# Neurotrophic Brain Formula

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## INGREDIENTS


Neurotrophins are an important class of signaling molecules in the brain responsible for neuron growth, maturation of synapses during development, and synaptic plasticity.[1,2] Among them, Brain Derived Neurotrophic Factor or BDNF is the most studied with an astounding number of publications appeared in the last three decades to establish its functional role in the brain and human brain diseases.[1,3-6] In fact, numerous studies have shown the critical role of BDNF in synaptic plasticity, memory, and cognitive functions.[7-10]

Neurotrophic Brain Formula is a unique combination scientifically formulated to promote the production of Brain Derived Neurotrophic Factor (BDNF) and support brain health.* Neurotrophic Brain Formula contains N-acetylcysteine (NAC), Green Tea Extract, Whole Coffee Fruit Extract, and Curcumin. All four ingredients are scientifically known to have beneficial effects on various cognitive functions by boosting memory, focus, higher thinking, and mood health.*[11-21] They are also known to have direct and indirect effects on promoting BDNF production. These brain health advantages have been clinically demonstrated in young adults as well as in the elderly population with age-related memory and mood issues.*[22]

## BENEFITS

- Helps support cognitive functions and brain health*
- Helps stimulate the production of BDNF*
- Helps fight oxidative stress and boost glutathione production*
- Helps support mood health*

## EXTENDED BENEFITS

### Helps support cognitive functions & brain health*

Neurotrophins are comprised of at least four family members known as NGF, BDNF, NT-3 and NT-4 and all are known to regulate neuronal viability, development, and function.[3,23] Because of its critical role in neuronal development, synaptic plasticity, and neuronal cell health, BDNF is a vital component to normal brain function. For this reason, it has been studied extensively in relation to psychiatric disorders associated with abnormal brain development and function.[1] BDNF is the only neutrophin that binds and activates TrkB receptors which in turn activate three major neuronal signaling pathways in the brain: Ras-MAPK signaling, which promotes neuronal differentiation and neurite outgrowth, PI3 Kinase-Akt signaling, which promotes survival and growth of neurons, and PLC-γ1-PKC signaling, which promotes synaptic plasticity.[24] Molecular changes in synaptic plasticity of neuronal networks are considered to be the cellular correlates of learning and memory, and the neurotrophin brain-derived neurotropic factor (BDNF) plays an important role in these processes.[6,25-26] Moreover, a large body of scientific literature has highlighted how keeping a high level of BDNF in our body can benefit various cognitive brain functions such as improving memory and mood, supporting learning processes, and slowing brain aging.*[27]

Regarding N-acetylcysteine (NAC), based on ample of literature, it has been suggested that its mechanisms of action overlap with the pathophysiology of a diverse range of neuropsychiatric ailments.[28] The major endogenous antioxidant molecule in the brain is glutathione (GSH), which is key to the mechanism of action of NAC. GSH reduction is one of the oldest biomarkers in psychiatry, known for almost a century and noted in studies of various neurological ailments.[29-30] GSH is a very efficient redox scavenger, carrying a free thiol group which can interact directly with reactive oxygen/nitrogen species and can maintain the oxidative status of key cellular enzymes. The cycle of GSH and the reduced species glutathione disulphide (GSSG) is a critical mechanism for regulation of cellular oxidative balance. Mice deficient in the rate-limiting enzyme for GSH synthesis show a range of behavioral symptoms reminiscent of various brain dysfunctions, including a heightened response to psychotomimetics. Treatment of these animals with NAC reverses some of these deficits.[31] Similarly, experimental GSH depletion in the brain induces spatial memory deficits which are reversed by NAC.

## Neurotrophic Brain Formula
## 90 Veggie Caps
### Supplemental Facts

**Supplement Facts**

Serving Size 3 Veggie Capsules
Servings Per Container 30

| Amount Per Serving | | %Daily Value |
|---|---|---|
| N-Acetyl-L-Cysteine (NAC) | 1000 mg | † |
| Green Tea Extract (*Camellia sinensis*) (Leaf) standardized to contain 50% EGCG | 500 mg | † |
| Turmeric Extract (*Curcuma longa*)(root) (Curcumin C3 Complex®) standardized to contain 95% Curcuminoids | 200 mg | † |
| Whole Coffee Fruit Extract (*Coffea arabica*)(NeuroFactor®) | 100 mg | † |

† Daily Value not established.

**Other Ingredients:** Hypromellose (vegetarian capsule), microcrystalline cellulose, magnesium stearate (vegetable source), silicon dioxide.

**Suggested Adult Use:** Take 3 capsules daily with food, or as recommended by a nutritionally informed physician.

**WARNING:** Consult a physician before taking this product if pregnant, nursing, taking medication, or have a medical condition. KEEP OUT OF REACH OF CHILDREN.

**Non-GMO / Gluten Free / Soy Free / Vegetarian**

This product contains natural ingredients that may vary in color. Store in a cool dry place.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Coffee is one of the world's most commonly consumed beverages. While it has been known that caffeine-rich coffee beans might be associated with beneficial brain health benefits, recent studies have discovered that coffee fruit extract may also possess valuable brain health benefits due to its capacity to modulate positively the level of BDNF in the body*[14,25]

Tea plants, originated from East Asia, come from the plant *Camellia sinensis*. Like coffee, tea is one of the most popular beverages enjoyed worldwide. In different parts of the globe, tea is consumed as green, black, or Oolong tea. The differences between these three types of tea come from how the tea is prepared after the tea leaves have been harvested. Based on a large body of literature, green tea has been observed as the one to possess the most significant positive effects on human health.* In particular, green tea comprises many active components that are known to be beneficial to human brain health. Among the bioactive components, polyphenols, also known as catechins, have shown to possess neurological activiities.[11] Moreover, it appears that green tea extracts may contain higher levels of polyphenols. One of the major polyphenols of green tea is known as epigallocatechin gallate or EGCG. Research has shown that EGCG has anti-amyloid effects that may result in supporting brain health and improvement in cognitive functions in elder populations.*[33-35]

According to Gómez-Pinilla and colleagues, antioxidant properties of EGCG can be associated with an increased expression of BDNF and higher cognitive function and better mood.*[36] Therefore, using green tea polyphenols would be a highly useful complementary approach for an inexpensive long-term option to support cognitive functions and brain health.*[36] Green tea extract has also been shown to enhance the neuronal activity in the prefrontal cortical areas of the brain concerned with the processing of working memory.*[16,37-39]

As a plant-based diarylheptanoid produced by the plant turmeric, curcumin is a component of yellow curry spice. This bright-yellow pigment was first isolated more than a century ago and has been used extensively in Indian medicine.[40] The antioxidant capabilities of curcumin appear to stem from its unique structure that can donate hydrogen atoms or transfer electrons from two phenolic sites, allowing it to scavenge free radicals easily. More recently, curcumin has attracted attention for its effects on neuroplasticity and its ability to support processes involved in brain aging and neurodegeneration.* Preclinical investigations in rats showed that dietary supplementation of curcumin 3 weeks prior to experimentally induced traumatic brain injury partially ameliorate the consequence of injury on markers of synaptic plasticity such as BDNF.[41]

## Helps stimulate the production of BDNF*

BDNF is involved in several processes that are essential for the optimal functioning of the brain. Evidence from preclinical studies and clinical trials suggests that strategies aiming to increase brain BDNF levels could have a beneficial effect on many brain disorders.*

It is well documented that enhanced cognitive functions are connected with an increase in serum BDNF level, which is strongly expressed in the brain and, to a lesser extent, in the skeletal muscle, in order to stimulate synaptic plasticity and neurogenesis.[42] Previous reports critically point to antioxidant actions of polyphenols in the brain, because they reached extremely low concentrations in this tissue.[43] Gundimeda and colleagues showed that green tea polyphenols (especially EGCG) in extremely low concentrations boost the neuritogenic activity of BDNF, by the binding of EGCG to brain laminin receptor, leading to activation of NADPH-oxidase and generation of hydrogen peroxide, which as a messenger influences the signaling pathway and therefore increases the neuritogenic ability of BDNF.[44]



The neuroprotective effect of curcumin is exerted via various mechanisms in the central nervous system, which are responsible for its antioxidant properties and its ability to increase BDNF.[19,45-46] Previous studies have shown that rats subjected to a chronic stress protocol had decreased hippocampal BDNF levels and a reduced ratio of phosphorylated cAMP response element-binding protein to CREB levels in the frontal cortex and hippocampus; however, curcumin administration reversed these changes at levels similar to imipramine (antidepressant drug) treatment.[47] Moreover, curcumin increased cAMP levels and activated cellular signal transduction pathways through extracellular signal–regulated kinases (ERKs) and p38 kinases, which are known to be involved in BDNF production, regulation of neuronal plasticity, and stress responses.[48] Therefore, it is possible that curcumin increased BDNF levels by increasing cAMP levels and activating ERKs and p38 kinases, or by reducing oxidative damage.*[49] It is noteworthy that a systematic review of the literature was conducted using PubMed, Scopus, ISIWeb of Science, Cochrane library, and Google scholar to evaluate the impact of curcumin supplementation on serum BDNF levels. It was found that in humans, the reduction of brain-derived neurotrophic factor (BDNF) can affect cognitive function, learning, and memory and causes behavioral disorders.* Several randomized controlled trials have examined the neuroprotective effects of curcumin and its ability to increase BDNF levels. The review arrived at the conclusion that the significant positive impact of curcumin supplementation on BDNF levels indicated its potential use for neurological ailments that are associated with low BDNF levels.*[20]

Coffee fruit extract, which is a powerful supplement separate from coffee beans, has been widely used as a superfood supplement for brain health because it is a natural nootropic that can boost the production of BDNF and therefore may support and improve certain cognitive functions such as learning, memory and focus.*[14]

## Helps fight oxidative stress and boost glutathione production*

The brain is acutely sensitive to changes in redox status. The high metabolic activity of this organ is a persistent source of oxidative species, as it uses oxygen through energy-generating mitochondria cells that constantly generates oxygen free radicals.[50] Neurotransmitter activity also generates free radicals, with auto-oxidation of dopamine and excitotoxicity related to glutamatergic signaling being important sources of oxidative stress.[51] More, neurons rely on the integrity of extensive axonal membranes for efficient information signaling, and these membranes, high in polyunsaturated fatty acids, are vulnerable to free radical damage. Compounding these factors, the levels of endogenous antioxidants in the brain may be often low relative to other highly metabolically active organs.[28]

Oxidative stress occurs when there is an imbalance between oxidants and antioxidants. ROS can modify or damage DNA, proteins, and lipids in cells by oxidation and peroxidation. Oxidative

stress plays a critical role in neuronal dysfunction and death in various neurodegenerative diseases. There are several antioxidant defense mechanisms available to human health. Antioxidants include vitamins C and E, and enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSHpx) as well as endogenous thiols, or sulfhydryl containing compounds such as glutathione (GSH).

N-acetylcysteine is a precursor of L-cysteine, which in turn is a component of the endogenous antioxidant glutathione, a tripeptide composed of glutamate, cysteine, and glycine. Glutathione (GSH) plays an important role in antioxidant activities, redox (oxidation-reduction reaction)-regulated cell signaling, and immune responses.[17] Among many, established roles for GSH are the following: antioxidant defense, detoxification of electrophilic xenobiotics, modulation of redox (oxidation–reduction reaction)-regulated signal transduction, and regulation of immune responses. GSH has an important role in maintaining the redox state of the cell and therefore it exerts a profound protective effect on cells. It has been established that the effects of NAC are most commonly attributed to its capability to scavenge ROS and elevate cellular GSH levels.[17,52] In a systematic review, it was also found that the use of NAC was quite favorable in several psychiatric and neurological ailments.*[53]

There is a growing body of evidence that potential brain health benefits of green tea are attributed to the antioxidant properties of green tea polyphenolic compounds that contain the phenolic hydroxyl groups attached to ring structures and act as hydrogen- or electron-donating free radicals and transition metal chelators. They can inhibit the activity of enzymes responsible for reactive oxygen species (ROS) production, such as xanthine oxidase, cyclooxygenase and lipoxygenase.[54] One of its main polyphenolic constituents known as epigallocatechin gallate (EGCG) has shown clinical importance in supporting brain health.* EGCG has been associated with anti-aging properties. It may improve redox status at the tissue level possibly preventing system neuronal cell level structural damage.*[38,55]

## Helps support mood health*

BDNF is broadly expressed in the developing and adult mammalian brain and has been implicated in development, neural regeneration, synaptic transmission, synaptic plasticity and neurogenesis. there is a growing body of data suggesting that BDNF plays a pivotal role in the pathophysiology of mood disorders.[27,56] Studies in humans have shown decreased plasma levels of BDNF in bipolar disorder, manic and depressed patients. Many preclinical and clinical studies provide direct evidence suggesting that modulation in expression of BDNF could be involved in behavioral phenomenon associated with depression.*[56]

The requirement for BDNF in antidepressant responses has also been investigated using animal experimental models. Current data suggests that conventional antidepressants mediate their antidepressant-like effects by increasing BDNF in forebrain regions, the hippocampus, making BDNF an essential factor in modulating mood health.*[57]

Curcumin is a major component of Curcuma longa with long traditional usage in improving various mood health states.* It has been known for the antistress and neurotropic effects. A study in rats revealed the neuroprotective effects of curcumin associated with antidepressant activity through long-term depression-associated neural plasticity.[58]

Other research demonstrated that curcumin exerts antidepressant effects that are comparable with the effects of well-known antidepressants drugs, such as fluoxetine and imipramine.*[45,59-60] This effect has been attributed to the increase in serotonin levels caused by curcumin.[19] It is noteworthy that serotonin plays important roles in the regulation of sleep, memory, learning, mood, and behavior.[61]

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## CLINICAL STUDIES

The objective of a study was to examine the association between green tea consumption and cognitive function in humans. They analyzed cross-sectional data from a community-based Comprehensive Geriatric Assessment (CGA) conducted in 2002. The subjects were 1003 Japanese subjects aged 70 years. They completed a self-administered questionnaire that included questions about the frequency of green tea consumption and evaluated cognitive function by using the Mini-Mental State Examination with cutoffs of 28, 26, and 24 and calculated multivariate-adjusted odds ratios (ORs) of cognitive impairment. Results showed that higher consumption of green tea was associated with a lower prevalence of cognitive impairment. At the 26 cutoff, after adjustment for potential confounders, the ORs for the cognitive impairment associated with different frequencies of green tea consumption were 1.00 (reference) for 3 cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4 – 6 cups/wk or 1 cup/d, and 0.46 (95% CI: 0.30, 0.72) for 2 cups/d (P for trend 0.0006). Corresponding ORs were 1.00 (reference), 0.60 (95% CI: 0.35, 1.02), and 0.87 (95% CI: 0.55, 1.38) (Pfor trend 0.33) for black or oolong tea and 1.00 (reference), 1.16 (95% CI: 0.78, 1.73), and 1.03 (95% CI: 0.59, 1.80) (P for trend 0.70) for coffee. The results were essentially the same at cutoffs of 28 and 24. Based on the data found, the authors concluded that a higher consumption of green tea is associated with a lower prevalence of cognitive impairment in humans.*[33]

The objective of the study was to determine whether the consumption of green tea, coffee, or black tea influences the incidence of memory problems and mild cognitive impairment in older people. They conducted a population-based prospective study with Japanese residents aged 60 years from Nakajima, Japan (the Nakajima Project). Participants received an evaluation of cognitive function and blood tests. The consumption of green tea, coffee, and black tea was also evaluated at baseline. Of 723 participants with normal cognitive function at a baseline survey (2007–2008), 490 completed the follow up survey in 2011–2013. The incidence of memory problems during the follow-up period (mean 6 SD: 4.960.9 years) was 5.3%, and that of mild cognitive impairment was 13.1%. The multiple-adjusted odds ratio for the incidence of overall cognitive decline was 0.32 (95% CI: 0.16–0.64) among individuals who consumed green tea every day and 0.47 (95% CI: 0.25–0.86) among those who consumed green tea 1–6 days per week compared with individuals who did not consume green tea at all. The multiple adjusted odds ratio for the incidence of memory problems was 0.26 (95% CI: 0.06–1.06) among individuals who consumed green tea every day compared with those who did not consume green tea at all. No association was found between coffee or black tea consumption and the incidence of memory problems or mild cognitive impairment. Based on all the data obtained from their study, the authors concluded that green tea consumption is significantly associated with reduced risk of cognitive decline, even after adjustment for possible confounding factors.*[62]

The main goal of the study was to evaluate the effects of a six-week green tea extract (GTE) supplementation combined with CrossFit workout on blood antioxidant status and serum BDNF in men. Sixteen young males involved in Cross Fit training were randomized into two groups supplemented with GTE or placebo for six weeks. Each participant performed an exercise test for the evaluation of maximum oxygen uptake (VO2max) twice, before starting (1st trial) and after completing the supplementation combined with Crossfit workout (2nd trial). Venous blood samples were drawn at rest, immediately post-test and after one hour of recovery in order to estimate activities of various antioxidant enzymes such as superoxide dismutase [SOD], glutathione peroxidase [GPx], non-enzymatic antioxidants (reduced glutathione [GSH], total antioxidant capacity (FRAP), lipid peroxidation products (TBARS), and BDNF. Results showed that except for a significantly higher SOD activity and FRAP level recorded at rest and post-exercise in the 2nd trial compared to the corresponding values in the 1st trial, no significant differences were recorded among other assayed measures such as GPx, GSH and BDNF. Moreover, a percentage increase in FRAP level was twice as high after six weeks of GTE consumption than after placebo. There was a significant inverse correlation between FRAP and TBARS in the GTE-supplemented group ($r = -0.40$, $p < 0.05$). The authors concluded that a six-week consumption of GTE had marginal effect on aerobic capacity and serum BDNF level in CrossFit-trained men, but it caused a marked increase in the blood antioxidant capacity and a moderate attenuation of the training-induced lipid peroxidation.[54]

In this study, the authors aimed to assess the protective effects of EGCG against sevoflurane-induced neurotoxicity in neonatal mice. Distinct groups of C57BL/6 mice were given EGCG (25, 50, or 75 mg/kg body weight) from postnatal day 3 (P3) to P21 and were subjected to sevoflurane (3%; 6 h) exposure on P7. EGCG significantly inhibited sevoflurane-induced neuroapoptosis as determined by Fluoro-Jade B staining. Sevoflurane-mediated down-regulation of cAMP/CREB and BDNF/TrkB signaling was inhibited by EGCG. Reverse transcription PCR analysis revealed enhanced BDNF and TrkB mRNA levels upon EGCG administration. Improved performance of mice in the Morris water maze tests suggested enhanced learning and memory. The authors concluded that EGCG was able to effectively inhibit sevoflurane-induced neurodegeneration and improve learning and memory retention of mice via activation of CREB/BDNF/TrkB–PI3K/Akt signalling.*[55]

A single-dose study was performed to assess the effect of whole coffee fruit concentrate powder (WCFC), green coffee caffeine powder (N677), grape seed extract powder (N31) and green coffee bean extract powder (N625) on blood levels of BDNF. Randomly assorted groups of fasted subjects consumed a single, 100mg dose of each material. Plasma samples were collected at time zero (T0) and at 30 min intervals afterwards, up to 120 min. Based on the collected data, treatments with N31 and N677 increased levels of plasma BDNF by about 31% whereas treatment with WCFC increased it by 143%, compared with baseline. These results indicate that WCFC could be used for modulation of BDNF-dependent health conditions.[14] Because this preliminary study was limited by the small number of participants and by the fact that the chosen placebo, silica oxide, unexpectedly reduced BDNF levels in the blood, the same research team conducted a larger clinical trial that further clarified the effect of WCFC on BDNF. Twenty healthy subjects with ages ranging from 25 to 35 participated in this study. All fasted and resting subjects received placebo on Day 1, WCFC on Day 2, and a cup of freshly brewed coffee on Day 3. Treatment with WCFC resulted in a statistically significant increase in plasma BDNF compared to placebo ($p = 0.0073$) or coffee ($p = 0.0219$) during the first 60 minutes. In addition, e isolated exosomes from serum and found that they contained BDNF. Furthermore, oral WCFC consumption acutely increased BDNF levels in serum exosomes. In summary, the authors concluded WCFC may be a tool to manage BDNF-dependent health conditions.[15]



The aim of this systematic review was to evaluate the impact of curcumin supplementation on serum BDNF levels. Using PubMed, Scopus, ISIWeb of Science, Cochrane library, and Google scholar to identify eligible studies up to January 2019, the authors reviewed randomized control trials of curcumin supplementation that reported the serum BDNF level as a primary outcome. Four randomized-control trials with 139 participants were included. Curcumin supplementation dose and duration ranged from 200 to 1820 mg/daily and 8 to 12 weeks, respectively. They found that curcumin supplementation significantly increased serum BDNF levels (weighted mean difference: 1789.38pg/mL, 95% confidence interval: 722.04-2856.71, $P < .01$). The authors concluded that the significant positive impact of curcumin supplementation on BDNF levels indicated its potential use for neurological disorders that are associated with low BDNF levels.*[20]

A research team investigated the neuroprotective and neural plasticity effects of curcumin in stressed rat model. Multielectrode array was applied on organotypic hippocampal slice cultures (OHSCs) to monitor the effect of 10 μM curcumin in long-term depression (LTD) through low-frequency stimulation (LFS) to the Schaffer collaterals and commissural pathways. In addition, the influence of oral curcumin administration on rat behavior was assessed with the forced swim test. Finally, protein expression levels of BDNF and cyclooxygenase-2 (COX-2) were measured by Western blot in chronically stressed rats. Our results demonstrated that 10 μM curcumin attenuated LTD and reduced cell death. It also recovered the behavior immobility of FST, rescued the attenuated BDNF expression, and inhibited the enhancement of COX-2 expression in stressed animals. These findings indicate that curcumin can enhance postsynaptic electrical reactivity and cell viability in intact neural circuits with antidepressant-like effects, possibly through the upregulation of BDNF and reduction of inflammatory factors in the brain.[58]

A scientific review evaluated the efficacy of curcumin as an add-on therapy in people affected by mood health in comparison to placebo or standard care alone. They also evaluated the efficacy of curcumin on anxiety symptoms, which are frequently present in comorbidity with mood imbalance. Their findings suggest that curcumin, if added to standard care, might improve depressive and anxiety symptoms in people with mood problems.* However, they also noted that further trials should be implemented, particularly in Western countries, where curcumin does not represent a usual component of dietary regimens.[60]

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