
Advanced Brain Health™ Formula

Goal

To supply nutrition that is often limited by typical diets and the inevitable factors of the natural aging process, and known to support healthy brain structure and function during aging.

Rationale

Until late in the 20th century, the basic theory was that we enter adult life with a set number of brain cells that deteriorate gradually until brain function falls apart. During the past 10 years, neuroscientists have proved that this does not need to be the case. The brain does continue to form new connections and to make changes in response to new demands. Like most every other part of the body, the brain is a “use it or lose it” organ.¹ This fact not only means performing regular brain activities but also includes physical activity because exercise helps the brain maintain structural integrity through increased blood flow.² Despite this new knowledge, it is common for people to experience overall decline in brain function with age. This tendency may be influenced by reduced use of the brain, sedentary lifestyles² and by common limitations in brain nutrition.

Several substances are showing the potential to support brain function and to slow (and possibly stop or reverse) age-related decline in mental function. Among these substances, **phosphatidylserine (PS)**, **acetyl-L-carnitine (ALC)**, **alpha-lipoic acid (ALA)**, and **vitamin B-12** have been found to offer support to the maintenance of aging brain function. Following the middle-age years, supplementation with these compounds may balance a decline in the body’s production or absorption of these substances that are essential for normal brain and neurological function.^{3,4,5,6} Clinical findings support the benefit of nutritional supplements for cognitive performance and mood/behavior and suggest that additional supplementation may be required for the elderly to support structure and function.^{7,8}

Phosphatidylserine (PS)

PS is a natural compound produced in the body and obtained in small amounts in some foods. PS is a special fat-like molecule called a phospholipid. It functions as a major component of cell and mitochondrial membranes. PS is thought to be especially important for the normal function of nerve and brain cells.^{9,10} PS is the major type of phospholipid in the brain and is known to support several essential components of brain cell function.^{11,12} PS in the brain is structurally and functionally important to 1) supporting brain nerve growth factor (NGF) receptors that decrease with age; 2) dopamine and acetylcholine release; 3) dendritic spines (storage site for synaptic strength and aid for transmission of electrical signals to the neuron's cell body), and 4) cellular antioxidant properties.^{13,14}

Many animal studies have demonstrated enhanced mental function from providing supplemental PS to older animals.⁵ Similarly, several human studies have found that PS supplementation benefited mental functions in older people with declining health.^{9,15,16} Since PS is present in virtually all cells in the body, it is not surprising that PS supplementation is being studied for its likely benefits to many functions of the body.¹⁷ A study involving 131 participants concluded that supplementing PS with DHA from fish oils significantly improved cognitive performance compared to placebo users in non-demented elderly with memory complaints.¹⁸ Once again these results support the use of supplementing *before* disease takes hold with the goal of staving off age-related declines due to lack of proper brain nutrition. Although optimal daily doses for healthy people have not been established, 200-400 mg per day have been used successfully clinically to improve cognitive performance. This suggests that no more, and possibly less, would be needed to help slow age-related brain decline.¹³ Recently the FDA gave “qualified health claim” status to phosphatidylserine, allowing labels to state that, “Consumption of phosphatidylserine may reduce the risk of dementia in the elderly” and “Consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly.”

A recent study using 300 mg of phosphatidylserine and 240 mg of phosphatidic acid (PA) demonstrated a positive influence on memory, mood, and cognition among elderly test subjects. Short-term supplementation with PS and PA

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was found to have a stabilizing effect on daily functioning, emotional state and self-reported general condition.¹⁹ Additionally supplementation of 400 mg/d with PS and PA compared to placebo, was effective in normalizing the ACTH salivary and serum cortisol (stress hormones) responses to chronically high but not in low stressed subjects.²⁰ Soy bean derived phosphatidylserine (SB-PS) appears to be the best alternative to the previously used bovine PS. An exploratory study demonstrated SB-PS having favorable effects on cognitive function in elderly with memory complaints and suggests that SB-PS is safe for human consumption and thus, may serve as a safe alternative to phosphatidylserine extracted from bovine cortex.²¹

Acetyl-L-Carnitine (ALC)

ALC is a specific form of carnitine that is used for a variety of functions in many types of cells, including brain cells.²² In addition to being central to energy production in brain cells, ALC has been shown to be a powerful antioxidant in stressed brain tissues.^{23,24} ALC is synthesized naturally in the body; however, ALC levels may decline in older adults.²⁵ Common foods such as red meats and milk products contain natural L-carnitine in modest amounts, but these amounts may not make up for the decline observed with aging. One theory of brain aging is based on observations that the energy generating components (mitochondria) in brain cells suffer increased amounts of oxidative damage with age.²⁶

The acetyl form of L-carnitine has been found to enhance mitochondrial function and to prevent brain mitochondrial decay and decline in mental function in aging animals.^{27,28} Several human studies have demonstrated a wide variety of potential benefits to brain and nerve function.^{29,30,31,32} Clinical trials have tested ALC supplementation in older people, showing benefits in the treatment of a variety of mental problems.^{31,33,34,35} In a 2003 meta-analysis by Montgomery et al. that examined double blind placebo-controlled trials of at least 3 months duration, ALC at doses between 1-3 g/d showed significant benefit over placebo.³⁶ Because of ALC qualities as a neuro/cyto protective agent, it continues to be aggressively studied for maintaining and improving brain health.^{37,38,39} In fact, ALC has diverse functions related with neuroplasticity. Animal and cellular models suggest that ALC's neuroplasticity effect, membrane modulation, and neurotransmitter regulation may play an important role in the brain health. A review of four randomized clinical studies (RCT) demonstrated the superior efficacy of ALC over placebo (PBO) in patients brain health medications, and two other RCTs showed ALC to be equally effective as fluoxetine and amisulpride.⁴⁰ Several studies have combined supplementation of ALC with alpha lipoic acid, resulting in a potentially enhanced beneficial effect on aging brain mitochondrial function (see next section).^{27,28,41}

Alpha Lipoic Acid (ALA)

Due to its essential functions, lipoic acid was initially thought to be a B-vitamin. It was soon realized that it is not a vitamin since the body can synthesize it. Despite its non-vitamin status, lipoic acid continues to be the subject of extensive research more than 50 years after its discovery.^{31,42,43,44,45} Much of the interest focuses on lipoic acid's central role in energy metabolism and in its ability to function as an antioxidant and free radical scavenger in mitochondria.^{46,47} Although ALA is produced naturally in the cells of humans and animals, there is evidence that boosting ALA levels through supplementation can benefit nerve and brain function in older animals.^{48,49,50,51,52,53}

Human studies of supplementation with ALA have focused primarily on its possible role in the treatment of those with age-related problems in brain function.^{43,54} Studies are needed to confirm that similar supplementation can slow age-related cognitive decline, but animal studies show that benefits are promising.^{28,55,56} And although healthy young humans can synthesize enough α -lipoic acid to scavenge reactive oxygen species and enhance endogenous antioxidants like glutathione and vitamins C and E, the level of α -lipoic acid significantly declines with age and this may lead to endothelial dysfunction effecting all parts of the body.⁵⁷

Lipoic acid supplementation is also being studied for its potential contribution in supporting the health of the nervous system, aging eyes, cardiovascular system including glucose management, etc.^{28,58,59} While supplement doses of α -

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lipoic acid designed for health maintenance (~200 mg/day) would be significantly lower than therapeutic doses (300-1200 mg/day), high doses used in therapy appear safe for long-term use.⁵⁹

Vitamin B-12

Among other functions, vitamin B-12 provides essential support for the maintenance of neural tissues, including neural tissues of the brain. Some studies have reported that as many as one out of seven people over the age of 65 develop B12 deficiency due to a declining capacity to absorb the vitamin from foods.^{60,61,62,63} This deficiency was especially prevalent in non-supplement users.⁶⁴ A deficiency may take years to develop, but a long-standing deficiency can result in permanent damage to neural tissues if diagnosis and treatment are delayed.^{65,66} In a review of all current literature on Vitamin B12 and cognition, the studies indicate that vitamin B12 serum concentrations <120–150 pmol/L and possibly even higher (e.g., 250 pmol/L) are likely to increase the risk of cognitive decline.⁶⁷ While B12 oral supplementation can correct B12 deficiencies over time,⁶⁸ B12 does not work in a vacuum to help maintain brain health.^{67,68} The long term synergy effect of specific nutrients in their positive respective levels to potentially support brain health such as Vitamin E and all other B vitamins, is the rationale to simultaneously ingest a daily multivitamin and mineral formula (MVM) to complement the B12 (and other substances) in this formula.⁶⁷ Moore and Ames et al. demonstrated that B vitamin intake, especially B12 and folic acid, should be in balance in order to correct deficiencies or insufficiencies that lead to age-related impaired cognitive functions. It is well known that supplemental folic acid will mask the vitamin B12 deficiency, meaning the anemia will be corrected, but the neurological damage associated with vitamin B12 deficiency will progress.⁶⁹

Skarupski and Tangney et al. showed that higher total intakes, which included supplementation of vitamins B-6 and B-12 were associated with a decreased likelihood of incident depression for up to 12 years of follow-up after adjustment for age, sex, race, education, income, and antidepressant medication use. For example, each 10 additional milligrams of vitamin B-6 and 10 additional micrograms of vitamin B-12 were associated with 2% lower odds of symptoms per year.⁷⁰ It has also been suggested that marginal deficiencies (i.e. not shown to be deficient by clinical testing) may lead to future brain health problems.⁷¹ Consequently, prophylactic supplementation with vitamin B12 has been suggested as a reasonable precaution to protect vitamin B12 status in older adults with a suggested dose ranging from six to 300 mcg/day.⁶⁰ Walker et al. demonstrated long-term daily oral supplementation of 400 µg folic acid and 100 µg vitamin B-12 promoted improvement in cognitive functioning after 24 months, particularly in immediate and delayed memory performance, once again suggesting prolong synergistic use is necessary for positive outcomes^{6,7,8}

Typical Use

Suitable for adults age 45 and older interested in supporting brain and nerve function during aging.

- Typical dosage based on age and split with meals throughout the day:
 - 45-55 years – one serving (4 caps) per day with any meal
 - 56-65 years – two servings (8 caps) per day. One serving with AM meal and one with PM meal
 - Over 65 years – three servings (12 caps) per day. One serving with AM meal and two with PM meal

Precautions

The dotFIT™ Advanced Brain Health is considered safe for the general population at the proper dosage in healthy users. Advanced Brain Health is designed to be safe to use along with any other dotFIT additional brain support elements that complement those already present in the dotFIT multivitamin formulas as well as the SuperiorAntioxidant™ and SuperOmega-3 formulas. Like any dietary supplement, users should consult with their physician and/or pharmacist before taking this supplement, especially if they are also taking any drugs for medical purposes.

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Phosphatidylserine is generally well-tolerated⁷² when taken at the suggested levels of one to three servings per day (100 to 300 mg/day). Phosphatidylserine in dotFIT Advanced Brain Health comes from soybean sources, removing concerns about any risk associated with bovine sources that were commonly used in the early research on the substance. Uncommon side effects of phosphatidylserine include gastrointestinal upset and insomnia.^{73,74}

Acetyl-L-carnitine is typically well-tolerated³⁸ when taken at the suggested dose of one to three servings per day (350 to 1,050 mg/day). Rare side effects have included nausea, gastrointestinal upset, and restlessness.^{75,76}

Alpha lipoic acid has been well-tolerated in clinical studies lasting from four months to two years at the suggested dose of one to three servings per day (100 to 300 mg/day).^{59,77,78,79} Studies of lipoic acid supplementation in people with conditions such as Type II diabetes and peripheral arterial disease have reported potential minor side effects such as tingling in legs and feet and mild stomach queasiness. However, it was difficult to determine if this was caused by the supplement or the condition.⁸⁰

Vitamin B-12 is very safe when taken at the dosage in this formula. Since toxicity from vitamin B12 is virtually unknown, no tolerable upper intake level has been established for Vitamin B12 by the Institute of Medicine.⁸¹

Contraindications

The dotFIT™ Advanced Brain Health formula is contraindicated in pregnancy and lactation and for anyone suffering adverse reactions to any of the ingredients.

Adverse Reactions

There should be no serious side effects in healthy users at the recommended doses.

Phosphatidylserine: Uncommon side effects include gastrointestinal upset (300 mg/day or more) and insomnia (600 mg/day or more)^{73,74}

Acetyl-L-carnitine: Side effects are uncommon; those reported include gastrointestinal upset and agitation.^{75,76,82} People with underactive thyroid, seizures or using blood thinners should check with their physician. Do not use if taking Acenocoumarol (Sintrom).

Alpha-lipoic acid: Side effects are usually not seen unless dosage exceeds 600 mg/day. Reported reactions include headache, skin rash and stomach upset.^{80,83}

Vitamin B12: Side effects unknown.

Upper Limit/Toxicity

The Institute of Medicine has not set an upper limit (UL) for any of the ingredients contained in the dotFIT Advanced Brain Health formula.

Phosphatidylserine: No upper limit has been established for human use. A 12-week study of people over 57 years of age concluded that PS is a safe supplement for elderly individuals at doses up to 600 mg per day (taken in doses of 200 mg three times daily).⁸⁴ The oral LD50 in rats is >5 g/kg body weight. In a tolerability and toxicity study of 130 patients, no significant changes were noted in CBC or serum chemistry results, except for a significant decrease in the liver enzyme alanine aminotransferase (ALT) and uric acid levels.⁸⁵

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Acetyl-L-Carnitine: A recent risk assessment for L-carnitine established an “Upper Level for Supplements” (ULS) for L-carnitine at 2000 mg per day which is equivalent to about 3000 mg of acetyl-L carnitine.⁸⁶

Alpha-lipoic acid: No upper limit has been established for human use. A two-year study of laboratory rats reported a no-observed-adverse-effect level (NOAEL) of 60 mg per kilogram body weight.⁸⁷ The dose in the dotFIT Advanced Brain Health formula is less than 1/10 of this dose.

Vitamin B12: No specific levels of intake are known to be toxic. Some theoretical concern has been expressed for excessively high intakes for extended periods of time.^{88,89}

Summary

Purpose

- The goal of the dotFIT™ Advanced Brain Health formula is to provide substances that help to support brain structure and function during aging
- Complement to the dotFIT multivitamin and mineral, SuperiorAntioxidant™, and SuperOmega-3 formulas
- The Advanced Brain Health formula rounds out the dotFIT longevity program by providing brain support substances to complement the dotFIT multivitamin, antioxidant, and Omega-3 supplements

Unique Features

- Contains only well-researched brain support substances in their proper amounts
- Accurately complements the dotFIT multivitamin, antioxidant, and Omega-3 formulas
- This formula considers use of other dotFIT products to help the user maintain a safe and optimal range of total nutrient intake
- Manufactured in a facility in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC

Supplement Facts Panel

Supplement Facts

Serving Size: 4 Softgel Capsules Servings Per Container: 60

	Amount Per Serving	%DV*
Calories	20	
Calories from Fat	20	
Vitamin B12 (as Cyanocobalamin)	100 mcg	1,667%
Acetyl-L Carnitine	500 mg	**
Phosphatidylserine	100 mg	**
Alpha Lipoic Acid	100 mg	**

* Percent Daily Value based on a 2,000 calorie diet.

** % Daily Value(DV) not established

Other Ingredients: Rice Bran Oil, Gelatin, Glycerin, Water, Beeswax, Sunflower Lecithin and Carob

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