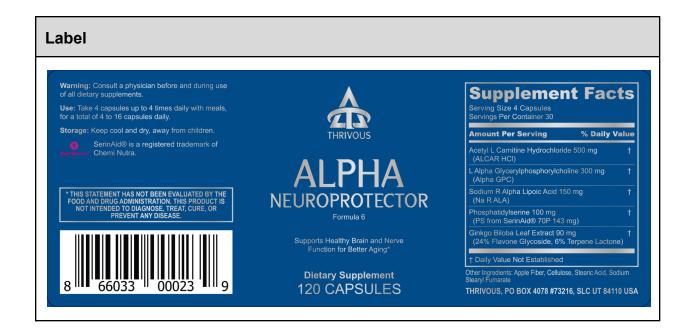


# SUMMARY OF CLINICAL STUDIES

Product	Alpha Neuroprotector
SKU	ALPHA
Barcode	866033000239
Formula	6
Date	25 August 2022



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# Acetyl L Carnitine to Support Healthy Brain Function by Decreasing Ammonia

Acetyl L Carnitine supplements may support healthy brain function by decreasing ammonia, according to these clinical studies on humans:

- Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: a double-blind, randomized, placebo-controlled clinical trial. In 2016, this study found that "mean scores of Frailty Index score [including cognitive function] and hand grip test were significantly improved in subjects supplemented with L-carnitine".
- Acetyl-L-carnitine Improves Cognitive Functions In Severe Hepatic <u>Encephalopathy: A Randomized And Controlled Clinical Trial.</u> In 2011, this study found that Acetyl-L-Carnitine supplementation resulted in "the improvement of cognitive deficits, the reduction of ammonia".
- Oral Acetyl-L-carnitine Therapy Reduces Fatigue In Overt Hepatic Encephalopathy: A Randomized, Double-blind, Placebo-controlled Study. In 2011, this study found that Acetyl-L-Carnitine supplementation resulted in "a decrease in the severity of both mental and physical fatigue and an increase in physical activity".

- Acetyl-L-carnitine reduces depression and improves quality of life in patients with minimal hepatic encephalopathy. In 2011, this study found that Acetyl-L-Carnitine "treatment is associated with significant improvement in patient energy levels, general functioning and well-being [and] the improvement of quality of life is associated with reduction of anxiety and depression".
- <u>Clinical outcomes and low-dose levocarnitine supplementation in psychiatric inpatients with documented hypocarnitinemia: a retrospective chart review.</u> In 2010, this study found that Acetyl-L-Carnitine supplementation "was associated with overall improved behavioral, cognitive, and motor functioning".
- <u>Carbohydrate, Protein, And Fat Metabolism During Exercise After Oral Carnitine</u> <u>Supplementation In Humans.</u> In 2008, this study found that Acetyl-L-Carnitine "supplementation might have the potential to reduce the metabolic stress of exercise or alter ammonia production or removal".
- <u>Acetyl-L-carnitine Treatment In Minimal Hepatic Encephalopathy.</u> In 2008, this study found that "the benefits of [Acetyl-L-Carnitine] in comparison with placebo are demonstrated in greater reductions in serum ammonia levels, as well as in improvements of neuropsychological functioning".
- <u>L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial.</u> In 2007, this study found that Acetyl-L-Carnitine "facilitates an increased capacity for physical and cognitive activity by reducing fatigue and improving cognitive functions".
- Exploratory open label, randomized study of acetyl- and propionylcarnitine in <u>chronic fatigue syndrome</u>. In 2004, this study found that "Acetylcarnitine significantly improved mental fatigue".

This clinical study review confirms that Acetyl L Carnitine supplements may support healthy brain function:

• The neurobiology of acetyl-L-carnitine. In 2016, this study observed that "dietary

supplementation of ALC exerts neuroprotective, neurotrophic, antidepressive and analgesic effects in painful neuropathies. ALC also has antioxidant and anti-apoptotic activity. Moreover, ALC exhibits positive effects on mitochondrial metabolism, and shows promise in the treatment of aging and neurodegenerative pathologies by slowing the progression of mental deterioration".

# Alpha GPC to Support Healthy Brain Function for Better Aging

Alpha GPC supplements may support healthy brain function for better aging, according to these clinical studies on humans:

- Efficacy and tolerability of choline alphoscerate (cereton) in patients with Parkinson's disease with cognitive disorders. In 2009, this study found that "marked and moderate improvement of cognitive functions was found in patients of the [Alpha-GPC] group compared to the control one ... Deterioration of cognitive functions was seen less often in the [Alpha-GPC] group than in the control group".
- <u>Cognitive improvement in mild to moderate Alzheimer's dementia after treatment</u> with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. In 2003, this study found "clinical usefulness and tolerability of [Alpha-GPC] in the treatment of the cognitive symptoms of dementia disorders of the Alzheimer type".
- <u>Alpha-Glycerophosphocholine in the mental recovery of cerebral ischemic</u> <u>attacks. An Italian multicenter clinical trial.</u> In 1994, this study found that "the trial confirms the therapeutic role of alpha-GPC on the cognitive recovery of patients with acute stroke or TIA, and the low percentage of adverse events confirms its excellent tolerability".
- <u>Multicentre study of I-alpha-glyceryl-phosphorylcholine vs ST200 among patients</u> with probable senile dementia of Alzheimer's type. In 1993, this study found "significant improvements in most neuropsychological parameters in the alpha GPC recipients".

- <u>A neurotropic approach to the treatment of multi-infarct dementia using</u> <u>L-α-glycerylphosphorylcholine</u>. In 1992, this study found that "patients receiving L-α-GPC showed a significant improvement of cognitive functions, behavior, and personality at the end of the treatment".
- <u>Nootropic therapy of cerebral aging.</u> In 1991, this study found that Alpha-GPC was "well tolerated and can be expected to be particularly effective in long-term patient management".
- <u>A multicentre trial to evaluate the efficacy and tolerability of</u> <u>alpha-glycerylphosphorylcholine versus cytosine diphosphocholine in patients</u> <u>with vascular dementia.</u> In 1991, this study found that Alpha-GPC "produced a definite symptomatic improvement and showed a very good tolerability".

These clinical study reviews confirm that Alpha GPC supplements may support healthy brain function for better aging:

- Effectiveness of nootropic drugs with cholinergic activity in treatment of cognitive deficit: a review. In 2012, this review observed that Alpha-GPC "enhances cognitive functioning and is, among several precursors, active in increasing acetylcholine levels in the brain."
- <u>Choline alphoscerate in cognitive decline and in acute cerebrovascular disease:</u> an analysis of published clinical data. In 2001, this review found "clear internal consistency of clinical data gathered by different experimental situations on [Alpha-GPC] effect, especially with regard to the cognitive symptoms (memory, attention) characterising the clinical picture of adult-onset dementia disorders".

Alpha GPC may be more bioavailable than choline alternatives such as Phosphatidylcholine or CDP Choline, according to these studies:

 <u>Cholinergic precursors in the treatment of cognitive impairment of vascular origin:</u> <u>ineffective approaches or need for re-evaluation?</u> In 2007, this study found that "phosphatidylcholine (lecithin) did not show any clear clinical benefit on symptoms of dementia disorders".

 A multicentre trial to evaluate the efficacy and tolerability of alpha-glycerylphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia. In 1991, this study found that "alpha-GPC possessed a statistical higher efficacy and an overall more satisfactory activity assessed by both patients and investigators compared with CDP".

# Alpha GPC and Acetyl L Carnitine to Increase Bioavailability

The combination of Alpha GPC (Choline) and Acetyl L Carnitine supplements may increase bioavailability, according to these clinical studies on humans:

- <u>Decreasing oxidative stress with choline and carnitine in women.</u> In 2005, this study found that "Choline and carnitine supplementation lowers lipid peroxidation, and promotes conservation of retinol and alpha-tocopherol in free-living women".
- Carnitine and Choline Supplementation with Exercise Alter Carnitine Profiles. <u>Biochemical Markers of Fat Metabolism and Serum Leptin Concentration in</u> <u>Healthy Women.</u> In 2003, this study found that "choline-induced decrease in serum and urinary carnitine is buffered by carnitine preloading".
- <u>Choline supplementation reduces urinary carnitine excretion in humans.</u> In 1996, this study found that "supplementary choline maintained serum carnitine concentrations by conserving urinary carnitine".
- <u>Choline supplementation alters carnitine homeostasis in humans and guinea</u> <u>pigs.</u> In 1995, this study found that "choline supplementation results in decreased urinary excretion of carnitine in young adult women".

#### Alpha Lipoic Acid and Acetyl L Carnitine to Support Healthy Brain Function

This clinical study review confirms that the combination of Alpha Lipoic Acid and Acetyl L Carnitine supplements may support healthy brain function:

• <u>Acetyl-L-carnitine and alpha-lipoic acid: possible neurotherapeutic agents for</u>

mood disorders? In 2008, this review observed that "L-carnitine and alpha-lipoic acid may offer neurotherapeutic effects (e.g., neurocognitive enhancement) via disparate mechanisms including antioxidant, anti-inflammatory, and metabolic regulation".

# Ginkgo Biloba to Support Healthy Brain Function for Better Aging

Ginkgo Biloba supplements may support healthy brain function for better aging, according to these clinical studies on humans:

- <u>Effectiveness and Safety Profile of Ginkgo biloba Standardized Extract</u> (<u>EGb761®</u>) in <u>Patients with Amnestic Mild Cognitive Impairment</u>. In 2021, this study found that Ginkgo "led to a significant improvement of cognitive decline, memory, activities of daily living, and depression."
- Effects of Six-Week Ginkgo biloba Supplementation on Aerobic Performance, Blood Pro/Antioxidant Balance, and Serum Brain-Derived Neurotrophic Factor in Physically Active Men. In 2017, this study found that Ginkgo supplementation may "elicit somewhat better neuroprotection".
- Effects of Ginkgo biloba extract EGb 761® on cognitive control functions, mental activity of the prefrontal cortex and stress reactivity in elderly adults with subjective memory impairment - a randomized double-blind placebo-controlled trial. In 2016, this study found "indications for improved cognitive flexibility without changes in brain activation, suggesting increased processing efficiency with [Ginkgo]".
- Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. In 2014, this study found that Ginkgo "improved [neuropsychiatric symptoms] and cognitive performance in patients with [mild cognitive impairment]. The drug was safe and well tolerated".
- Effect of Western medicine therapy assisted by Ginkgo biloba tablet on vascular cognitive impairment of none dementia. In 2012, this study found that Ginkgo

"can improve the therapeutic efficacy as well improve cognitive ability and cerebral blood flow supply of patients with vascular cognitive impairment of none dementia (VCIND)".

- <u>Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg.</u> In 2012, this study found that "treatment with [Ginkgo] was safe and resulted in a significant and clinically relevant improvement in cognition, psychopathology, functional measures and quality of life of patients and caregivers".
- Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. In 2012, this study found that Ginkgo "improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia".
- <u>Ginkgo biloba special extract in dementia with neuropsychiatric features. A</u> <u>randomised, placebo-controlled, double-blind clinical trial.</u> In 2007, this study found that "the data add further evidence on the safety and efficacy of [Ginkgo] in the treatment of cognitive and non-cognitive symptoms of dementia".
- <u>A double-blind placebo-controlled trial of tanakan in the treatment of idiopathic</u> <u>cognitive impairment in the elderly.</u> In 2004, this study found that Ginkgo "might be helpful in treating the early stages of primary degenerative dementia".
- <u>Treatment of age-related memory complaints with Ginkgo biloba extract: a</u> <u>randomized double blind placebo-controlled study.</u> In 1998, this study found that "use of Ginkgo extracts in elderly individuals with cognitive impairment might be promising".

These clinical study reviews confirm that Ginkgo Biloba supplements may support healthy brain function for better aging:

• Effects of Ginkgo biloba on dementia: An overview of systematic reviews. In 2017, this overview of systematic reviews observed that Ginkgo "has potentially

beneficial effects for people with dementia".

- Efficacy of Ginkgo biloba extract EGb 761(®) in dementia with behavioural and psychological symptoms: A systematic review. In 2016, this systemic review observed "evidence of efficacy of [Ginkgo] in the treatment of out-patients suffering from Alzheimer's, vascular or mixed dementia with BPSD".
- <u>Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A</u> <u>Systematic Review and Meta-Analysis of Randomized Controlled Trials.</u> In 2016, this meta-analysis found that Ginkgo "is potentially beneficial for the improvement of cognitive function, activities of daily living, and global clinical assessment in patients with mild cognitive impairment or Alzheimer's disease".
- <u>Meta-analysis of the efficacy and safety of Ginkgo biloba extract for the treatment</u> of dementia. In 2015, this meta-analysis found that "taking [Ginkgo] is effective and safe in the treatment of dementia".
- Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. In 2015, this meta-analysis found that Ginkgo "is able to stabilize or slow decline in cognition, function, behavior, and global change at 22-26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms".

These clinical studies reported divergent results:

- Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. In 2012, this study (GuidAge) found that Ginkgo "did not reduce the risk of progression to Alzheimer's disease compared with placebo".
- <u>Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial.</u> In 2009, this study (JAMA) found that "compared with placebo, the use of [Ginkgo] did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment".

These clinical study reviews challenge the studies that reported divergent results:

- Analysing time to event data in dementia prevention trials: The example of the guidage study of EGB761®. This 2016 analysis of the GuidAge study advised "performing another randomised clinical trial of [Ginkgo] explicitly testing the hypothesis of a late treatment effect" because "a significant treatment-by-time interaction for the incidence of [Alzheimer's] was observed in a protocol-specified subgroup analysis, suggesting that the hazard ratio is not constant over time."
- Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. Regarding the GuidAge and JAMA studies, respectively five and six years in length, this 2015 meta-analysis (summarized above) observed that "due to the particularly long pre-dementia phase, expecting a preventive effect of Ginkgo biloba on the incidence of dementia over a period of 3–6 years may be overoptimistic".
- <u>Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up</u> <u>Population-Based Study.</u> Regarding the GuidAge study, this 2013 study observed that "another alternative interpretation of [its] negative results might be that [Ginkgo] is no longer effective once the neurodegenerative process of dementia is too advanced. In this case, dementia outcome over a relatively short follow-up would not be the most relevant outcome to assess the efficacy of [Ginkgo] on cognitive aging."

# Phosphatidylserine to Support Healthy Brain Function for Better Aging

Phosphatidylserine supplements may support healthy brain function and improve memory for better aging, according to these clinical studies on humans:

 Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with <u>Alzheimer's disease and dementia.</u> In 2014, this study found that "a positive influence of [Phosphatidylserine] on memory, mood, and cognition was demonstrated among elderly test subjects". Participants used Phosphatidylserine derived from soy at 300 mg daily for 3 months.

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- Phosphatidylserine containing omega-3 Fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. In 2014, this study (continuation of a 2010 study listed below) found that Phosphatidylserine "might be associated with improving or maintaining cognitive status in elderly subjects with memory complaints". Participants used Phosphatidylserine derived from krill at 300 mg daily for 4 months and 100 mg daily for another 4 months.
- <u>The effect of soybean-derived phosphatidylserine on cognitive performance in</u> <u>elderly with subjective memory complaints: a pilot study.</u> In 2013, this study found that Phosphatidylserine "may have favorable effects on cognitive function in elderly with memory complaints". Participants used Phosphatidylserine derived from soy at 300 mg daily for 3 months.
- <u>Soybean-derived phosphatidylserine improves memory function of the elderly</u> <u>Japanese subjects with memory complaints.</u> In 2010, this study found that Phosphatidylserine supplementation "could improve the memory functions of the elderly with memory complaints". Participants used Phosphatidylserine derived from soy at 300 mg daily for 6 months.
- Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: a double-blind placebo-controlled trial. In 2010, this study found that Phosphatidylserine "may improve cognitive performance in non-demented elderly with memory complaints". Participants used Phosphatidylserine derived from krill at 300 mg daily for 4 months.
- <u>The effect of phosphatidylserine-containing omega-3 fatty acids on memory</u> <u>abilities in subjects with subjective memory complaints: a pilot study.</u> In 2010, this study found that "may have a favorable effect on memory in subjects with subjective memory complaints". Participants used Phosphatidylserine derived from soy and fish at 300 mg daily for one and a half months.
- <u>An open trial of plant-source derived phosphatydilserine for treatment of</u> <u>age-related cognitive decline.</u>In 2000, this study found that "healthy elderly volunteers meeting Age Associated Memory Impairment inclusion and exclusion

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criteria were treated ... all but two outcome measures elicited a significant drug over time effect". Participants used Phosphatidylserine derived from plants at 300 mg daily for 3 months.

- Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. In 1993, this study found that "statistically significant improvements in the phosphatidylserine-treated group compared to placebo were observed both in terms of behavioral and cognitive parameters". Participants used Phosphatidylserine derived from cows at 300 mg daily for 6 months.
- <u>Double-blind cross-over study of phosphatidylserine vs. placebo in patients with</u> <u>early dementia of the Alzheimer type.</u> In 1992, this study found that "clinical global improvement ratings showed significantly more patients improving under [Phosphatidylserine supplementation] than under placebo". Participants used Phosphatidylserine derived from cows at 300 mg daily for 2 months.
- Effects of phosphatidylserine in Alzheimer's disease. In 1992, this study found that "those treated with [Phosphatidylserine] improved on several cognitive measures relative to those administered placebo". Participants used Phosphatidylserine derived from cows at 100 mg daily for 3 months.
- Effect of Phosphatidylserine on Cerebral Glucose Metabolism in Alzheimer's <u>Disease.</u> In 1990, this study found that Phosphatidylserine supplementation resulted in "an increment of glucose metabolism" relevant to "cognitive, neuropsychological and daily life performance". Participants used Phosphatidylserine at 500 mg daily for 1 month.
- <u>Double-blind randomized controlled study of phosphatidylserine in senile</u> <u>demented patients.</u> In 1986, this study found "a trend toward improvement in the [Phosphatidylserine] treated patient". Participants used Phosphatidylserine derived from cows at 300 mg daily for one and a half months.

This clinical study reported divergent results:

• The influence of soy-derived phosphatidylserine on cognition in age-associated

memory impairment. In 2001, this study (Jorissen) found that Phosphatidylserine "does not affect memory or other cognitive functions in older individuals with memory complaints". Participants used Phosphatidylserine derived from soy at 300 mg daily for 3 months.

This clinical study challenged the study that reported divergent results:

 <u>The effect of soybean-derived phosphatidylserine on cognitive performance in</u> <u>elderly with subjective memory complaints: a pilot study.</u> Regarding the Jorissen study, this 2013 study (summarized above) observed, "one possibility for the ineffectiveness of [Phosphatidylserine] in their study was due to degradation of the [Phosphatidylserine] with time ... Powder [Phosphatidylserine] is more stable than liquid".

# Phosphatidylserine and Ginkgo Biloba to Enhance Brain Performance

The combination of Phosphatidylserine and Ginkgo Biloba supplements may enhance brain performance, according to this clinical study on humans:

 Acute cognitive effects of standardised Ginkgo biloba extract complexed with phosphatidylserine. In 2007, this study found that combined Phosphatidylserine and Ginkgo Biloba supplementation "resulted both in improved secondary memory performance and significantly increased speed of memory task performance".