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ORIGINAL RESEARCH

A Randomized, Double-Blind, Placebo-Controlled, Parallel Study Investigating the Efficacy of a Whole Coffee Cherry Extract and Phosphatidylserine Formulation on Cognitive Performance of Healthy Adults with Self-Perceived Memory Problems

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ABSTRACT

Introduction: Cognition refers to brain functions including memory, learning, and thought processing and is increasingly important to individuals. However, impairment of cognitive function is a concern among North American adults. Therefore, effective and reliable treatments are needed.

Methods: This randomized, double-blind, placebo-controlled study examined the effects of 42 days of Neuriva® supplementation, a whole coffee cherry extract and phosphatidylserine supplement, on memory, accuracy, focus and concentration and learning among 138 healthy adults (40–65 years) with self-reported memory problems. Plasma brain-derived neurotrophic factor (BDNF) levels, Computerized Mental Performance Assessment System (COMPASS) tasks, the Everyday Memory Questionnaire (EMQ), and Go/No-Go tests were assessed at baseline and day 42.

Results: As compared to placebo, Neuriva® supplementation elicited greater improvements at day 42 in numeric working memory COMPASS task accuracy outcomes ($p \leq 0.024$) which assessed memory, accuracy, and focus and concentration, and reaction time outcomes ($p \leq 0.031$) which assessed memory as well as focus and concentration. Neuriva® supplementation improved overall accuracy ($p = 0.035$) in the picture recognition task that assessed memory, accuracy, and learning compared to placebo. No significant differences between groups were observed for BDNF, the EMQ, or Go/No-Go tests.

Conclusion: Results suggest 42 days of Neuriva® supplementation was safe, well tolerated, and beneficial in improving memory, accuracy, focus and concentration, and learning in a healthy adult population with self-reported memory problems.

Keywords: Cognition; Dietary supplement; Memory; Nutraceutical

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Key Summary Points

Why carry out this study?

Improving and maintaining cognition are increasingly important because of the aging population, increase in life expectancy, and impact of cognitive decline on quality of life

Effective and reliable options to support cognition are warranted

This study investigated the effects of Neuriva®, a supplement containing whole coffee cherry extract and phosphatidylserine, on cognitive performance in healthy adults with self-reported memory problems

What was learned from the study?

Neuriva® supplementation was safe well tolerated, and significantly improved measures of memory, accuracy, focus and concentration, and learning compared to placebo in a healthy adult population with self-reported memory problems

Future larger studies of longer duration are needed to confirm the current study's findings

INTRODUCTION

Improving and maintaining brain health and cognition, including memory, learning, and thought processing [1], are increasingly important among individuals and public health agencies because of the aging population, increase in life expectancy, and impact of cognitive decline on quality of life [2–4]. A recent systematic review showed a range in North American prevalence of cognitive impairment of 7.1–28.3% among community-dwelling adults aged 50 years or older [5]. An important brain protein that stimulates neurogenesis and is essential for neuronal plasticity, central nervous system development [6], and supports overall cognitive function [7] is brain-derived neurotrophic factor (BDNF). Aging may be associated with a decline in BDNF levels, and this decline may be one of the many factors contributing to cognitive impairment [8].

Currently, interventions to manage cognitive decline include pharmacological agents, cognitive training, and physical exercises [9]. However, there are limitations to their use or inconsistencies in study findings [10–18]. The brain health supplement market size was valued at US $7.68 billion in 2021 and projections indicate a compound annual growth rate of 8.3% from 2022 to 2030 [3] as individuals are increasingly interested in brain health supplements. Therefore, efficacious natural treatment options are warranted to support and improve cognition with aging.

Whole coffee cherry extract (WCCE) is rich in polyphenols which may contribute to its potential to improve cognition [19, 20]. A WCCE-containing beverage was reported to improve cognition related to alertness and attenuate fatigue after an acute dose in healthy adults [21]. Moreover, a post hoc analysis revealed significant reductions in reaction time after 7 and 28 days of WCCE supplementation, compared to placebo, in older adults with mild cognitive impairment who were otherwise healthy [22]. Reaction time was also significantly improved from baseline after acute supplementation with WCCE in adults with memory complaints [23]. Cotter et al. [24] summarized findings of studies related to WCCE and BDNF, which included two randomized, placebo-controlled trials that showed an increase in BDNF levels compared to placebo [25] and baseline values [23].

Phosphatidylserine (PS) is an important phospholipid in the brain that is needed for healthy nerve cell membranes and myelination and plays an important role in signaling pathways [26, 27]. PS comprises 13–15% of total phospholipids in the cerebral cortex [27]; however, physiological changes associated with aging result in a reduction of PS [26]. Previous research in animal models [28] and humans [29–31] have shown beneficial effects of PS supplementation on cognitive function.

While WCCE and PS supplementation have independently been found to improve cognition, there may be differences in their potential mechanisms. Therefore, research investigating the efficacy of these active ingredients in combination is warranted. The objective of this study was to investigate the efficacy of a combination of WCCE and PS on cognitive performance in healthy adults with self-reported memory problems.

METHODS

Study Design and Approvals

This was a randomized, double-blind, placebo-controlled, parallel study conducted at KGK Science Inc. in London, ON, Canada from February 14, 2020 to May 15, 2021. Participants consumed either Neuriva® or placebo for 42 days and visited the clinic at screening, baseline (day 0), and day 42.

The study was approved by the Natural and Non-Prescription Health Products Directorate, Health Canada, Ottawa, Ontario on December 18, 2019. Research ethics board approval was granted on December 24, 2019, from the Institutional Review Board Services, Aurora, Ontario (Pro00040971). The study was conducted in compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki guidelines and its subsequent amendments. The trial followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized controlled trials [32] (Supplementary Material Table S1). Written informed consent was obtained from all participants prior to any study procedures being initiated.

Participants

Eligible participants were 40–65 years old, had a body mass index (BMI) between 18.5 and 34.9 kg/m^2, self-reported memory problems as assessed by questions 1, 2, and 18 of the Everyday Memory Questionnaire (EMQ; a score sum of ≥ 6 was deemed eligible as it indicated memory problems were experienced once or twice a week or they had a deficit in one question area), and did not have dementia or other significant cognitive impairments as assessed by the Mini Mental State Exam-2 (MMSE-2) Standard Version (score ≥ 24). Exclusion criteria were women who were pregnant, breastfeeding, or planning to become pregnant during the trial, allergy to the study products, self-reported confirmation of neurophysiological condition and/or cognitive impairment that could have interfered with participation, medical or chronic use of cannabinoid products, tobacco use, alcohol intake of more than two standard drinks per day or more than 10 standard drinks per week, alcohol or drug abuse within the last 12 months, any unstable chronic disease or condition, or any prescribed or over-the-counter medications or supplements that could have interfered with the study outcomes or participant safety.

Participants were instructed to maintain their lifestyle habits including physical activity and diet as well as medications and supplement routines which were monitored through use of a daily study diary.

Investigational Product and Placebo

The investigational product, Neuriva®, contained 100 mg of WCCE and 100 mg of PS. Excipients included microcrystalline cellulose, silica, water, ascorbyl palmitate, mixed tocopherols, titanium dioxide, pectin, soy lecithin, rice bran, carrageenan, and hypromellose. The placebo comprised all the investigational product's excipient ingredients.

Participants were instructed to consume one serving of Neuriva® or placebo daily for 42 days in the morning with water, with or without food, and record consumption in their study diary. If a dose was missed, participants were instructed to consume the dose as soon as possible and advised not to exceed one serving per day.

Randomization and Blinding

Participants were assigned a randomization number according to the order of the randomization list (www.randomization.com) and randomized at baseline to each study arm in a 1:1 ratio by a blinded investigator. A randomization schedule was created and provided to the investigator indicating the order of randomization.

The Neuriva® and placebo capsules, and the bottles they were sealed in, were identical in appearance. The bottles were labelled according to the requirements of the ICH-GCP guidelines and applicable local regulatory guidelines by unblinded personnel who were not involved in any study assessments. Investigators, other site personnel, statistician, and participants were blinded to the product.

Compliance

Participants were instructed to record daily study product consumption and return all unused capsules for compliance assessment. Compliance was calculated by dividing the total number of capsules consumed by the total number of capsules expected to be consumed multiplied by 100. In the event of discrepancy between the information in the study diary and the number of capsules returned, compliance was based on the product returned unless an explanation for loss of product was provided.

Outcomes

The objective of this study was to investigate the efficacy of Neuriva® on cognitive performance in healthy adults with self-perceived memory problems. To address the study objective, two co-primary outcomes were identified including the difference in the change from baseline to day 42 in (1) plasma BDNF and (2) memory, accuracy, focus and concentration, and learning as assessed by the Computerized Mental Performance Assessment System (COMPASS). Secondary outcomes included the difference in the change in (1) everyday memory as assessed by the EMQ and (2) sustained attention using the Go/No-Go assessment. Safety outcomes included incidence of adverse events (AEs), vital signs, clinical chemistry, and hematology.

Laboratory Analysis

Blood samples were collected by a qualified phlebotomist at baseline and day 42 to assess the change in plasma BDNF and safety outcomes. Plasma BDNF was analyzed using the Milliplex MAP Human Myokine Magnetic Bead Panel (HMYOMAG-56K, Millipore) by Mount Sinai Services Laboratory (Toronto, ON, Canada). Safety outcomes of clinical chemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, electrolytes (sodium, potassium, chloride), and estimated glomerular filtration rate) and hematology (white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit, platelet count, and red blood cell indices, namely mean platelet volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width) were analyzed by Dynacare (London, ON, Canada) using standardized procedures.

COMPASS

COMPASS (Northumbria University, Newcastle-upon-Tyne, UK) was used to assess cognition including memory, accuracy, focus and concentration, and learning. This tool was selected for cognitive assessment as it has been shown to be sensitive to nutritional interventions [33, 34]. COMPASS is a pre-programmed cognitive testing system that delivers randomized stimuli for every assessment performed by each participant. COMPASS tasks used in the current study included choice reaction time, digit vigilance, simple reaction time, numeric working memory, computerized Corsi blocks, picture recognition, and word recognition. A combination of COMPASS tasks and corresponding outcomes assessed the different cognitive

Table 1 COMPASS tasks, descriptions, and outcomes with corresponding cognitive domains

COMPASS task	Description	Outcomes	Cognitive domains assessed
Choice reaction time	Participants were required to indicate whether a left- or right-pointing arrow appeared on the screen as quickly as possible after it appeared	Overall accuracy (%) Correct reaction time (ms)	Accuracy (accuracy outcomes only) Focus and concentration
Digit vigilance	On the right side of the screen a number appeared while on the left side of the screen a series of numbers were displayed and when the left side number matched the right side, participants were required to respond	Overall accuracy (%) False alarms (count) Correct reaction time (ms)	Accuracy (accuracy outcomes only) Focus and concentration
Simple reaction time	As soon as an arrow pointing up appeared on the screen, participants were required to respond as quickly as possible	Overall reaction time (ms)	Focus and concentration
Numeric working memory	Numbers were displayed on the screen one at a time and participants were required to memorize the numbers. Following this, numbers appeared one at a time on the screen and participants were required to indicate whether or not each number appeared in the previous set	Overall accuracy (%) "No" accuracy (%) "Yes" accuracy (%) Correct reaction time (ms) "No" reaction time (ms) "Yes" reaction time (ms)	Memory Accuracy (accuracy outcomes only) Focus and concentration
Computerized Corsi blocks	Nine blue squares were displayed on the screen. Some squares turned red then back to blue. Participants were required to memorize the sequence of red squares. This task was repeated five times at each level with increasing levels of difficulty until the participant could not recall the sequence	Span score	Memory Accuracy Focus and concentration
Picture recognition	A series of pictures were displayed on the screen. Participants were required to memorize the pictures. Following this, those pictures plus decoys were displayed on the screen one at a time and the participant was required to indicate whether each picture was displayed previously	Overall accuracy (%) "No" accuracy (%) "Yes" accuracy (%) Overall reaction time (ms) Correct reaction time (ms) "No" reaction time (ms) "Yes" reaction time (ms)	Memory Accuracy (accuracy outcomes only) Learning

Table 1 continued

COMPASS task	Description	Outcomes	Cognitive domains assessed
Word recognition	A series of words were displayed on the screen. Participants were required to memorize the words. Following this, those words plus decoys were displayed on the screen one at a time and the participant was required to indicate whether each word was displayed previously	Overall accuracy (%) "No" accuracy (%) "Yes" accuracy (%) Overall reaction time (ms) Correct reaction time (ms) "No" reaction time (ms) "Yes" reaction time (ms)	Memory Accuracy (accuracy outcomes only) Learning

domains (Table 1). The individual COMPASS tasks in relation to the cognitive domains assessed are mapped in Fig. 1 [35–37]. Participants received instructions from a clinic coordinator on how to perform the cognitive tasks at baseline and day 42.

Go/No-Go Assessment

The Go/No-Go task, part of the Test of Attentional Performance, is a computerized test that assesses sustained attention and inhibitory control, an executive cognitive process, that allows the participant to stop motor activity even after quick initiation [38]. Participants had to react using simple keypresses to discriminable non-verbal stimuli. The response accuracy of each No-Go trial was used as a measure for inhibitory control [39]. Both forms, "1 of 2" and "2 of 5" were used and involved participants responding as quick as possible to one correct stimuli among two and two correct stimuli among five, respectively, that appeared on a screen in varying sequence. These forms were completed by participants at baseline and day 42.

EMQ

The EMQ is a subjective measure of memory failure in everyday life [40]. Questions are grouped into five categories including speech, reading and writing, faces and places, action, and learning new things. Participants completed this questionnaire at baseline and day 42.

Adverse Events

Participants were instructed to record any AEs in their study diary which were reviewed at each study visit. AEs were classified on the basis of the description, duration, intensity, frequency, and outcome and were assessed for causality and intensity by the qualified investigator (QI). The Medical Dictionary for Regulatory Activities terminology version 23.0 was used for coding.

Statistical Analysis

A sample size calculation was completed for each co-primary outcome. The larger of the two sample sizes computed was used to ensure the study was sufficiently powered for each co-primary outcome. On the basis of previous studies [25, 29], a total of 138 participants ($n = 69$ per group) were required to enable detection of a difference in mean change in memory score of 5.64 and mean difference of 76% in BDNF between Neuriva® and placebo groups with a 5% significance level, 80% power, and accounting for a 20% attrition rate.

Baseline demographic summary statistics were computed and presented as mean ± standard deviation (SD) for quantitative variables

and frequency with percentage for qualitative variables. Baseline variables were compared between groups using the *t* test and the test of independence. All data were evaluated for normality using the Shapiro–Wilk's test. The change in plasma BDNF, EMQ scores, and Go/No-Go scores, from baseline at day 42, were compared between groups using Wilcoxon's rank sum test. Change in COMPASS scores were compared between groups using a two-sample *t* test. Changes from baseline at day 42 were evaluated using a paired *t* test for all measures except plasma BDNF which was evaluated using Wilcoxon's signed-rank test.

The intention-to-treat (ITT) population included all participants who received either study product, and had post-randomization efficacy data available. The per protocol (PP) population included all participants who consumed at least 80% of either study product, did not have any major protocol violations, and completed all study visits and procedures associated with both co-primary outcomes. Results presented are for the PP population unless otherwise stated. All statistical analyses were completed using R Statistical Software Package Version 3.5.2 or newer for Microsoft Windows [41] with $p < 0.05$ considered statistically significant.

RESULTS

Study Population

A total of 205 individuals were screened and 138 were enrolled in the study (Fig. 2). There were 138 participants included in the ITT population and 128 in the PP population (Table 2). Five participants in the Neuriva® group were excluded from the PP population because of early termination ($n = 1$) and major protocol deviations ($n = 4$). Five participants in the placebo group were excluded from the PP population because of early termination ($n = 4$) and less than 80% compliance ($n = 1$). Participant treatment compliance rates in the Neuriva® and placebo groups for the PP population were 99.7% ± 3.35% and 100.5% ± 2.62% (mean ± SD), respectively. In the PP population, six participants in the Neuriva® group and one participant in the placebo group reported they quit smoking within the last 10 years.

Plasma BDNF

There was no significant difference in plasma BDNF between Neuriva® and placebo groups at day 42. There was a significant decrease in plasma BDNF concentration from baseline at day 42 in the placebo group (−427.7 ± 1937.8 pg/mL; $p = 0.041$). No significant changes in BDNF were observed with Neuriva® supplementation (−480.7 ± 2296.0 pg/mL; $p = 0.306$).

COMPASS

Various combinations of COMPASS tasks and corresponding outcomes assessed cognitive domains (memory, accuracy, focus and concentration, learning) (Table 1, Fig. 1).

Memory

There were 5/21 significant differences between Neuriva® and placebo groups across the numeric working memory and picture recognition tasks. Participants supplemented with Neuriva® had significantly greater improvements in overall accuracy ($p = 0.024$), "yes" accuracy ($p = 0.01$), reaction time for correct responses ($p = 0.031$), and "yes" reaction time ($p = 0.016$) when tasked with memorizing numbers from a previous list compared to those on placebo (Fig. 3; Supplementary Material Table S2). The Neuriva® group also had a significantly greater improvement ($p = 0.035$) in overall accuracy in identifying whether they had seen a picture in the previous display from baseline at day 42 (Fig. 4; Supplementary Material Table S2).

The Neuriva® and placebo groups had 17/21 ($p \leq 0.033$) and 11/21 ($p \leq 0.009$), respectively, changes in COMPASS scores from baseline at day 42 (Table 3). There were 11 outcomes wherein both groups had significant improvements from baseline at day 42, with those supplemented with Neuriva® having reported

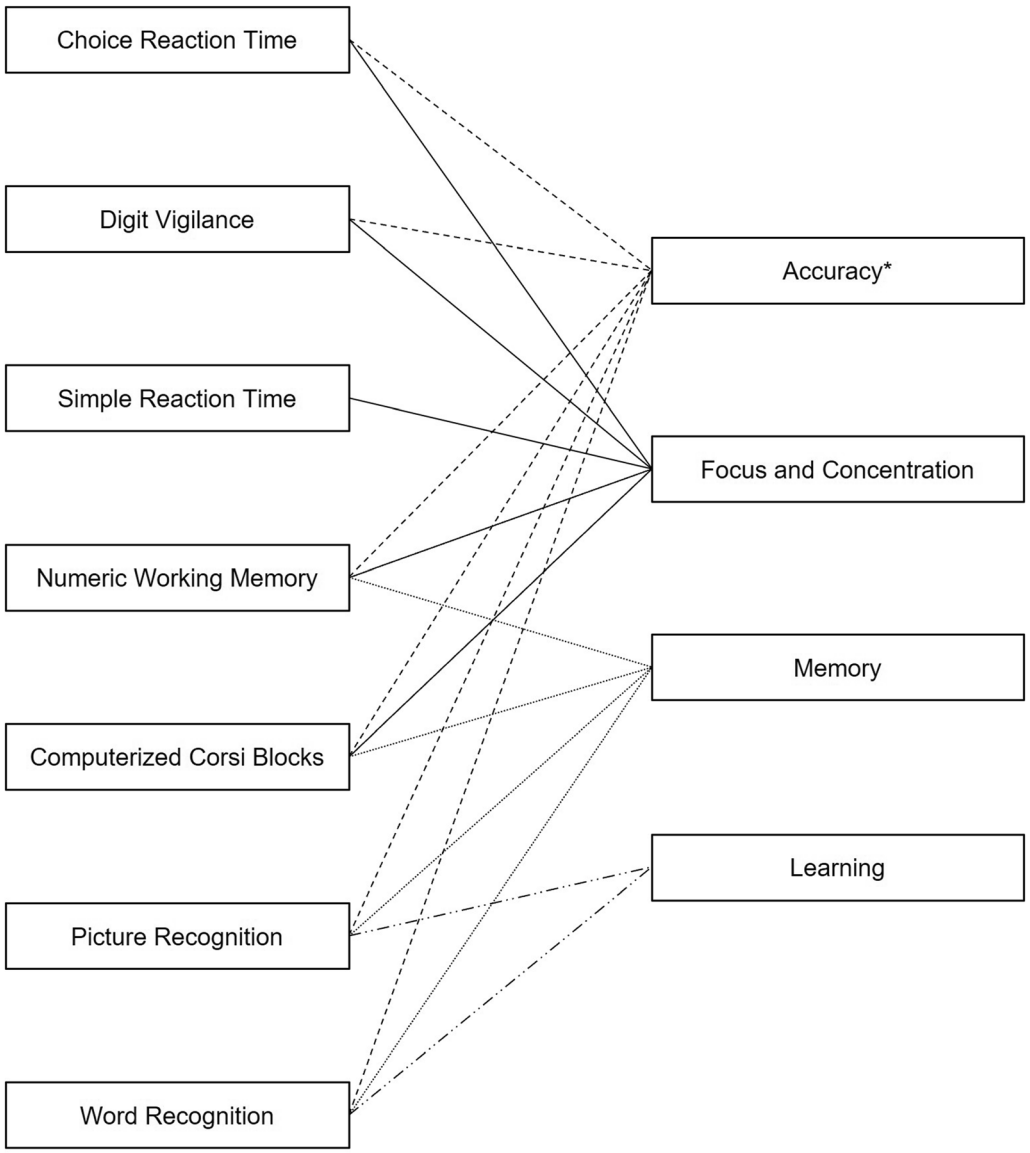

Fig. 1 Mapping of COMPASS tasks to cognitive domains

greater score improvements than placebo for six of these outcomes.

Focus and Concentration

The numeric working memory task also assessed focus and concentration wherein 4/13 changes in task outcome scores were significantly different between Neuriva® and placebo. Participants supplemented with Neuriva® had significantly ($p \leq 0.031$) greater score improvements in all four cases compared to placebo (Fig. 3; Supplementary Material Table S2).

Neuriva® and placebo groups had 9/13 ($p \leq 0.033$) and 7/13 ($p \leq 0.049$) score

improvements, respectively, from baseline at day 42 (Table 3). There were seven outcomes wherein both groups had score improvements from baseline at day 42 with Neuriva® having greater score improvements than placebo in five of these outcomes.

Accuracy

There were 3/13 significant differences between Neuriva® and placebo across the numeric working memory (accuracy outcomes only) and picture recognition tasks. The Neuriva® group had significantly greater improvements in score change for overall accuracy and "yes" accuracy ($p \leq 0.024$) compared to placebo in numeric working memory (Fig. 3; Supplementary Material Table S2). The Neuriva® group also had a significantly greater improvement in score change from baseline at day 42 for overall accuracy ($p = 0.035$) for the picture recognition task (Fig. 4; Supplementary Material Table S2).

There were 8/13 ($p \leq 0.033$) and 3/13 ($p \leq 0.049$) improvements in accuracy tasks for the Neuriva® and placebo groups, respectively, from baseline at day 42 (Table 3). Of the three task outcomes wherein both groups observed significant improvements at day 42 compared to baseline, the Neuriva® group had greater score improvements than placebo in one outcome.

Learning

There was one (1/14) significant difference between Neuriva® and placebo in learning-related outcomes which occurred in the picture recognition task. The Neuriva® group had a significantly greater improvement in score for overall accuracy ($p = 0.035$) compared to placebo at day 42 (Fig. 4; Supplementary Material Table S2).

There were 11/14 ($p \leq 0.022$) and 7/14 ($p \leq 0.009$) changes for the Neuriva® and placebo groups, respectively, from baseline at day 42 (Table 3). There were seven outcomes wherein both groups had significant improvements from baseline at day 42 with three of those improvements greater for the Neuriva® group than placebo.

Go/No-Go Test

There were no significant differences between the Neuriva® and placebo groups in either Go/No-Go test forms (Supplementary Material Table S3). In test form "1 of 2", participants supplemented with Neuriva® and those on placebo had one significant improvement (-1.0 ± 3.9 and -0.8 ± 3.0, respectively; $p \leq 0.002$) in number of false alarms/errors from baseline at day 42 with a greater score reduction in the Neuriva® group. The Neuriva® and placebo groups had 6/7 ($p \leq 0.022$) and 4/7 ($p \leq 0.015$) significant changes, respectively, from baseline at day 42 for test form "2 of 5" with greater score improvements observed with Neuriva® supplementation (Supplementary Material Table S3).

Everyday Memory Questionnaire

There were no significant differences between Neuriva® and placebo groups in the EMQ (data not shown); however, there were 26/35 significant improvements for both groups from baseline at day 42. The Neuriva® group reported greater score improvements than placebo in 4/23 questions wherein both groups showed improvements from baseline at day 42. The Neuriva® and placebo groups had 5/6 ($p \leq 0.032$) and 3/6 ($p \leq 0.014$) significant improvements, respectively, at day 42 compared to baseline in learning new things. There were significant ($p \leq 0.041$) improvements in all question scores of the speech and reading and writing categories for both groups from baseline at day 42, and for 1/6 questions for faces and places ($p < 0.001$). For questions related to actions, there were 3/6 and 5/6 significant ($p \leq 0.042$) score improvements at day 42 compared to baseline for Neuriva® and placebo groups, respectively.

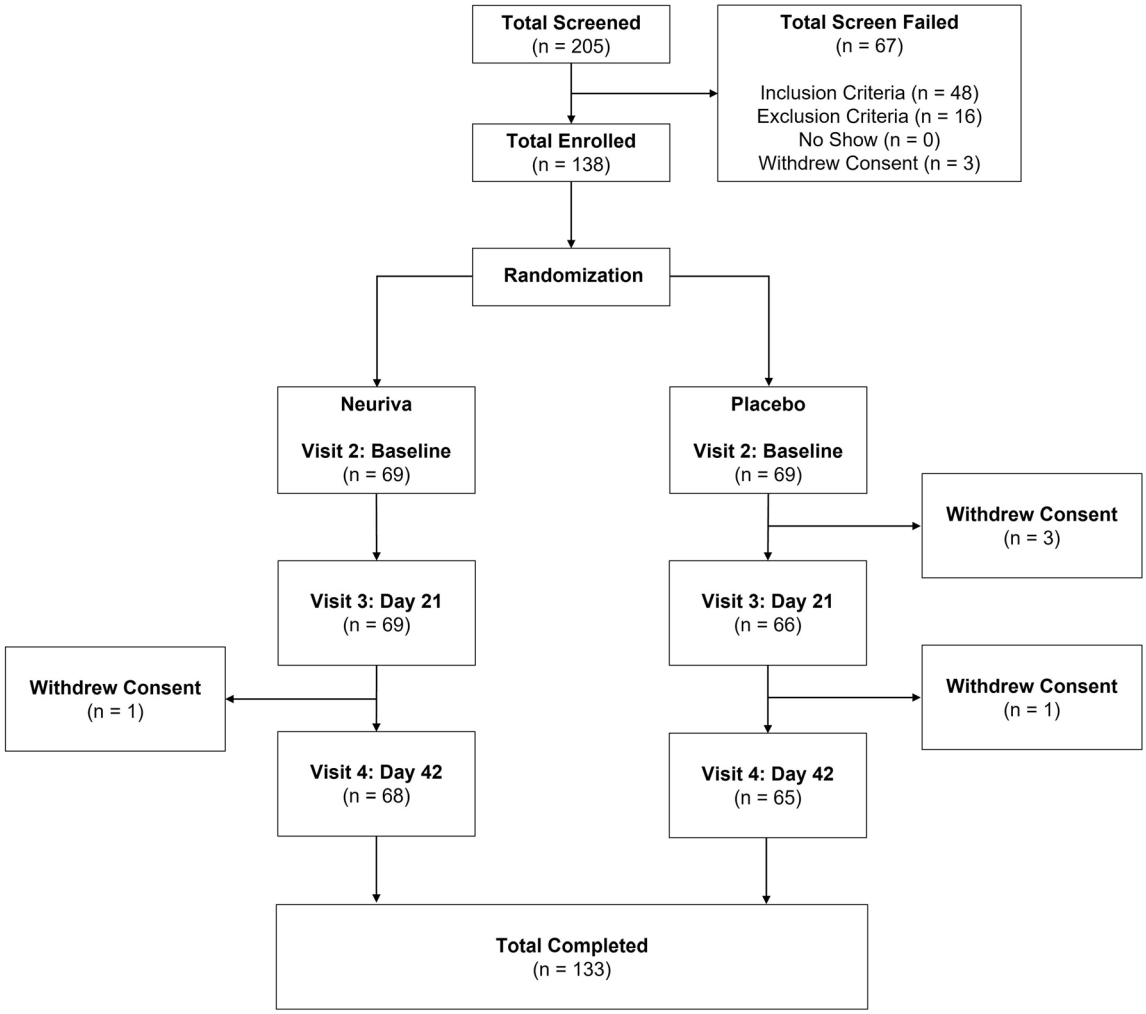

Fig. 2 Disposition of study participants

Adverse Events and Safety Measures

There were a total of 72 adverse events reported by 48 unique participants, 23 participants in the Neuriva® group and 25 in the placebo group. There was one report each of dry mouth and anxiety categorized as possibly related to Neuriva® and placebo, respectively. All adverse events were resolved by the end of study.

Any clinically relevant potassium values were repeated and no longer clinically relevant except for one participant who was lost to follow-up. All other participants' clinical chemistry and hematology as well as vital signs for all participants were deemed healthy as assessed by the Qualified Investigator.

DISCUSSION

Forty-two days of Neuriva® supplementation was shown to improve memory outcomes in a population with self-reported memory problems. Memory was objectively and subjectively assessed using COMPASS and the EMQ, respectively. Neuriva® supplementation elicited greater score improvements compared to placebo in five objective assessments of memory using COMPASS. Both groups showed significant improvements from baseline in the subjective assessment of memory using the EMQ. The improvements in memory-related COMPASS outcomes in the current study are consistent with a previous study that showed

Table 2 Baseline demographic characteristics for the PP population (n = 128)

Characteristic	Neuriva® (n = 64)	Placebo (n = 64)	P value
Age, mean ± SD	53.92 ± 6.08	54.66 ± 6.95	0.53[a]
Gender, n (%)			
Female	47 (73.4)	39 (61.0)	0.21[b]
Male	17 (26.6)	25 (39.0)	
Alcohol use, n (%)			
None	9 (14.0)	19 (30.0)	
Daily	2 (3.0)	0 (0.0)	0.19[b]
Weekly	32 (50.0)	28 (43.0)	
Occasionally	21 (33.0)	17 (27.0)	
Tobacco use, n (%)			
Ex-smoker	14 (22.0)	5 (8.0)	0.020[b]
No	50 (78.0)	59 (92.0)	
Recreational cannabis use, n (%)			
No	60 (94.0)	63 (98.0)	0.15[b]
Yes	4 (6.0)	1 (2.0)	

n number, SD standard deviation
[a]P value generated by the t test
[b]P values generated using the test of independence on untransformed data. $p < 0.05$ considered statistically significant

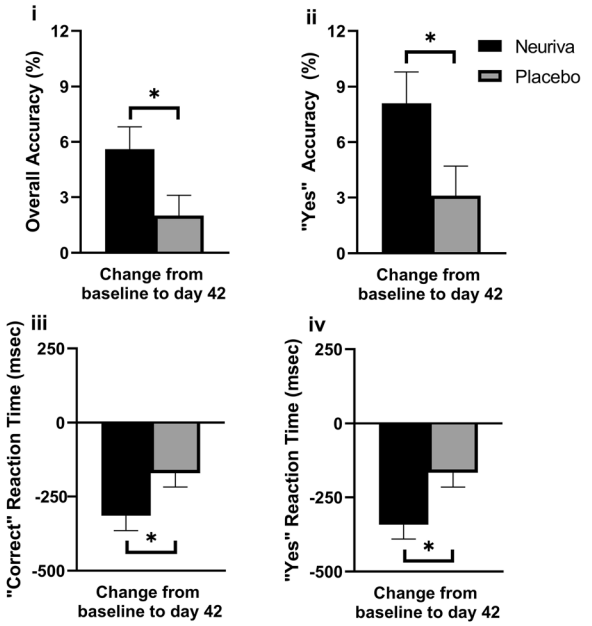

Fig. 3 Numeric working memory change in scores for (i) overall accuracy (%; p = 0.024), (ii) "yes" accuracy (%; p = 0.01), (iii) reaction time for correct responses (ms; p = 0.031), and (iv) "yes" reaction time (ms; p = 0.016) from baseline at day 42 for Neuriva® and placebo in the PP population (n = 128). Memory, accuracy, focus and concentration were assessed by (i) and (ii), and memory and focus and concentration were assessed by (iii) and (iv). All values presented are mean ± SEM. Between group differences were compared using a two-sample t test with $p < 0.05$ considered statistically significant. Asterisk indicates a statistically significant difference between Neuriva® and placebo

significant improvements in memory outcomes after 12 weeks of supplementation with 300 mg/day PS among elderly participants [29]. In contrast, Kato-Kataoka et al. [31] found 100 mg/day of PS, the same amount used in the current study, significantly improved memory after 6 months whereas the current study found improvements after 6 weeks [31]. It is possible that the combination of PS and WCCE in the current study contributed to the favorable effects on memory seen earlier.

Improving memory is important given declines in working memory have been shown to begin as early as 30–40 years of age [42]. In addition, working memory is a subdomain of executive function, as defined in the Diagnostic and Statistical Manual of Mental Disorders-5 [43], which has an important role in everyday life including future planning, problem-solving, and focus attention [42]. It is possible to suggest that the improvements in memory outcomes observed with Neuriva® supplementation may help attenuate the age-related decline in memory and support cognition. This is particularly important for individuals with self-reported memory problems who may be at risk of cognitive impairment [44].

The current study showed no trade-off between accuracy and speed, important factors in everyday decision-making, for memory or

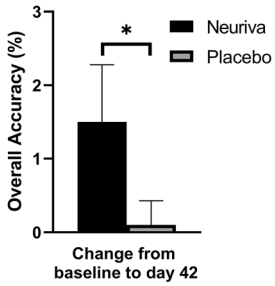

Fig. 4 Picture recognition change in scores for overall accuracy (%; $p = 0.035$) from baseline at day 42 for Neuriva® and placebo in the PP population ($n = 128$). Memory, accuracy, and learning were assessed by overall accuracy by the picture recognition task. All values presented are mean ± SEM. Between group changes were compared using a two-sample t test with $p < 0.05$ considered statistically significant. Asterisk indicates a statistically significant difference between Neuriva® and placebo

focus and concentration with Neuriva® supplementation. This was supported by a greater number of improvements from baseline in the Go/No-Go tests for Neuriva® than placebo. The speed–accuracy trade-off involves either speed or accuracy being sacrificed when making decisions, depending on which factor is more favorable in a given situation [45]. Typically, decisions made quicker are less accurate and decisions made slower are more accurate [45]. However, Neuriva® supplementation improved both accuracy and speed when participants were challenged with a numeric memory task. Given decision-making is important for executive cognitive functioning and declines with age [46] interventions to help support and maintain factors involved in decision-making are important during the aging process.

Despite the improvements in cognitive domains, there was no significant difference in plasma BDNF concentration, a growth factor part of the neurotrophin family, between Neuriva® and placebo at day 42. This is consistent with a previous nutraceutical study [47] suggesting other mechanisms of action exerted by WCCE and PS may be contributing to their cognitive benefits. While previous studies have shown supplementation with 100 mg WCCE significantly increased BDNF levels compared to placebo [25] and baseline [23], inter-individual variation in plasma BDNF concentration and response to supplementation could be factors contributing to the absence of a significant difference in the current study. This variation is comparable to previous studies reported in the literature [48, 49] which may be attributed to potential confounding factors such as age, cognitive state, lifestyle including exercise, and disease state [50–54]. Genetic polymorphisms of the *BDNF* gene have been identified as a contributor to high variability of BDNF concentrations [55, 56] and future studies should consider this factor when examining changes in BDNF. There was, however, a significant mean decrease in BDNF concentration in the placebo group at day 42 that was not observed in the Neuriva® group. This suggests a possible protective effect of Neuriva® on BDNF which may be due to the presence of PS in the current study's product, but more research is warranted. Studies of longer duration will further the understanding of Neuriva® supplementation on BDNF concentrations and mechanisms of action.

The current study showed 42 days of Neuriva® supplementation was safe in healthy adults. Only one adverse event, dry mouth, was reported in the Neuriva® group which was deemed possibly related to the study product but was resolved by the end of the study. Supplementation tolerability was also favorable given the low rate of attrition (1.5%) and high rate of compliance in the Neuriva group.

It is relevant to consider the potential for the placebo effect in cognition studies as it has been previously reported in the literature [57, 58]. The current study showed the placebo effect accounted for 6–100% of the response for memory-related COMPASS tasks. This is comparable to what has been reported previously in the literature for memory-related outcomes [31, 35]. Moreover, a previous study showed positive effects on memory and attention performance after 2-week consumption of a placebo pill compared to no pill among healthy older adults [57]. Another study showed university students who thought they were consuming a cognitive-enhancing drug had improved cognitive performance compared to those who thought they were consuming a

Table 3 Change in COMPASS scores from baseline at day 42 for memory, accuracy, focus and concentration, and learning for Neuriva® and placebo in the PP population (n = 128)

Task	Neuriva® (n = 64) Mean ± SD Within-group P value	Placebo (n = 64) Mean ± SD Within-group P value
Choice reaction time (focus and concentration)		
Reaction time: correct (ms)	− 388.8 ± 591.1	− 382.5 ± 584.0
	< 0.001	< 0.001
Digit vigilance (accuracy, focus and concentration)		
Accuracy: overall (%)	7.0 ± 13.9	4.1 ± 13.3
	< 0.001	0.049
False alarm (count)	− 1.1 ± 2.9	− 1.2 ± 2.1
	0.003	< 0.001
Numeric working memory (memory, accuracy*, focus and concentration)		
Accuracy: overall (%)	5.6 ± 9.7	2.0 ± 8.8
	< 0.001	0.219
Accuracy: yes (%)	8.1 ± 13.5	3.1 ± 12.8
	< 0.001	0.096
Reaction time: correct (ms)	− 314.8 ± 402.7	− 170.7 ± 376.7
	< 0.001	0.001
Reaction time: no (ms)	− 280.1 ± 497.3	− 220.3 ± 448.5
	< 0.001	< 0.001
Reaction time: yes (ms)	− 341.9 ± 393.5	− 166.8 ± 388.0
	< 0.001	0.006
Computerized Corsi blocks (memory, accuracy, focus and concentration)		
Span score	0.4 ± 1.4	0.5 ± 1.3
	0.033	0.003
Picture recognition (memory, accuracy*, learning)		
Accuracy: overall (%)	1.5 ± 6.2	0.1 ± 2.6
	0.012	0.994
Accuracy: yes (%)	1.9 ± 8.2	0.2 ± 4.4
	0.022	0.952

Table 3 continued

Task	Neuriva® (*n* = 64) Mean ± SD Within-group *P* value	Placebo (*n* = 64) Mean ± SD Within-group *P* value
Reaction time: overall (ms)	− 217.6 ± 390.3	− 140.6 ± 240.2
	< 0.001	0.001
Reaction time: correct (ms)	− 206.0 ± 370.5	− 144.3 ± 231.1
	< 0.001	< 0.001
Reaction time: no (ms)	− 167.8 ± 332.1	− 155.4 ± 253.8
	< 0.001	< 0.001
Reaction time: yes (ms)	− 267.4 ± 495.1	− 125.8 ± 264.9
	< 0.001	0.095
Word recognition (memory, accuracy*, learning)		
Accuracy: yes (%)	5.4 ± 15.3	1.5 ± 16.1
	0.012	0.716
Reaction time: overall (ms)	− 179.6 ± 303.8	− 192.2 ± 453.6
	< 0.001	< 0.001
Reaction time: correct (ms)	− 156.3 ± 294.6	− 187.1 ± 427.1
	< 0.001	< 0.001
Reaction time: no (ms)	− 130.9 ± 372.3	− 144.0 ± 474.1
	0.020	0.009
Reaction time: yes (ms)	− 228.3 ± 419.7	− 240.4 ± 519.9
	< 0.001	< 0.001

*Accuracy was assessed by accuracy outcomes only

ms milliseconds, *n* number, *SD* standard deviation

Within-group changes were evaluated using a paired *t* test with $p < 0.05$ considered statistically significant

Data not shown for non-significant within group changes

placebo [58]. Therefore, it is important to consider the presence of a placebo effect when interpreting results from the current study.

Further, physical activity has a positive impact on cognition [59, 60]; however, though participants were instructed to maintain their usual physical activity level during the study, detailed information on participant activity was not captured. The interaction between physical activity, particularly cardiovascular exercise [60], and Neuriva® could be explored in future studies. In addition, education level is an important factor to consider when evaluating cognition which was not controlled for and is a limitation of the current study that should be considered in future randomized controlled trials.

CONCLUSIONS

Results of the current study showed 42 days of Neuriva® supplementation significantly improved measures of memory, accuracy, focus and concentration, and learning compared to

placebo in healthy adults with self-reported memory problems. These findings were supported by improvements in these cognitive domains from baseline with Neuriva® supplementation. Neuriva® supplementation was found to be safe and well tolerated in the population studied. Future larger randomized controlled trials with longer durations are needed to further explore the efficacy of Neuriva® on cognition, and confirm the current study's findings. Moreover, research is warranted in more vulnerable populations such as those with mild cognitive impairment and advanced age.

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Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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