set of computer-delivered online cognitive assessments using CNS Vital Signs (Morrisville, NC, USA). This neurocognitive performance testing procedure is internationally recognized as a standardized neurocognitive performance assessment tool (https://www.cnsvs.com/).[32]

Participants were randomly assigned stratified by age cohort to either the Braini supplement or placebo group using block randomization with groups of 4 to achieve a 1:1 allocation by a research colleague. Sequentially numbered containers were assigned by A.C.M. who also enrolled the participants. Both experimenters and participants were blinded to group assignment.

A series of CNS Vital Signs cognitive assessments were given, which included psychomotor speed, reaction time, processing speed, cognitive flexibility, executive function, and motor speed. The participants were given a practice test and within 1 week they took a baseline test. Then after consuming the active or placebo supplement for 28 days, they took their final test. All testing was completed on the same computer in private spaces at the university.

Nutritional supplement and placebo intervention

Braini is a proprietary nutraceutical formulation comprising ingredients generally recognized as safe (GRAS) or registered by the FDA. The daily dose of Braini contains 400 mg of Peptylin; Neurxcel oil delivered as 500 mg of micro-encapsulated powder (containing 250 mg Neurxcel oil), in a cornstarch and corn syrup solids powder base carrier; and 100 mg wild blueberry powder. All active ingredients are at safe concentrations.

The placebo (rice starch) utilized in this clinical trial was formulated by a Good Manufacturing Practice-compliant dietary supplement contract manufacturer and made to be as similar as possible to the active dietary supplement in appearance, odor, and other key characteristics.

Participants were randomized into either active or placebo supplement groups and were instructed verbally and in writing to consume 2 capsules per day of the product they received for a total of 56 capsules over the 28-day intervention period.

Each day during the trial, study staff sent a text or an email to participants with a link to a form to remind and ask participants whether they took their supplements that day. The email communication also prompted participants to respond on whether they had experienced any changes in health or health behaviors. Compliance was measured from the daily surveys (98.4% of respondents reported taking their supplements daily). The participants were instructed to report any adverse events to the study staff immediately and were reminded to do so on each daily survey.

At each visit (day = 0 and day = 28), study staff asked participants whether they had experienced any adverse events, changed their dietary habits, or experienced any other notable changes to their lifestyles. If participants reported an adverse event, this was reported to the study physician (94.8% of survey responses reported no concerns on their daily forms). The concerns that were noted were metallic taste in mouth, trouble concentrating, lightheadedness, vertigo, difficulty sleeping, headaches, and feeling flushed. No serious adverse events were expected or observed.

Cognitive assessment

Our primary outcome measure was a suite of computer-based tests established and validated by CNS Vital Signs. They provide a computer-based 30-minute assessment suite measuring neurocognitive performance parameters to provide aggregated outcome measures for Processing Speed, Psychomotor Speed, Reaction Time, Cognitive Flexibility, Executive Function, and Motor Speed. A comprehensive reliability and validity analysis of the CNS Vital Signs platform was published in 2006 in the *Archives of Clinical Psychology*.[32] The MoCA was used for screening to exclude any participants with cognitive impairment.

Statistical analysis

CNS Vital Signs outcome measures for Processing Speed, Psychomotor Speed, Reaction Time, Cognitive Flexibility, Executive Function, and Motor Speed, along with the correct response Shifting Attention Test Reaction Time (SAT-RT), were assessed. The difference score was calculated by subtracting the post-intervention CNS Vital Signs domain scores from the baseline CNS Vital Signs domain scores. These standard scores have a mean value = 100 and standard deviation = 15.

We analyzed the SAT-RT as a raw score in milliseconds to evaluate changes on executive reaction time. The CNS Vital Signs difference scores were then used for analyses to reflect change from baseline. Independent-samples *t*-tests with bootstrapping (1000 samples at 95% confidence interval) were utilized. Levene's test was not significant, so equal variances were assumed.

In addition, due to the small and unequal sample size for the groups, nonparametric Mann–Whitney *U* tests were also used and confirmed the findings of the independent-samples *t*-tests. The results were analyzed using the statistical package SPSS v.27. For the older adult cohort, the analysis of the active Braini and placebo for all CNS tests and the SAT-RT analysis was done by the pharmaceutical consulting firm Pharma Initiatives (Chapel Hill, NC, USA) using R Studio Version 1.1.456 software (RStudio, Inc.).

Results

Participants

Thirty-eight younger adults enrolled in the study. One withdrew, and four did not finish. Thirty-three younger participants completed the study. Thirty-six older adults enrolled in the study. Three withdrew, and two did not finish. Thirty-one older adults completed the study. In addition, four participants, two in the younger cohort and two

in the older cohort, had invalid CNS Vital Signs data. Analysis was performed on 31 young adults ($n = 12$ treatment; $n = 19$ placebo) and 29 older adults ($n = 13$ treatment; $n = 16$ placebo).

Reasons for participant withdrawal: vertigo ($n = 1$), urinary tract infection ($n = 1$), unspecified no show on day 28 ($n = 1$), and difficulty concentrating ($n = 1$). Only subjects who completed the study with valid data on both the pre- and post-test were analyzed. See Figures 1 and 2 for CONSORT flow diagrams. Participant demographics and health behaviors are presented in Table 1.

Young adult cohort

In healthy younger adults ages 18–30, participants taking Braini for 28 days experienced significant improvement

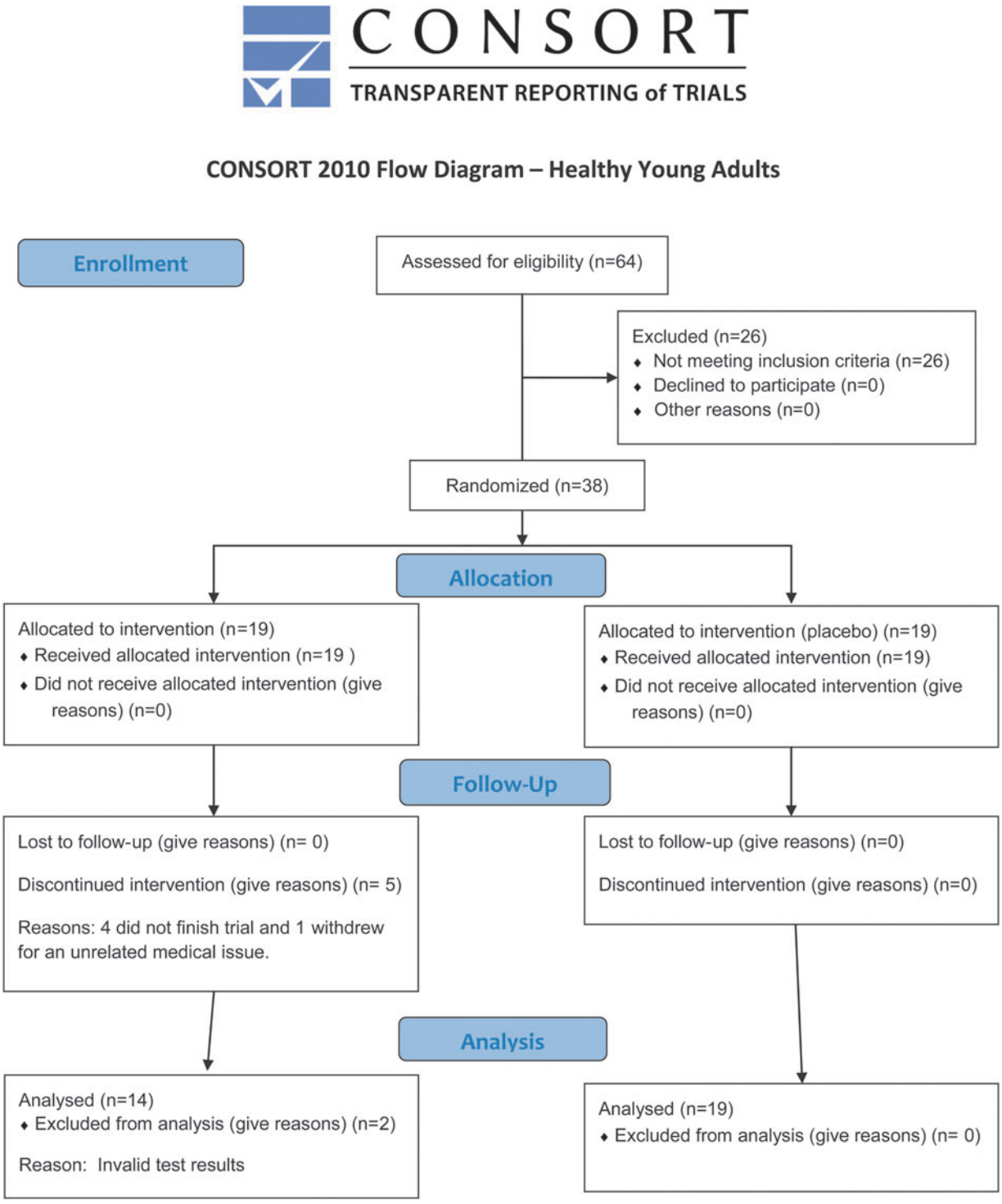

FIG. 1. CONSORT diagram for participant recruitment to study completion for young adult cohort.

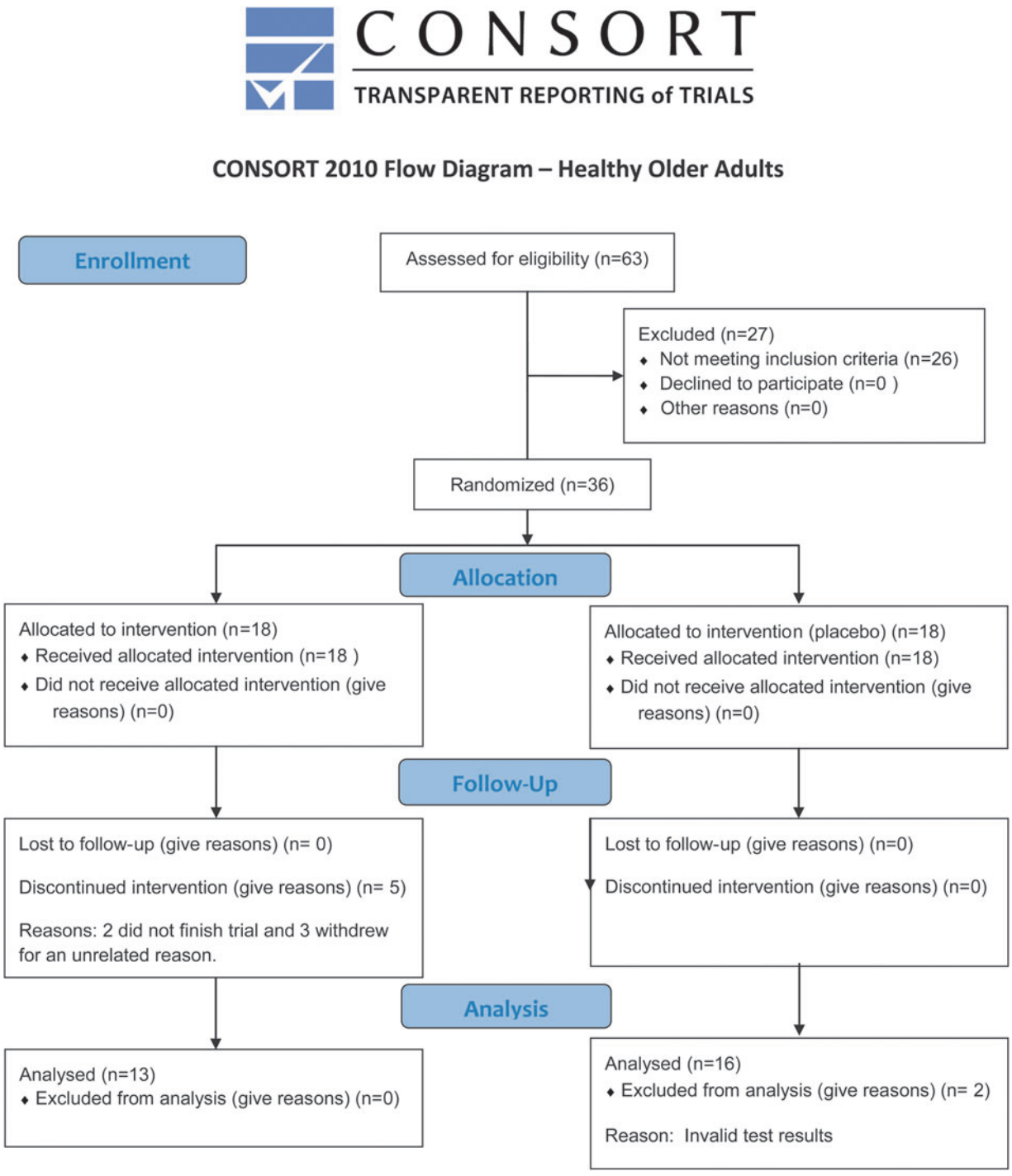

FIG. 2. CONSORT diagram for Healthy Older Adults cohort.

versus placebo, significant differences were found for two CNS Vital Signs measurements, Cognitive Flexibility [mean difference 9.715, $t(29) = 2.151$, $p = 0.040$], Executive Function [mean difference 7.745, $t(29) = 2.190$, $p = 0.037$]. For both of these domains, a larger difference score represented improved performance at post-test compared with pre-test or baseline (Fig. 3a).

Significant differences were also found in the component measure SAT-RT (mean difference 83.285 [$t(29) = 3.131$, $p = 0.004$]), with the treatment group ($n = 12$) having improved performance compared with the placebo group ($n = 19$) at post-test compared with baseline. For SAT-RT, the treatment group's mean difference score was 87.917 ± 78.885 and the placebo group's mean difference score was 4.632 ± 67.689. This is a raw score in milliseconds; thus, a larger number indicates a faster reaction time at post-test compared with baseline (Fig. 4).

Cohen's d was calculated and resulted in $d = 0.707$ for the group difference on Cognitive Flexibility, $d = 0.807$ for the group difference on Executive Functioning, and $d = 1.154$

Table 1. Baseline Demographic and Behavior Information

	Study A: Younger cohort		*Study B: Older cohort*	
	Braini supplement (n = 12)	*Placebo (n = 19)*	*Braini supplement (n = 13)*	*Placebo (n = 16)*
Age (mean years)	20.6	21.6	68.6	66.3
MOCA score (mean)	24.7	25.1	25.3	25.4
Gender	8 F 4 M	14 F 5 M	10 F 3 M	10 F 6 M
Exercise (% yes)	75	74	77	88
Caffeine use (% yes)	42	74	77	75
Tobacco use (% yes)	0	5	0	0
Alcohol use (% yes)	83	89	85	88
Mental health concern (% yes)	42	63	38	31
Trouble sleeping (% yes)	—	—	23	23

MOCA, Montreal Cognitive Assessment.

for SAT average correct reaction time. These values constitute large effect sizes that would be considered clinically significant.

Older adult cohort

Positive trends are seen across all the CNS Vital Signs outcome measures, though none reach statistical significance (Fig. 3b). A potential ''ceiling effect'' is noted with the population studied. Among this cohort of healthy older adults, the average Executive Function outcome measure @ day 0 was 109 (average = 100) $\sim$1 standard deviation above average cognitive performance, leaving less room for the effects of an intervention to manifest.

Nonetheless, in these healthy high-functioning older adults aged 55–80, taking Braini for 28 days improved the SAT-RT versus placebo ($p = 0.05$). In both age groups, significant decreases in SAT-RT demonstrate the Braini cohort's improvement, with faster reaction times with a correct response after 28 days, compared with placebo (Fig. 4).

Discussion

This is the first randomized, double-blinded, placebo-controlled dietary intervention trial investigating the effects of a natural nutraceutical supplement consisting of a novel combination of silk protein peptide, plant-derived essential fatty acids, and wild Canadian blueberry, on standardized neurocognitive performance measures obtained over a short 28-day period while allowing healthy subjects to carry on with their typical diets and daily activities.

CNS Vital signs tests provide aggregated outcome measures for executive function, cognitive flexibility, reaction time, processing speed, psychomotor speed, and motor speed. Executive function relates to how well a subject recognizes rules, categories, and manages or navigates rapid decision making. Executive function is recognized as one of the most difficult aspects of cognitive performance to influence meaningfully, because executive function and its component SAT-RT represent a complex of neurophysiological structures and functions that are deep-seated and difficult to influence over just 28 days.[33,34]

Measures of executive function translate to valuable everyday tasks such as managing time effectively, paying attention to and sequencing instructions correctly using short-term memory, switching focus between activities requiring memory, planning and organizing activities, recalling details, and thinking creatively. Braini showed significant improvements in Executive Function and Cognitive Flexibility domains.

CNS Vital Signs identifies Executive Function and Cognitive Flexibility as testing parameters for attention deficit disorder, attention deficit/hyperactivity disorder, non-amnestic mild cognitive impairment (MCI), sleep, depression, chemobrain, and concussion. In addition, Cognitive Flexibility is used as a testing parameter for MCI, early dementia.

The SAT-RT correct response measurement is a key component of the CNS Vital Signs Executive Function outcome score. SAT-RT improvement creates safer environments where one's capacity to respond in shifting attention environments (e.g., driving an automobile, or playing sports) with more efficiency, speed, and accuracy can be vital.

Among younger adults, a significant difference in executive function from baseline to 28 days was observed between Braini and placebo. The fact that any statistically significant differences were found with small cohort sizes (<20 individuals per arm) is remarkable,[33] especially with executive function in healthy young subjects whose brains are generally at their physiological peak in terms of brain mass and integrity over their entire normal life course.[34] These differences were noted in the absence of any other controlled variables involving diet or lifestyle behaviors (i.e., in free-living participants).

In addition, clinically relevant increases in cognitive flexibility were observed in younger adults taking Braini compared with those receiving placebo. Measures of cognitive flexibility translate to skills such as reasoning, decision making, impulse control, and strategy formation. This supports a person's ability to adapt to changes in complex sets of instructions.

Improvements in executive functions and cognitive flexibility allow people to focus attention on specific tasks, successfully solve problems, and plan ahead; thus, these are important for everyday life.[34]

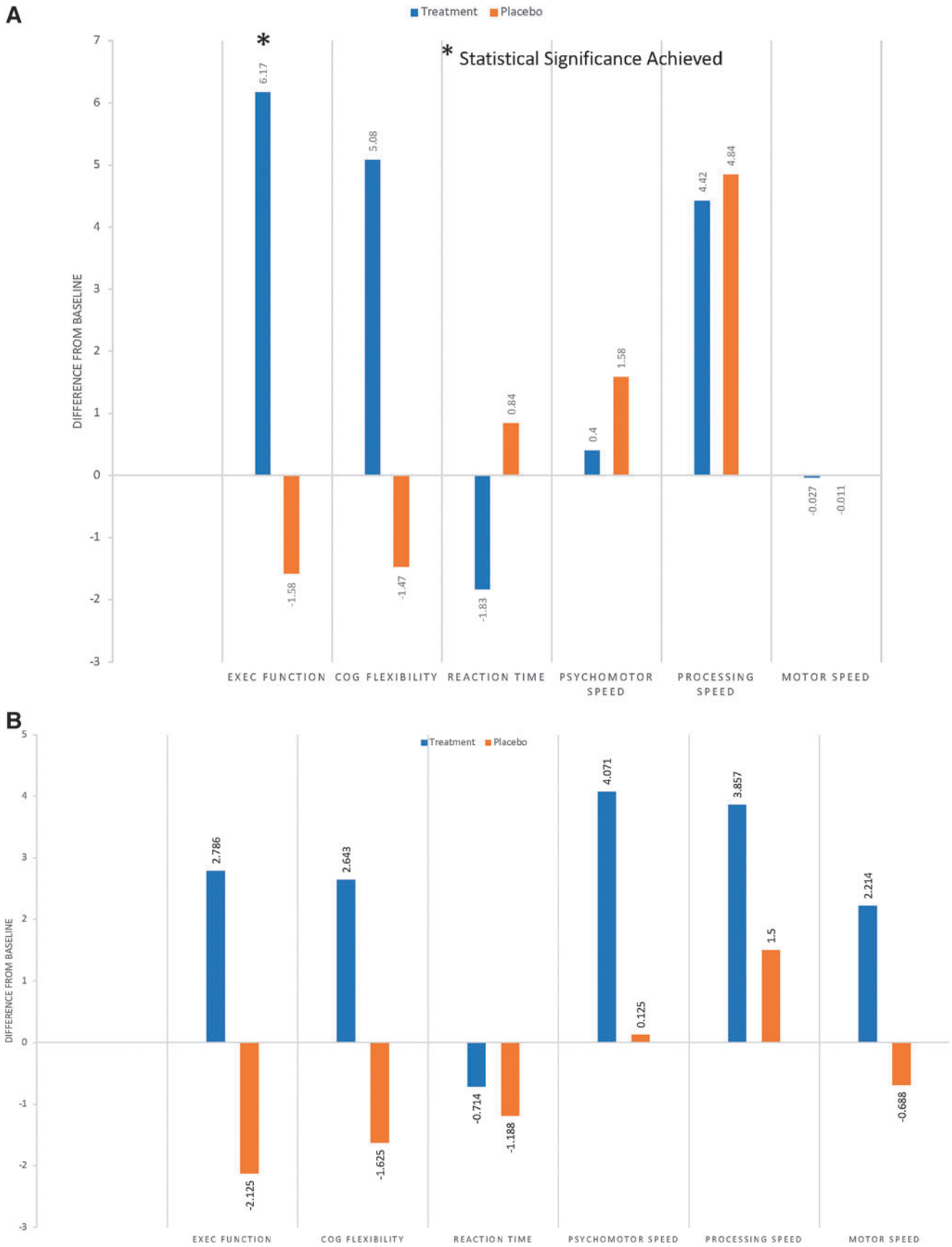

FIG. 3. **(A, B)** Differences between the baseline and the final scores after 28 days are presented for both the younger **(A)** and the older **(B)** cohorts for all six tests. These results demonstrate the significant improvement in executive function and cognitive flexibility for the younger adults consuming the Braini supplement. For both domains, a larger difference score represented improved performance at post-test compared with pre-test or baseline.

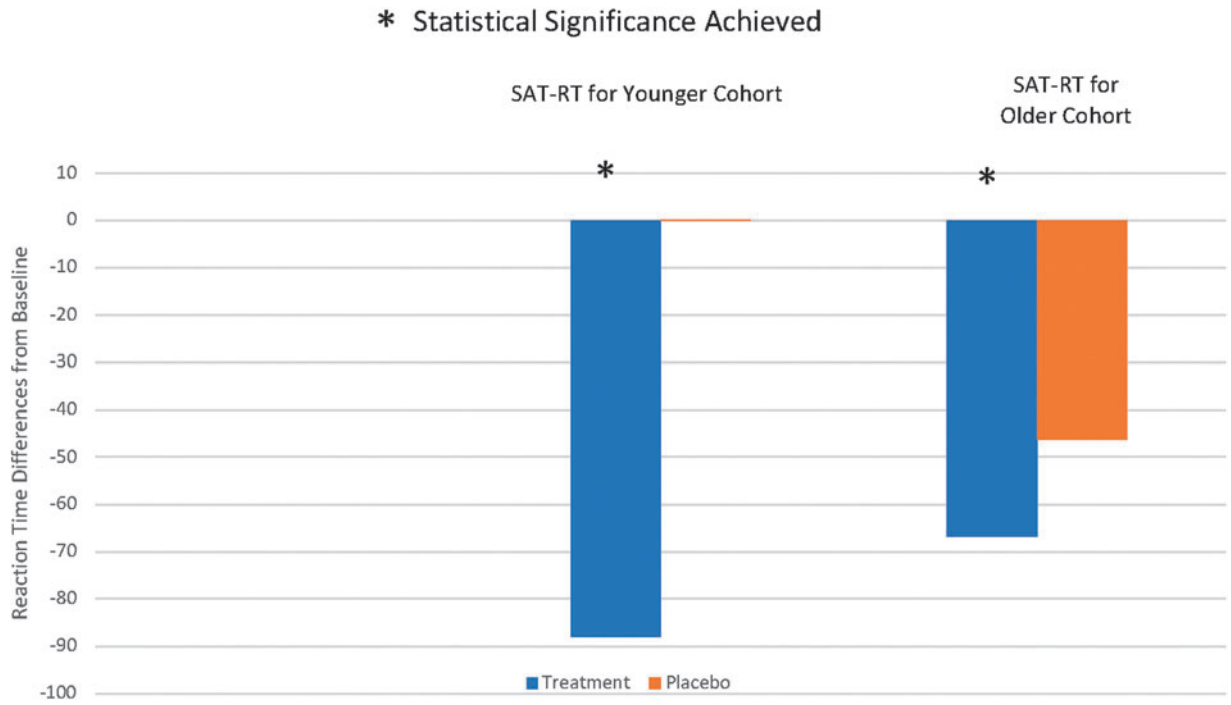

FIG. 4. These results show the significant change between baseline and the final values for Shifting Attention Reaction times for both the younger and the older participants treated with the Braini supplement.

Limitations

Study strengths include participants who largely complied with the study protocol and experienced no serious side effects, suggesting that the Braini supplement was well tolerated. And the CNS Vital Signs testing protocol is validated and well studied. Study limitations include testing at 2 time points (day 0 and 28) rather than 3 or 4. This means that a single invalid test forced the participant to be dropped from the analysis.

A further limitation in the older adult cohort was the ''ceiling effect'' noted, which is likely due to the population enrolled. The OLLI @ UNCA attracts many retired professionals with advanced degrees, which may have led to the above average baseline scores. Another limitation was the study time period being cut short by the pandemic (UNCA closed to visitors while the study was underway). Based on our power analyses, we anticipated needing 50 participants in each age cohort with random assignment into placebo and control groups of $\sim$25 participants each. Instead, we had to stop the study when we had enrolled 74 participants totally (38 and 36 in younger and older adult cohorts, respectively) and some of these enrolled participants were not able to complete their 28-day test (6)—leading to smaller than planned sample sizes.

All three ingredients have peer-reviewed evidence of positive effects on known factors affecting neurotransmitter function and/or physiological responses to oxidative and inflammatory stressors.[10,28,35,36] The Braini supplement appears to act rapidly (4 weeks) to cross the blood-brain barrier and supply important ''building blocks'' for enhanced neurotransmitter support and/or assistive anti-oxidative and/or anti-inflammatory activities that result in measurable benefits in cognitive functioning.

Additional placebo-controlled trials involving larger cohort sizes and biomarkers confirming changes in neurophysiological capacity are warranted. Additional research may elucidate and identify possible mechanisms of action and guide researchers toward safe, effective, and natural alternative dietary interventions that do not incur the known side-effects nor the societal infrastructure costs of conventional pharmaceutical interventions.

Conclusion

Daily use of the novel dietary supplement, Braini, taken for 4 weeks significantly increased cognitive flexibility and executive function among younger generally healthy adults compared with a placebo. Executive Function Shifting Attention Test (SAT RT) correct response reaction time was clinically and statistically significant creating improvement in both younger and older adults.

This combination of safe dietary ingredients shows promise for supporting cognitive function among adults as measured by CNS Vital Signs and may indicate support for improved efficiency of mental processes and a healthier brain. Further studies that are representative of the general population and adequately powered are needed to confirm this finding and to better understand the effectiveness of this brain supplement in supporting cognitive function.

Acknowledgments

The authors thank Mark Shapiro for assistance with statistical analysis, Camden Spade for data collection, and Greg Cumberford, Marcus Goddard, and Troylyn Ball for their contributions.

Authors' Contributions

A.J.L. led the study design, IRB negotiations; participated in data collection; and drafted and finalized the manuscript. A.C.M. participated in the study design, led the data collection, and reviewed the manuscript. B.D.H. conducted the analysis of the results, participated in drafting the manuscript and the presentation of the results, and consulted on the use of CNS Vital Signs. S.S.K. consulted on the use of the active ingredients in Braini but did not have a role in data collection or analysis. P.H. participated in study design, dietary supplements manuscript drafting, and led the review and editing of the manuscript.

Author Disclosure Statement

S.S.K. is an owner in Braini, LLC. The other authors have no conflicts of interest to report.

Funding Information

This study was funded and sponsored by Braini, LLC.

References

1. Taylor CA, Bouldin ED, McGuire LC. Subjective cognitive decline among adults aged ≥45 years—United States, 2015–2016. MMWR Morb Mortal Wkly Rep 2018;67:753–757; doi: 10.15585/mmwr.mm6727a1
2. Assessing Cognitive Impairment in Older Patients, NIH National Institute on Aging; 2022. Available from: https://www.nia.nih.gov/health/assessing-cognitive-impairment-older-patients [Last accessed: December 27, 2022].
3. Hammond BR, Miller LS, Bello MO, et al. Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: A randomized, double-masked, placebo-controlled trial. Front Aging Neurosci 2017;3:254; doi: 10.3389/fnagi.2017.00254
4. Kato M, Ochiai R, Kozuma K, et al. Effect of chlorogenic acid intake on cognitive function in the elderly: A pilot study. Evid Based Complement Alternat Med 2018;2018:8608497; doi: 10.1155/2018/8608497
5. Ito N, Saito H, Seki S, et al. Effects of composite supplement containing astaxanthin and sesamin on cognitive functions in people with mild cognitive impairment: A randomized double-blinded, placebo-controlled trial. J Alzheimers Dis 2018;62(4):1767–1775; doi: 10.3233/JAD-170969
6. Tanev KS, Federico LE, Terry DP, et al. Cognitive impairment and predicting response to treatment in an intensive clinical program for post-9/11 veterans with posttraumatic stress disorder, J Neuropsychiatry Clin Neurosci 2019;31:337–345; doi: 10.1176/appi.neuropsych.18090208
7. Kim DH, Kim OH, Yeo JH, et al. The improvement of short- and long-term memory of young children by BF-7. J Korean Social Food Sci Nutr 2010;39:376–382.
8. Chea HS, Kang YK, Shin YK, et al. The role of BF-7 on neuroprotection and enhancement of cognitive function, Korean J Physiol Pharmacol 2004;8:173–179.
9. Lee SH, Kim YS, Kim SS, et al. Association between cerebral blood flow and cognitive improvement effect by B. mori extracted component. J Sericultural Entomol Sci 2004;46:77–79.
10. Lee SH, Kim YS, Kang YK, et al. The improvement of learning and memory ability of normal persons by BF-7. Korean J Physiol Pharmacol 2004;8:307–312.
11. Lee MY, Lee SH, Lee JS, et al. BF-7 Improved memory function and protected neuron from oxidative stress. Korean J Phys Anthropol 2004;17:313–320.
12. Lee JY, Lee SH, Sung JJ, et al. The effect of BF-7 on the ischemia-induced learning and memory deficits. Korean J Anat 2005;38:181–188.
13. Kim DK, Lee JY, Sung JJ, et al. The role of BF-7 on enhancement of memory and cognitive function. Korean J Anat 2004;37:519–527.
14. Kim KW, Park S, Yoo HK, et al. Brain factor-7 extracted from Bombyx mori enhances cognition and attention in normal children. J Med Food 2009;12:643–648; doi: 10.1089/jmf.2008.1236
15. Kim DH, Lee HJ, Choi GH, et al. Milk containing BF-7 enhances the learning and memory, attention, and mathematical ability of normal persons. Korean J Food Sci Anim Resour 2009;29:278–282; doi: 10.5851/kosfa.2009.29.2.278
16. Kim DH, Lee HJ, Lee KG, et al. Milk with Brain Factor-7 (BF-7 milk) enhances attention and cognition in normal persons. Milchwissenschaft 2009;64:300–304.
17. Choi GH, Jo MN, Moon SH, et al. Neuroprotective effects and physicochemical characteristics of milk fortified with fibroin BF-7. Food Sci Anim Resour 2008;28:431–436.
18. Cumberford GW, Ball T, Goddard M. Compositions with Purified Bombyx mori Cocoon Silk Peptide Fiber and Refined Buglossides Arvensis Seed Oil Having Synergistic Effects for Improving Memory, Focus, and Cognitive Function, and Related Methods. United States Patent Office, USPTO Number 11,357,810, June 14, 2022.
19. Barnes S, Prasain J, D'Alessandro T, et al. The metabolism and analysis of isoflavones and other dietary polyphenols in foods and biological systems. Food Funct 2011;2:235–244; doi: 10.1039/c1fo10025d
20. Grace MH, Ribnicky DM, Kuhn P, et al. Hypoglycemic activity of a novel Anthocyanin-rich formulation from lowbush blueberry, Vaccinium angustifolium Aiton. Phytomedicine 2019;16:406–415; doi: 10.1016/j.phymed.2009.02.018
21. Grace MH, Esposito D, Dunlap KL, et al. Comparative analysis of phenolic content and profile, antioxidant capacity and anti-inflammatory bioactivity in wild Alaskan and commercial Vaccinium berries. J Agric Food Chem 2014;62:4007–4017; doi: 10.1021/jf403810y
22. Strathearn KE, Yousef GG, Grace MH, et al. Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinson's disease. Brain Res 2014;1555:60–77; doi: 10.1016/j.brainres.2014.01.047
23. Shukitt-Hale B. Blueberries and neuronal aging. Gerontology 2012;58:518–523; doi: 10.1159/000341101
24. Mechanism of Oxidative Stress in Neurodegeneration; n.d. Available from: https://www.hindawi.com/journals/omcl/2012/428010/ [Last accessed: January 15, 2021].
25. Salim S. Oxidative stress and the central nervous system. J Pharmacol Exp Ther 2017;360:201–205; doi: 10.1124/jpet.116.237503
26. Luca M, Luca A, Calandra C. The role of oxidative damage in the pathogenesis and progression of Alzheimer's disease and vascular dementia. Oxid Med Cell Longev 2015; doi: 10.1155/2015/504678
27. Cumberford GW, Ball T, Goddard M. Braini LLC, Compositions with Purified Bombyx mori Cocoon Silk Peptide Fiber and Refined Buglossides Arvensis Seed Oil Having Synergistic Effects for Improving Memory, Focus, and Cognitive Function, and Related Methods. United States, Patent Application, US 2021/0220418 A1, July 22, 2022.

28. Zamroziewicz MK, Paul EJ, Zwilling CE, et al. Determinants of fluid intelligence in healthy aging: Omega-3 polyunsaturated fatty acid status and frontoparietal cortex structure. Nutr Neurosci 2018;21:570–579; doi: 10.1080/1028415X.2017.1324357
29. Lefort N, LeBlanc R, Surette ME. Dietary Buglossoides arvensis oil increases circulating n-3 polyunsaturated fatty acids in a dose-dependent manner and enhances lipopolysaccharide-stimulated whole blood interleukin-10. Nutrients 2017;9:261; doi: 10.3390/nu9030261
30. Bowtell J, Aboo-Bakkar, Conway ME, et al. Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation. Appl Physiol Nutr Metab 2017;42:773–779; doi: 10.1139/apnm-2016-0550
31. Cumberford GW, Ball T, Goddard M. Methods and compositions with purified Bombyx Mori cocoon silk peptide fiber and refined Buglossoides Arvensis seed oil providing anti-inflammatory effects and neuroprotection for disease states, United States Patent Application 17/721,343 April 14 2022.
32. Gualtiere CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol 2006;21:623–643; doi: 10.1016/j.acn.2006.05.007
33. Rypma B, D'Esposito M. Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci 2000;3:509–515; doi: 10.1038/74889
34. Ferguson HJ, Brunsdon VEA, Bradford EEF. The developmental trajectories of executive function from adolescence to old age. Sci Rep 2021;11:1382; doi: 10.1038/s41598-020-80866-1
35. Ammar A, Trabelsi K, Boukhris O, et al. Effects of polyphenol-rich interventions on cognition and brain health in healthy young and middle-aged adults: Systematic review and meta-analysis. J Clin Med 2020;9:1598; doi: 10.3390/jcm9051598
36. Riso P, Klimis-Zacas D, Del Bo' C, et al. Effect of a wild blueberry (Vaccinium angustifolium) drink intervention on markers of oxidative stress, inflammation and endothelial function in humans with cardiovascular risk factors. Eur J Nutr 2013;52:949–61; doi: 10.1007/s00394-012-0402-9.

Address correspondence to:
Amy Joy Lanou, PhD
Department of Health and Wellness
University of North Carolina Asheville
One University Heights
Asheville, NC 28804
USA

E-mail: alanou@unca.edu