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Technical Literature

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The Science Behind Neumentix®

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Introduction

Cognition is a vital yet complex dimension of human health. Cognitive performance can be impacted by our sleep, diet, physical activity and emotional state (Blazer D.G., 2015). Cognitive performance also changes across our lifespan, with some domains of cognition, such as working memory, peaking in our early 20s and showing a 5-10% decline per decade while other areas of cognition, such as our memory of facts and knowledge (semantic memory) remaining fairly constant or even improving as we age (Park & Reuter-Lorenz, 2009). An ingredient with the potential to improve specific aspects of cognition could appeal to individuals looking to boost their brain performance.

Neumentix® is a natural, plant-based ingredient designed to enhance cognitive performance in healthy adults. The ingredient is grown in the U.S. from patented lines of non-GMO spearmint purposely developed to be rich in key polyphenols (Patent No. US 9545075, US 9545076). The all-natural extract is produced from a gentle water extraction process of the patented spearmint harvested from fields that are certified sustainably grown. The manufacturing process involves an innovative drying step to protect the polyphenolic content and identity of the raw materials (Patent No. US 9839661). The finished ingredient is safe and natural with self-affirmed Generally Recognized as Safe (GRAS) status in the United States and four human clinical studies supporting the ingredients efficacy and safety.

The spearmint in Neumentix is superior because of the key polyphenols found inside. In fact, Neumentix contains more 50 powerful polyphenols (Cirlini et al., 2016). These polyphenols, including rosmarinic acid, salvianolic acids A and B and lithospermic acid are suggested to work through mechanisms that have the potential to enhance cognitive performance. For example, rosmarinic acid and salvianolic acid B have been shown to increase the growth of new neurons in animal models (Ito et al., 2008; Zhuang et al., 2012). In addition, daily supplementation with Neumentix in an animal model has been shown to reduce levels of oxidative stress in areas of the brain specifically related to learning and memory (Farr et al., 2016). Furthermore, in other animal in vivo studies, both rosmarinic acid and salvianolic acid B have been shown to increase acetylcholine levels in the brain, a neurotransmitter that is critical for learning and retaining information (Fale, Madeira, Florencio, Ascensao, &

KEY CONCLUSIONS

- ***Neumentix is a natural ingredient derived from spearmint that was designed to support cognitive performance in healthy adults.***
- ***Neumentix has been evaluated in 4 human clinical trials, 3 mechanism of action studies, 2 genotoxicity studies, and 2 animal safety studies.***
- ***Daily use of Neumentix (900 mg) has been shown to improve working memory and focus in healthy adults along with choice reaction performance. Importantly, Neumentix supports cognitive performance without disrupting sleep.***
- ***The cognitive performance benefits of Neumentix are likely associated with the greater than 50 polyphenols including rosmarinic, salvianolic, lithospermic and caftaric acids which in vitro and in vivo studies suggest can act in numerous ways to promote cognition.***
- ***Neumentix has also shown to be safe and well-tolerated for daily use, when taken as recommended.***

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Serralheiro, 2011; Lee et al., 2014). Finally, the unique combination of polyphenols found in Neumentix was shown to produce significant new neuron growth in primary hippocampal neuronal cells (Fonseca, 2016). The growth of new neurons in the brain is called neurogenesis and is critical for new learning in an area of the brain called the hippocampus.

Human Clinical Studies with Neumentix

Four human clinical trials have been completed to date with Neumentix and have been detailed in five peer-reviewed publications (Falcone et al., 2019; Falcone et al., 2018; Herrlinger et al., 2018; Nieman, 2015; Ostfeld, Ben-Moshe, Hoffman, Shalev, & Hoffman, 2018). These studies all indicate improvements in cognitive performance with daily supplementation of Neumentix. Specifically, the improvements in cognition were observed for the executive function domains of working memory and attention. These two areas of cognition are closely related in purpose and are dependent on optimal performance in the hippocampus along with the prefrontal cortex of the brain. Details of the four human clinical studies can be found in the table below.

Table 1. Published Human Clinical Studies with Neumentix

Author	Study Design	Subjects	Treatment	Results
Falcone et al. 2019, Makoto Study, Part 2	90-day R, DB, PC	142 healthy recreationally active males and females 18-50 years of age	* 900 mg Neumentix * Placebo	900 mg Neumentix led to an 11% increase in sustained attention from baseline, significant compared to placebo at Day 30 and Day 90 (p=0.003). Significant improvements were observed in the individual tests of shifting attention and the 4-part continuous performance test (p=0.01 and p=0.03, respectively).
Falcone et al. 2018, Makoto Study, Part 1	90-day R, DB, PC	142 healthy recreationally active males and females 18-50 years of age	* 900 mg Neumentix * Placebo	900 mg of Neumentix improved reaction time in a stationary test of choice reaction performance as early as 7 days (p=0.04) and enhanced hit rate in both stationary and multi-directional choice reaction performance (p=0.02 and p=0.02 respectively) testing following 30 days of supplementation with the effect still present at 90 days. The unique testing tool used in this study was specifically selected because it links cognitive function to physical performance.
Herrlinger et al. 2018	90-day R, DB, PC	90 healthy males and females with age associated memory impairment 50-70 years of age	* 900 mg Neumentix * 600 mg Neumentix * Placebo	Daily supplementation of Neumentix led to a 15% improvement in working memory in the 900 mg group compared to placebo (p=0.04). Significant improvements in the reported ability to fall asleep faster were observed in the 900 mg Neumentix group compared to placebo (p=0.02).

Ostfeld et al. 2018	17-day R, DB, PC	10 healthy males from active counterterrorism military unit. Mean age of 35 years	* 900 mg Neumentix * Placebo	Subjective feelings of energy, alertness and focus were very likely, likely and possibly better for the 900 mg Neumentix group compared to placebo based on magnitude-based inference testing.
Nieman et al. 2015	30-day single-arm study	11 healthy males and females with self-reported memory issues 50-70 years of age	* 900 mg Neumentix	Cognitive function scores improved in attention and planning after acute administration at 2 hours (p=0.04 and p=0.03 for attention 1 and 2 respectively) and 4 hours (p=0.001, p=0.002, and p=0.004 for attention 1,2 and planning respectively). Cognitive function scores also improved in attention and reasoning following chronic 30-day administration of Neumentix compared to baseline (p=0.02, 0.002 and 0.09 for reasoning 1, attention 2 and planning 2 respectively). Blood plasma increases in RA (approximately 10 nM) and RA metabolites detected at 0.5 and 2 hours after dosing (p<0.05 for all) confirming Neumentix absorption and uptake of Neumentix polyphenols into the serum.

All outcomes are statistically significant (p< 0.05) for all tested doses and all indicated treatment groups unless otherwise indicated
R=Randomized, DB Double-Blind, PC=Placebo Controlled

Safety Studies with Neumentix

The safety of Neumentix has been evaluated in a 14-day dose range finding toxicity study; 90-day subchronic toxicity study in accordance with OECD and FDA Redbook; Ames-reverse mutation study; Cytogenetic Assay and all human clinical trials to date. The genotoxicity and animal studies are published in Regulatory Toxicology and Pharmacology (Lasrado, Trinker, Ceddia, & Herrlinger, 2015). The Kemin-sponsored clinical trials include an open label trial (Nieman, 2015) and two randomized double-blind placebo-controlled trials (Falcone et al., 2018; Lasrado et al., 2017) . The test article used in all the safety studies was Neumentix meeting a specification of rosmarinic acid between 14.5% - 17.5%. Safety studies conducted with Neumentix are described in Table 2 below.

Table 2. Published studies examining the safety of Neumentix

Author	Study Design	Subjects	Treatment	Results
Lasrado et al. 2015	Ames assay and chromosomal aberration study	in vitro	**313, 625, 1250, 2500 and 5000 µg Neumentix /plate**	Neumentix showed no mutagenic activity in Ames assay and did not induce chromosomal aberrations when tested with human peripheral blood lymphocytes in cytogenetic assay.

Lasrado et al. 2015	14 and 90 day oral gavage animal study	80 male and female Sprague Dawley rats	0, 422, 844, 1948 mg Neumentix/kg body weight per day equivalent to 0, 65, 130, or 300 mg rosmarinic acid/kg bw/day, respectively	Neumentix was well-tolerated. NOAEL was determined as 1948 mg extract/kg body weight per day, the highest dose tested.
Nieman et al. 2015	30-day single arm study	11 healthy 50-70 year old men and women with self-reported memory impairment	900 mg Neumentix per day	Daily supplementation with 900 mg Neumentix is well-tolerated. No significant alteration in gastrointestinal tolerability, whole blood hematology and no serious adverse events in any of the study subjects. **No significant differences in the number or subjects reporting adverse events and adverse events that were likely related to the study product**
Lasrado et al. 2017	90-day R, DB, PC	90 healthy 50-70 year old men and women with age related memory issues	0, 600, 900 mg Neumentix per day	Safety was assessed through adverse events, changes in vital signs and laboratory values including clinical chemistry profile, whole blood hematology, hormone analysis and lipid profile at baseline and day 90. No reported severe adverse events, no significant between group differences in the number of subjects reporting adverse events no significant differences in the number or subjects reporting adverse events and adverse events that were likely related to the study product act. Daily supplementation with 900 mg Neumentix for 90 days was well-tolerated.
Falcone et al. 2018	90-day R, DB, PC	142 healthy recreationally active males and females. 18-50 years of age	* 900 mg Neumentix * Placebo	Safety was evaluated using complete blood count, comprehensive metabolic panel, and blood lipids evaluated on days 7, 30 and 90 of supplementation. Neumentix was well-tolerated for the 90-day duration of the study. There was no difference in the number of adverse events between groups or the number of adverse events related to study product. No overall treatment effects were observed for complete blood count, complete metabolic profile, lipids, body metrics or vital signs.

All outcomes are statistically significant ($p < 0.05$) for all tested doses and all indicated treatment groups unless otherwise indicated
R=Randomized, DB Double-Blind, PC=Placebo Controlled

Plant Characterization Studies with Neumentix

Neumentix is an aqueous extract of Kemin's patented native spearmint (*Mentha spicata*, L.) lines. These non-genetically modified propagated lines were developed from an open-pollinated spearmint population via conventional selection techniques and are capable of accumulating greater than 100 mg/g rosmarinic acid on a dry weight basis (Narasimhamoorthy, Zhao, Liu, Yang, & Greaves, 2015). Spearmint varieties such as what would be found in a grocery store generally contain 7.1 to 58.1 mg/g rosmarinic acid on a dry weight basis (Fletcher, Slimmon, McAuley, & Kott, 2005; Shekarchi, Hajimehdipoor, Saeidnia, Gohari, & Hamedani, 2012). Neumentix is comprised of approximately 10.5% protein, 1% fat, 11% dietary fiber, 4% sugars, 22% other carbohydrates 3.5% moisture, 21% ash and 27% total polyphenols expressed as gallic acid equivalents (GAE). Ultra High-Performance Liquid Chromatography (UHPLC)-Mass Spectrometer analyses have revealed that Neumentix contains over 50 polyphenolic compounds including rosmarinic acid, salvianolic acid A and B, lithospermic acid and caftaric acid (Cirlini et al., 2016). The published studies characterizing the spearmint plant and extract are described in Table 3 below.

Table 3. Published studies examining the plant characterizations of Neumentix

Author	Test Article	Design	Results
Narasimhamoorthy et al. (2015)	Patented Spearmint Plants	Traditional Plant Breeding	The patented spearmint plants produced significantly higher levels of rosmarinic acid than commercially grown spearmint Carvone was the dominant molecule in the commercial spearmint oil (54% of oil content) and in contrast, was below the detection levels in the oils of the patented spearmint plants The chemical fingerprints of the patented spearmint clearly differentiated them from commercial spearmint DNA of the patented plants was fully sequenced
Cirlini et al (2016)	Neumentix (extract of patented spearmint plants)	U-HPLC Mass Spectrometry	More than 50 phytochemicals identified Rosmarinic acid derivatives and salvianolic acids were most abundant

Preclinical and Mechanism of Action Studies with Neumentix

The key polyphenolic constituents identified in Neumentix including rosmarinic aid, salvianolic acids, lithospermic acid and caftaric acid have all been studied to determine how they may work to promote cognitive performance. The published literature describing *in vitro* and animal studies suggests that these polyphenols may positively impact cognitive performance in humans through at least four potential mechanisms of action. These include:

1. A reduction in oxidative stress (in select areas of the brain)
2. Increase in acetylcholine (a neurotransmitter actively involved in learning and memory processes)
3. Neuroprotection (the ability to help keep neural cells healthy)
4. Neurogenesis (promoting the healthy growth of new neurons)

While the health benefits of an ingredient should be tested in humans, ascertaining the mechanisms by which molecules can act at the cellular level is best accomplished using *in vitro* and animal models, due to the obvious limitations of human

cognitive research. Therefore, Table 4 outlines *in vitro* and animal models describing the mechanisms of action by which Kemin's patented spearmint extract may act to positively impact cognitive performance.

Table 4. Published studies and abstracts examining the mechanisms of action of Neumentix

Author	Study Design	Subjects	Treatment	Results
Farr et al. (2016)	*In vivo* Animal Study	9-month-old SAMP8 mice (n=60)	90 Day Oral Gavage 0, 32, 320, 640 mg extract/kg bw/day Neumentix (diluted, containing 5% rosmarinic acid)	Improved T-maze acquisition (med & high doses) & retention (all doses) indicating declarative learning and memory improvements, p<0.05. Improved novel object recognition (med & high doses, p<0.03. Selective reduction in oxidative stress (hippocampus & cortex, p<0.05).
Fonseca et al. (2016)	*In vitro* Cell culture with Neumentix, BrdU, NeuN and DAPI	Primary rat hippocampal neurons	Neumentix dissolved in medium at 10 nM, 100 nM, 1 µM, and 10 µM rosmarinic acid	Neurons responded differentially to various concentrations of Neumentix with a significant treatment effect, p=0.02. Cells in the lowest dose group (10 nM RA) displayed significantly greater levels of neurogenesis than vehicle treated cultures, p=0.02.
Fonseca et al. (2017)	*In vivo* Paw edema model of local inflammation	44 male Wistar Rats	I.P. injection of 0, 10, 30 or 100 mg Neumentix /kg containing 1.5, 4.5 and 15 mg/kg Rosmarinic acid respectively Rosmarinic acid standard at 15 or 50 mg/kg Indomethacin at 10 mg/kg	Neumentix significantly attenuated carrageenan-induced inflammation (equally as well as indomethacin) at all doses tested, p<0.05 for all. Rosmarinic acid alone attenuated inflammation at both doses, p<0.05. Neumentix had a significantly greater impact on inflammation than the equivalent amount of rosmarinic acid alone, p<0.05.

Conclusions

Consumers are interested in cognition, with their number one concern being to stay mentally sharp (Skufca, 2015). They also realize that in many areas of mental performance, including focus, they may not be performing as well as they used to. In fact, research suggests that for several domains of cognition, peak performance likely occurs in one's 20s (Park & Reuter-Lorenz, 2009). A more natural and gradual approach to promote cognitive improvement rather than a quick fix

may be important for consumers looking for trusted solutions that are scientifically-backed, safe, and natural, and offer sustainable benefits to meet cognitive demands.

Neumentix® is a water-extracted natural dietary ingredient that is derived from spearmint and selectively bred to be high in polyphenols. Targeted to support cognitive performance, this distinct ingredient is redefining the approach to attain cognitive improvements, in domains such as focus and working memory.

Improvement of working memory is one of the unique benefits of Neumentix. Working memory is part of short-term memory that allows for the storage and manipulation of information (Cowan, 2016). It is controlled by the prefrontal cortex and hippocampus (Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015). Working memory is a critical cognitive function and is closely associated with cognitive abilities such as sustained attention, focus and concentration (Adams, Nguyen, & Cowan, 2018). Due to the nature of working memory, improvements in this domain will likely help improve one's ability to manage workloads and improve productivity (Nyberg & Eriksson).

Consumers today expect safe and quality ingredients. Neumentix (standardized to a minimum of 14.5% rosmarinic acid) is recommended for healthy adults at a dose of 900 mg taken once daily, preferably with meals in the morning. Neumentix has been affirmed as GRAS. The human clinical studies performed had durations between 15 and 90 days and have demonstrated Neumentix to be safe and well-tolerated with no adverse events related to the study product.

A significant number of studies have demonstrated how the key polyphenolic constituents in Neumentix may play important roles in promoting cognitive performance. The ability of these molecules to influence cognition falls into four main categories consisting of antioxidant capabilities, increased acetylcholine levels, neurogenesis, and neuroprotection. Consumer research suggests that adults of all ages are looking for improvements in cognitive performance. A natural botanical such as Neumentix could serve as part of a healthy diet and lifestyle to positively impact cognitive performance.

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