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A 30-Day Open-Label Clinical Study Shows Neumentix™ Phenolic Complex K110-42 Enhances Acute and Chronic Cognitive Function.

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INTRODUCTION

Across the globe, the aging population is growing at an increasing rate. As of 2013, the number of people over the age of 65 reached more than 43 million in the US, 88 million in the EU and 127 million in China (1). As life expectancy continues to rise, individuals are choosing to stay in the work force until later in life (2). These older, active populations have expressed great concern for brain health and cognitive functioning. A recent survey found that adults are more than twice as likely to fear losing their mental capacity (62%) as their physical ability (29%). (3) At the same time, nearly 9 out of 10 people believe it is possible to improve their own mental fitness (4). As a result, the demand for natural, safe and efficacious ingredients to enhance brain health is expected to increase dramatically in the coming years.

Two of the hallmarks of the aging process are oxidative stress and inflammation in the brain. Phytochemical molecules that have the ability to cross the blood-brain barrier may have a positive role in decreasing the oxidative damage and reducing inflammation in the brain. In addition, molecules that can increase the amount of acetylcholine in the brain have the potential to directly affect memory. Certain polyphenolic compounds, such as rosmarinic acid (RA), have been found to be effective at crossing the blood-brain barrier, reducing damage due to oxidative stress, reducing inflammation, and inhibiting cholinesterase, an enzyme that breaks down acetylcholine in the brain (5-7).

Several previous investigations have suggested that extracts of plants within the Lamiaceae family, which are considered to be rich in polyphenolic compounds (8), may enhance cognitive function in healthy volunteers (9-12) and provide antioxidant and anti-inflammatory properties. However, few studies have been published which have investigated the safety and tolerance of consuming extracts within the Lamiaceae family.

Kemin has developed a patent-pending spearmint extract, Neumentix™ Phenolic Complex K110-42, from non-GMO, USA-grown spearmint lines capable of high expression of rosmarinic acid and including 65 additional phenolic compounds

Previous studies with Neumentix found that the extract at doses of 320 and 640 mg/kg body weight was effective at improving memory and learning using the well-established SAMP8 animal model of accelerated aging (13). Preclinical safety studies conducted with Neumentix demonstrated that the proprietary spearmint extract is non-mutagenic at concentrations up to 5000 µg/plate in the Ames bacterial reverse mutation assay and is non-clastogenic at dose levels up to 5000 µg/ml in the chromosomal aberration assay (14). The No Observed Adverse Effect Level (NOAEL) for Neumentix containing 15.4% RA from the 90 day toxicity study in Sprague-Dawley rats was 1948 mg extract/kg bw/day and 300 mg RA/kg bw/day. The above NOAEL for Neumentix containing 15.4% RA supports the safety of up to 19.48 mg Neumentix/kg bw/day and 3.0 mg RA/kg bw/day in humans (14). These studies provide evidence that Neumentix may be both a safe and efficacious ingredient for brain health improvements. Hence, to investigate the tolerance and cognitive health benefits of Neumentix, an open label human clinical trial was conducted in men and women with self-reported memory impairment.

STUDY DESIGN

The study was an open-label human clinical study conducted by Biofortis Clinical Research, Addison IL. Eleven healthy male and female adults ranging in age from 50 to 70 years were enrolled in the 30 day supplementation study. Eligible participants had self-reported memory loss associated with normal aging as defined by scoring ≥ 25 on the Memory Assessment Clinic Scale (MAC-Q) (15) and lacked any signs of dementia as determined by scoring ≥24 on the Mini-Mental State Exam

(MMSE) (16). The study design overview is provided in Figure 1.

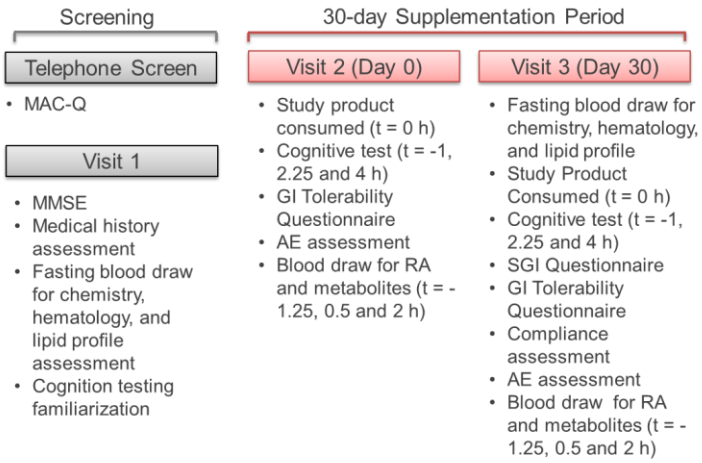

Figure 1. Study Design Overview. Primary and secondary outcomes were assessed acutely at day 0 and again acutely and chronically following 30 days of supplementation.

Participants consumed 900 mg of Neumentix (two capsules, 450 mg/capsule) daily with breakfast for the 30 day study duration. The spearmint extract contained 15.2% RA in addition to more than 65 other phenolic compounds (Mena, Del Rio et al., manuscript in preparation).

Fasting (10-14 hour) blood samples were collected at screening (visit 1) and day 30 (visit 3) for plasma chemistry, whole blood hematology and plasma lipid profiles. In addition, blood was drawn (-1.25 hours pre-dose, and 0.5 and 2 hours post-dose) on day 0 for acute assessment of plasma RA metabolites and on day 30 for chronic assessment. Vital signs and adverse events were assessed at day 0 and adverse events were assessed again at day 30. Additionally, a gastrointestinal (GI) tolerability questionnaire that asked subjects to recall their GI symptoms over the last 30 days was administered at day 0 and 30.

Cognitive function was assessed via the Subject Global Impression (SGI) Scale of Cognition (17) and a battery of online computerized cognition tasks (http://www.cambridgebrainsciences.com (Cambridge Brain Sciences, London, Ontario, Canada) (18). The Cambridge Brain Sciences cognitive battery used in the study consisted of eight tasks with two tasks designed to assess each of the following cognitive domains: memory, reasoning, attention, and planning (Figure 2). A brief description for each task is provided in Table 1.

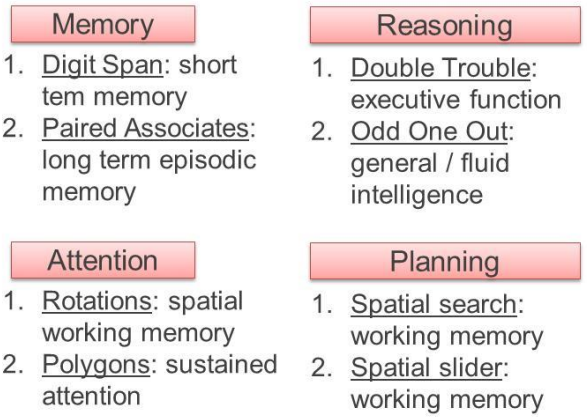

Figure 2. Cognitive Domains Overview. Eight tasks of the Cambridge Brain Sciences cognitive battery grouped by cognitive domain assessed.

Participants completed the SGI at the beginning of day 30. The computerized test battery was administered in a controlled environment on day 0 and 30 at t = -1 hour (pre-dose) and t = 2.25 and 4 hours (post-dose) where t = 0 hour corresponded to consumption of Neumentix with a standardized breakfast. Each battery took approximately 30-45 minutes to complete. The alpha level for significance was $p<0.100$ with all data presented from the intent to treat sample group (n = 11) as mean ± SEM.

Table 1. Overview of the Cognitive Function Test Battery. Cambridge Brain Sciences, London Ontario, Canada.

Designation	Task	Brief Description
Memory 1	Digit Span	A sequence of numbers is presented for subject to remember and recall. Test ends when three errors are made.
Memory 2	Paired Associates	Subject recalls an object and the location it appeared in. Test ends when three errors are made.
Reasoning 1	Double Trouble	Subject determines the word at the bottom of the screen that describes the color of ink of the word at the top of the screen. Solves as many problems as possible in 1.5 minutes.
Reasoning 2	Odd One Out	Subject determines which pattern does not match the other patterns on the screen. Solves as many problems as possible in 3 minutes.
Attention 1	Rotations	Subject decides if rotating one shape would result in it matching the other shape on the screen. Solves as many problems as possible in 1.5 minutes.
Attention 2	Polygons	Subject decides if a single shape is identical to one or two overlapping shapes. Solves as many problems as possible in 1.5 minutes.
Planning 1	Spatial Search	Subject must find hidden tokens, remember where the tokens are hidden, and identify tokens in each box without clicking on previously identified tokens. Test ends when three errors are made.
Planning 2	Spatial Slider	Subject must rearrange numbered tiles in order by dragging them in and out of open spaces in as few moves as possible. Solves as many problems as possible in 3 minutes.

RESULTS

Subjects

In total, 20 participants were screened for this trial, 11 eligible subjects were identified and 10 participants completed the study with one subject withdrawing consent after the baseline visit due to an inability to understand the cognitive function tests. The participants were 8 females and 3 males with a mean age of 58.7 ± 1.6 years and an average BMI of 27.4 ± 1.0 kg/m^2. Mean scores for the MAC-Q and MMSE were 29.7 ± 1.0 and 28.9 ± 0.4, respectively. Average overall compliance with study product consumption was 103.2 ± 1.6%.

Acute Cognitive Improvements

Acute assessment on the first day of supplementation revealed significant improvements in two measures of attention and one measure of planning/executive function. Attention 1 (Rotations) scores increased by 30% at 2.25 hours post dose (19 ± 8.1 points, p=0.042) and by 46% at 4 hours post-dose (29 ± 6.6 points, p=0.001) relative to the pre-dose assessment at -1 hours. Similarly, Attention 2 (Polygons) scores showed a 93% improvement at 2.25 hours post dose (17 ± 6.4 points, p=0.025) and a 121% improvement compared to pre-dose 4 hours after taking Neumentix (22 ± 5.3 points, p=0.002). In addition, there was a significant increase of 39% in the Planning 2 (Spatial Slider) score from pre-dose to 4 hours post-dose (12 ± 3.2 points p=0.004) (Figure 3).

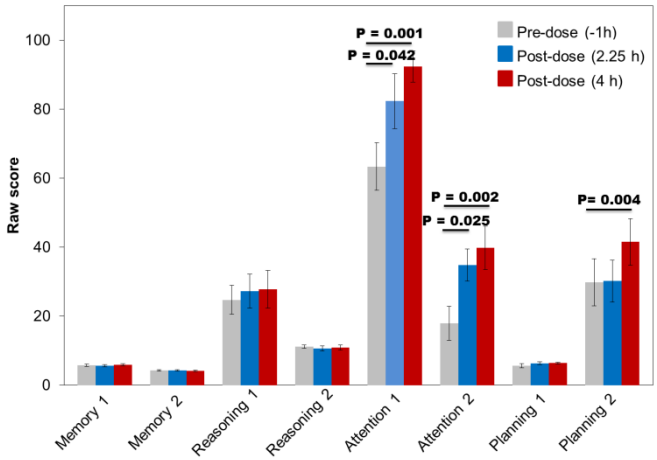

Figure 3. Acute cognitive function scores at day 0 pre-dose (-1 hour) and post-dose (2.25 and 4 hours). Bars represent mean scores ± SEM (N=11).

Chronic Cognitive Improvements

After 30 days of Neumentix supplementation participants reported a significant improvement in their cognition as measured by the average composite score from the SGI questionnaire (p = 0.063) (Table 2). Chronic changes in specific cognitive domains were assessed by comparing -1 hour pre-dose scores at day 0 versus day 30. As can be seen in Figure 4, a 35% improvement was observed in scores from Reasoning 1 (Double Trouble) (6.4 ± 2.3 points; p=0.023), while Planning 2 (Spatial Slider) showed a 48% improvement (11.3 ± 5.91 points, p=0.088) and

subjects demonstrated a gain of 125% in Attention 2 (Polygons) scores from day 0 to day 30 (22.9 ± 5.33 points, p=0.002).

Table 2. SGI Questionnaire scores at the end of treatment (day 30) in response to Neumentix supplementation[1]

Parameter	Mean (SEM)	P-value[2]
Memory	3.7 (0.2)	0.500
Attention	3.5 (0.2)	0.125
Speed of thinking	3.4 (0.3)	0.125
Average score	3.5 (0.2)	**0.063**

Abbreviations: SEM, standard error of the mean.

[1]The Subject Global Impression (SGI) Scale of Cognition Questionnaire was administered at the end of the 30 d treatment and subjects were asked to compare their current condition to their condition prior to inclusion in the study. Scores were coded as: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

[2]P-values were calculated from Wilcoxon sign rank test, testing the difference from 4 (no change; n = 10) at the end of treatment.

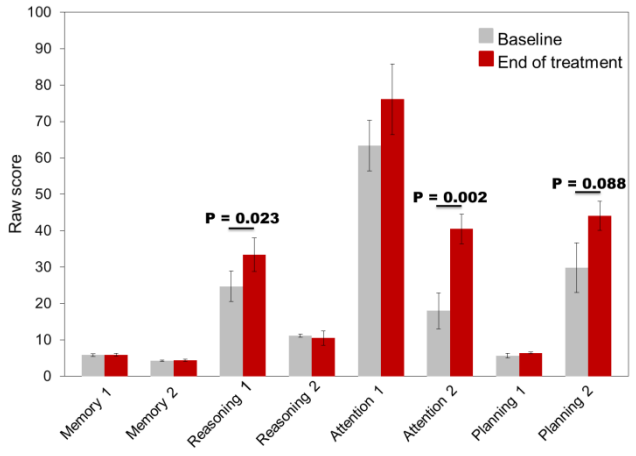

Figure 4. Chronic Cognitive Function Pre-Dose Scores at baseline and following 30 days of Neumentix supplementation. Bars represent mean scores ± SEM (N=10).

Tolerability Outcomes

Consumption of Neumentix at 900 mg/day for 30 days was well-tolerated. No significant differences were observed in GI tolerability or whole blood hematology assessments. In addition, there were no reported study product-related adverse events. A single adverse event, back pain, was reported during the treatment period and was deemed unrelated to study product consumption. Plasma chemistry and vital sign results yielded significant differences in calcium, anion gap, total protein and heart rate between baseline (day 0) and end of treatment (day 30) (Table 3 and data not shown). However, these changes were not considered clinically significant as all values were within normal ranges and biological variability.

Table 3. Vital signs and fasting lipoprotein lipids at baseline and end of treatment after 30 days of supplementation with Neumentix.

Parameter	Baseline[1] (N = 11)	EOT[2] (n = 10)	Difference (Δ)	P-value[3]
	Mean (SEM) or Median (Interquartile Limits)			
SBP (mm Hg)	121.1 (3.6)	121.7 (3.3)	-0.9 (2.4)	0.706
DBP (mm Hg)	75.3 (2.5)	78.3 (2.6)	1.3 (2.3)	0.603
Heart rate (bpm)	63.2 (2.2)	68.0 (2.7)	3.7 (1.8)	**0.077**
Body weight (kg)	77.1 (2.6)	77.8 (2.9)	0.4 (0.3)	0.212
LDL-C (mg/dL)	138.6 (11.5)	148.6 (11.4)	5.2 (5.4)	0.361
Non-HDL-C (mg/dL)	156.6 (10.8)	163.7 (11.6)	3.1 (5.5)	0.584
TC (mg/dL)	213.1 (11.5)	222.3 (12.5)	3.4 (6.0)	0.586
HDL-C (mg/dL)	56.6 (3.4)	58.6 (3.2)	0.3 (1.6)	0.858
Triglycerides (mg/dL)	88.2 (8.8)	75.7 (6.1)	-9.3 (8.3)	0.293
TC/HDL-C	3.7 (3.1, 4.3)	3.6 (3.4, 4.5)	0.1 (-0.1, 0.3)	0.432

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

[1]Baseline refers to pre-dose values on day 0.

[2]End of treatment (EOT) refers to pre-dose values on day 30.

[3]P-values were calculated from paired t-tests or Wilcoxon sign rank test, between baseline and end of treatment.

Plasma Rosmarinic Acid Levels

Acute increases in plasma RA and RA metabolite levels are shown in Figure 5. At the baseline (day 0) pre-dose (-1.25 hours) draw, RA was undetectable in plasma. By 0.5 hours after Neumentix supplementation, RA was detectable in the plasma and reached a statistically significant elevation in the plasma by 2 hours post supplementation (p=0.016). Significant increases were also observed in RA metabolites including vanillic acid sulfate, caffeic acid sulfate and ferulic acid sulfate at 0.5 and 2 hours (p<0.02 for all comparisons) and for methyl rosmarinic acid glucuronide at 0.5 hours (p=0.034) relative to pre-dose (-1.25 hours).

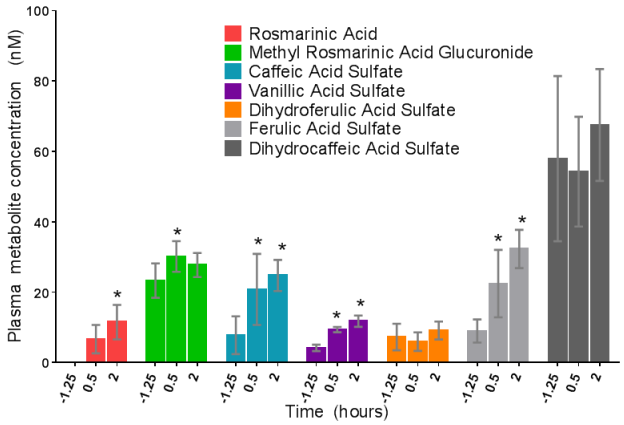

Figure 5. Acute assessment of plasma rosmarinic acid metabolites following Neumentix supplementation during the baseline test visit (day 0). Bars represent mean scores ± SEM (N = 10) *P < 0.05 vs. -1.25 h. P-values are generated from a paired t-test or sign-rank test.

DISCUSSION

In this study, Neumentix (Kemin's patent-pending non-GMO spearmint extract) was well-tolerated with no serious adverse events or negative clinically relevant findings for gastrointestinal or blood parameters. Participants showed significant improvements in subjective cognition function following 30 days of supplementation with Neumentix. Furthermore, objective computerized cognitive testing showed both acute improvements in attention and planning and significant chronic improvements in reasoning, attention, and planning. Improvements in these cognitive areas with Neumentix supplementation both acutely and chronically suggests that Neumentix may benefit working memory, since participants showed better concentration and ability to use and manipulate information, two key components of working memory.

The results of this study, in addition to previous studies conducted, provide further evidence that Neumentix is a safe ingredient with promising efficacy for improving cognitive performance. Kemin is currently sponsoring additional human clinical studies to further evaluate the cognitive effects of this proprietary spearmint extract, Neumentix.

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