

# Botanicals and Natural Compounds that Promote Cognitive and Brain Health

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## Discussion

### COGNITIVE HEALTH

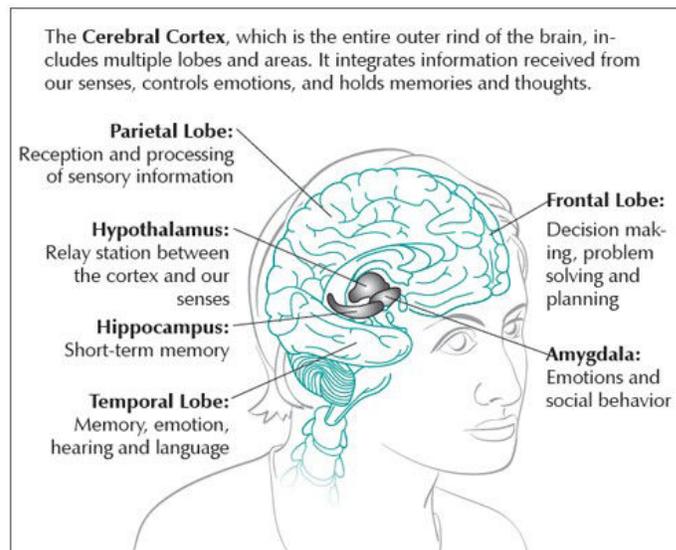
Healthy cognitive capacity is essential for work, self-care and the social interactions, which form the foundation of our daily life. While people of all ages are effected by cognitive issues, there is great interest in cognitive health in the aging population. This includes issues of memory, attention, focus and mood, which influence quality of life.

The healthy adult brain, part of our vast neurological system, has about 100 billion neurons (nerve cells). As these branch and interconnect to form multiple connections with other neurons, chemical compounds called neurotransmitters flow across the junctures, or synapses. There are about 100 trillion synapses in the adult brain that facilitate biochemical signals that create, maintain and change memories, thoughts, emotions, motor skills and a multitude of other functions.<sup>1</sup>

All parts of the brain are related in some way to memory. There are many kinds of memory including short-term, long-term, emotional, episodic and factual, as well as visual and verbal memory. Procedural memory is involved with learning skills and habits. In truth, all these intertwine to form our own unique memories. Multiple factors influence our ability to learn and remember.

Many people are affected by loss of memory and ability to focus. With aging, even healthy adults can lose as much as half their cognitive ability in relation to everyday tasks.<sup>2</sup> This loss, found to correlate with a decrease in neuron density in the cortex and hippocampus, is described in terms of the degree of cognitive impairment.<sup>2</sup>

Mild cognitive impairment (MCI), a phase between normal aging and early dementia, is considered the most favorable time for therapeutic treatment. Dementia refers to severe cognitive decline where social and daily functioning is so impaired that a person loses their ability to function independently.<sup>3</sup> Alzheimer's disease (AD) is the most prevalent neurodegenerative disease effecting the elderly



*Cognitive processes make use of many parts of the brain. Nerve cells throughout the brain (neurons) communicate with each other, creating thoughts, feelings and memories.*

(See reference #4)

population although it is not considered a normal progression of aging. It is estimated that one in three seniors die with AD or other forms of dementia.<sup>1</sup>

### ETIOLOGY OF COGNITIVE DECLINE

Changes in cognition, mood and neurological function are influenced by hormonal balance, vascular health, nutrition, exercise and genetics. The brain is adversely affected by chronic inflammation, oxidative stress, traumatic stress, brain injury and environmental pollutants. Obesity, hypertension, diabetes and smoking increase risk of cognitive impairment.

Nourished by a rich vascular network, the brain receives about 25% of our blood flow, which carries oxygen and nutrients required by brain cells. The brain can use 20% to 50% of our fuel and oxygen during daily activity and work. Lack of blood flow, nutrients and oxygen contributes to nerve cell dysfunction and death. Brain cells are sensitive to nutrients and dietary components that can influence mood, cognition and brain function. Many nutrients are implicated in cognitive

health including omega-3 oils, DHA, B-complex vitamins, vitamins D, E and C; minerals, choline, and flavonoids.<sup>5</sup>

Studies find that healthy diet, exercise and nutrient intake are vital to support multiple brain processes, regulate synaptic transmission, support membrane fluidity and facilitate cell-signaling.<sup>1</sup> Diet and exercise can exert a positive influence on cellular energy metabolism and on synaptic plasticity. This is mediated via the ATP (adenosine triphosphate) produced in the energy-production cycle of the cell. One hypothesis is that ATP activates BDNF (brain-derived neurotrophic factor) and IGF1 (insulin-like growth factor 1), both of which support synaptic plasticity and cognition. The BDNF gene is also a potential target for the influence of diet on epigenetics.<sup>5</sup>

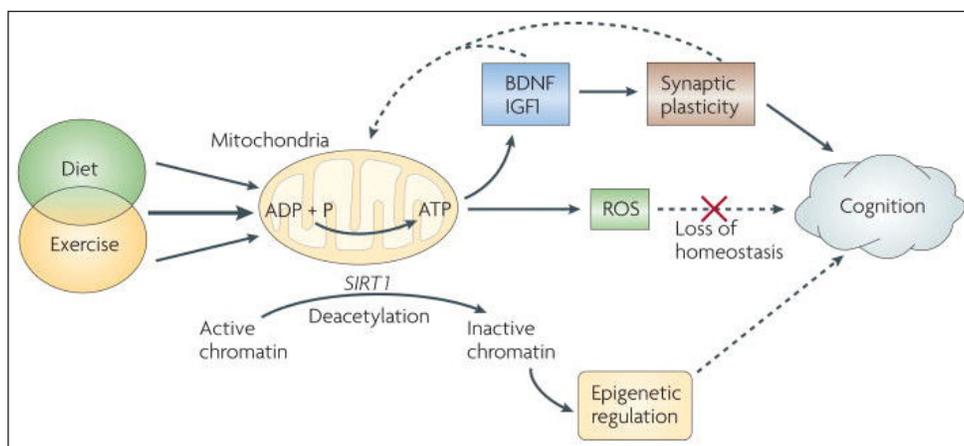
Many structural brain changes accompany aging and influence cognition. These include brain volume decline, neuron shrinkage and fewer synapses. Changes occur in areas of the brain including the frontal and temporal cortex, among others.<sup>6</sup> Chronic stress or poor ability to deal with stress is linked to decline in hippocampal and cognitive function.<sup>3</sup> Nerve cell membranes, comprised mostly of proteins and phospholipids, are places of specialized activity involving energy production and neurotransmitter function. Changes in the lipid composition, enzyme activity and fluidity of the cell membrane occur with aging and are found to impair neurotransmission, learning and memory.<sup>7</sup>

Neurotransmitter balance influences multiple facets of mood and cognition. Acetylcholine, vital to memory formation and retention, is the primary neurotransmitter in the cholinergic nervous system, which includes the parasympathetic nervous

system, brain stem, basal forebrain and neuromuscular system. The enzyme cholinesterase inhibits the action of acetylcholine by breaking it down, thereby increasing the amount of available acetylcholine.

Chronic stress causes HPA (hypothalamic-pituitary-adrenal) axis dysfunction and increases allostatic load, thereby contributing to the risk and severity of neurocognitive disease. There is a direct correlation between elevated stress hormones, such as cortisol, and increased oxidative damage.<sup>8,9,10</sup> Mitochondrial DNA are susceptible to attack by ROS (reactive oxidative species), which are a major causative factor for nerve cell damage, cell breakdown and neurodegenerative conditions. Nerve cells, the cellular matrix and the capacity for cellular repair are all influenced by levels of inflammation and oxidative stress.<sup>11,12,13</sup> In normal tissues and cells, the balance between generation of ROS and antioxidant protection is mediated through antioxidant enzymes. When out of balance, increased oxidative stress causes damage to the lipids, proteins, RNA and DNA of cells. Oxidative stress promotes damage to phospholipids present in the plasma membrane and compromises synaptic plasticity and cognitive ability.<sup>11,12,14</sup>

Chronic inflammation is found to be a consistent determining factor in cognitive health.<sup>15</sup> Two markers, hs-CRP and IL-6 are proposed as possible predictors of cognitive decline. During the inflammatory process the highly sensitive C-reactive protein (hs-CRP) is produced.<sup>16-19</sup> IL-6, a proinflammatory cytokine, is found to be a more sensitive marker and CRP to be a secondary “downstream” marker.<sup>15</sup>



Possible pathways depicting the influence of diet and exercise on cognition (See reference #5)

## Botanicals and Natural Compounds that Promote Cognitive and Brain Health



### Bacopa (*Bacopa monnieri*)

Bacopa, used for centuries in Ayurvedic medicine, is recognized for its benefits to enhance memory and learning and as a sedative. Indian Yogis were said to drink Bacopa tea before meditation to relax the brain and facilitate a deep, relaxed state of consciousness.

Bacopa is rich in steroidal saponins, bacosides A and B, which help modulate the HPA axis and protect the hippocampus, a key area of the brain involved with short-term memory. Bacosides are found to enhance nerve transmission. Bacopa supports GABA production, which has a calming effect on the brain, enhancing the ability to concentrate and retain information. Bacopa is neuroprotective, enhances cognition and memory and can benefit those with memory loss.<sup>20</sup>

Studies find that Bacopa extracts scavenge free radicals and help prevent aluminum neurotoxicity.<sup>20</sup> An extract of Bacopa, bacoside A, is reported to prevent neuronal apoptosis and protect the mitochondrial membrane from structural and oxidative damage during cigarette smoking.<sup>21,22</sup>



### Ginkgo (*Ginkgo biloba*)

With a history of medicinal use dating back to 2800 BC, Ginkgo was traditionally used to relieve cough and asthma. Modern research focuses on Ginkgo's unique ability to increase cerebral blood and oxygen flow and to protect and enhance brain health. Studies report that Ginkgo extract is a powerful antioxidant with anti-inflammatory and neuroprotective qualities.<sup>23</sup> Evidence suggests that long-term administration of Ginkgo extract improves selective attention, executive processes and long-term memory for both verbal and non-verbal content.<sup>24</sup> It is reported to improve episodic memory in those with mild cognitive impairment.<sup>25</sup>

Ginkgo is found to protect brain cells during a stroke and to reduce brain damage after stroke.<sup>26</sup> Ginkgo extract suppresses amyloid-B toxicity which contributes to neuronal degeneration.<sup>27</sup> A study with mice found Ginkgo helped reduce copper-induced neurotoxicity in Parkinson's by reducing overall copper content.<sup>28</sup>

Ginkgo is high in flavonols, which exert complex activity including well-established antioxidant effects. It is especially high in the flavonol quercetin, which is found to reduce memory and learning impairment in rodents with cerebral ischemia.<sup>5</sup>



### Rosemary (*Rosmarinus officinalis*)

Traditional European herbalists called Rosemary the "Herb of Remembrance". They valued it as a tonic for the heart, brain and nervous system. It was used to increase circulation, mental outlook and vitality. Rosemary has also been valued to calm anxiety, alleviate tension and depression and help promote sleep. Dr. Rudolf Weiss, highly regarded as the founding father of German phytotherapy, used rosemary extract to treat cerebral arteriosclerosis.

Rosemary possesses powerful antioxidant activity, containing numerous antioxidant compounds that are neuroprotective, hepatoprotective and anti-inflammatory. It contains at least six phenolic diterpenoids with antioxidant activity. The most potent of these is carnosic acid which transforms into another antioxidant compound called carnosol while it quenches free radicals. This transformation or cascade of antioxidant activity repeats several times. Rosemary inhibits ROS-induced mutagenicity and cell mediated oxidation of low-density lipoproteins (LDL).<sup>29,30</sup>

Rosemary also contains significant amounts of the phenolic acid, rosmarinic acid. This is a water-soluble antioxidant that scores extremely high on the ORAC (Oxygen Radical Scavenging Activity) analysis, a method used to measure dietary antioxidant capacity of substances. Rosmarinic acid is anti-inflammatory, inhibiting COX-2.<sup>31</sup> Some of Rosemary's other antioxidants including limonene, terpinene and thymol, are shown to inhibit aging of the brain acting through acetylcholinesterase inhibition.<sup>32</sup>



### Gotu Kola (*Centella asiatica*)

Gotu Kola is highly esteemed as a powerful restorative tonic known as a Rasayana in Ayurvedic medicine. In this ancient tradition, Gotu Kola is long-recognized as a brain tonic and is used to improve memory, cognition and brain function. In modern times, Gotu Kola is found to increase brain levels of GABA, thus inhibiting the uptake of glutamate by the brain<sup>33</sup> and exerting a relaxing influence on the nervous system.

A recent study found that one of the main triterpenes in Gotu Kola dramatically reduced the build-up of amyloid plaque.<sup>34,35</sup> It is found to be beneficial in cases of cerebral ischemia.<sup>36</sup> Water extract of Gotu Kola is found to be neuroprotective and to enhance mitochondrial function in the brain. This is attributed to its ability to enhance GSH (glutathione), thiols and antioxidant activity in the brain.<sup>37,38</sup>



Gotu Kola shows a significant neuroprotective role in calming oxidative stress and reactive oxygen species in the corpus striatum and hippocampus with possible benefit to slow the neurodegenerative changes that occur with aging including Parkinson's disease.<sup>39</sup> Gotu Kola is also rich in flavonoids, including quercetin, fatty acids and phytosterols.<sup>40</sup>

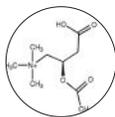


### Chinese Salvia (*Salvia miltiorrhiza*)

Known as Dan Shen in Chinese medicine, Salvia is one of the "shen" or spirit herbs that can be safely used long-term with multiple benefits. Traditionally used to nourish the blood and invigorate blood circulation it is also valued as a restorative tonic.

One of its constituents, salvianic acid, is being researched for neuroprotective and antioxidant activity. Another constituent, salvianolic acid, exhibits a protective effect on brain injury, enhances cognitive performance<sup>41</sup> and is found to improve brain mitochondria.<sup>42</sup> In one study, the antioxidant activity of salvianolic acid is found to exceed that of Ginkgo extract and, like Ginkgo, shows promise in treating oxidative damage-derived neurodegenerative disorders.<sup>43</sup>

In a study where 52 of 106 patients with ischemic stroke/TIA were given a Salvia herbal formula, blood levels of C-reactive protein (an inflammatory marker) decreased significantly. The researchers concluded that Salvia can reduce risk for stroke recurrence through its anti-inflammatory effects.<sup>44</sup>



### Acetyl-L-Carnitine

Acetyl L-carnitine (ALC), a derivative of the amino acid L-carnitine, exerts specific influence on brain and cognitive function. Synthesized in the brain, liver and kidney by the enzyme ALC-transferase, ALC crosses the blood-brain barrier more effectively than L-carnitine.<sup>3</sup> ALC provides acetyl-compounds essential for the production of acetylcholine and is found to increase levels of the precursors for phospholipid metabolism.<sup>3</sup> This makes it a potentially synergistic companion with phosphatidyl serine.

Studies on animals show that ALC improves age-related cognitive dysfunction and neurodegeneration and decreases oxidative damage and lipid peroxidation in the brain.<sup>45</sup> ACL effectively enhances neuronal function, benefits repair from neuronal damage and helps stabilize the mitochondrial membrane of neurons.<sup>46,47</sup> ACL is neuroprotective particularly to dopaminergic cells in relation to drug toxicity but also in aging rat brains.<sup>47,48</sup>

ACL benefits ischemia and reperfusion of the brain. Cerebral ischemia disrupts normal respiration at the cellular level in the mitochondria. Testing for safety and efficacy in early stages of AD, dementia and vascular dementia gave

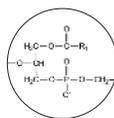
encouraging results. Clinical improvement as measured by neuropsychological tests was significant.<sup>49</sup>



### *Polygala tenuifolia*

This herb has been used in Chinese medicine (where it is known as Yuan Zhi) to help calm the "shen" or spirit (mind) and nourish the heart. Recent studies indicate that Polygala root extract supports cognition and memory and exerts neuroprotective benefits.<sup>50-54</sup>

Polygala root extract is found to inhibit cholinesterase activity and can enhance cholinergic neurotransmission. Polygala extract passes through the blood-brain barrier where it is thought to improve cognitive ability through influencing the cholinergic system.<sup>55</sup>



### Phosphatidylserine

Phosphatidylserine (PS), a phospholipid, is a main component of cellular membranes and is highly concentrated in the brain. The two main constituents of cell membranes are proteins and phospholipids. Phospholipids play an essential role in cellular communication and facilitate signal transduction – the transfer of biochemical messages into the cell, which activates cellular response.<sup>56</sup> PS regulates several signaling proteins in the cellular membrane.<sup>57</sup> It is vital to the structure and function of healthy neurons and influences membrane fluidity which is essential for neurotransmission.<sup>58,2</sup>

Multiple clinical trials and human studies in the United States and Europe demonstrate that PS supplementation supports memory, learning, verbal ability, adaptability and concentration. Clinical studies demonstrate its ability to improve learning and memory-related tasks.<sup>57</sup> In a double-blind, placebo-controlled study, Japanese subjects reported improved cognitive performance and memory function after six months of taking phosphatidylserine.<sup>59</sup>



### Saffron (*Crocus sativus L.*)

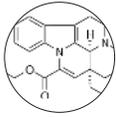
Saffron has been highly valued as a medicinal and food spice for millennia. Saffron is rich in carotenoids, which impart its red-orange color. In Chinese medicine it is known to enhance blood circulation and oxygenation with a slightly warming effect. Studies show Saffron to be a potent cell oxygenator that scavenges free radicals. Saffron extract is found to exert a positive benefit on learning and memory<sup>60</sup> and demonstrates neuroprotective ability.<sup>61</sup>



### Black Pepper

Black pepper is widely known for its ability to enhance the bioavailability of herbs and nutrients.

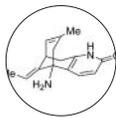
In Chinese and Ayurvedic medicine it is added to formulas for its ability to “move” other compounds, which allows them to be carried throughout the body. Piperine, an active alkaloid of Black Pepper, has been studied for its influence on memory and performance, and for its neuroprotective ability. It is found to improve impaired memory and neurodegeneration in the hippocampus. This is attributed to its ability to decrease lipid peroxidation and to inhibit the acetylcholinesterase enzyme. Piperine has neurotrophic effects on the hippocampus.<sup>62</sup>



### Vinpocetine

Vinpocetine is a semisynthetic derivative alkaloid from the Periwinkle plant (*Vinca minor*). Considered safe for long-term use, it is widely used to enhance vasodilation and memory.<sup>63,64</sup> Vinpocetine is considered a powerful vasodilator as it relaxes vascular smooth muscle. Studies show that it enhances cerebral blood flow.<sup>65</sup> Chronic cerebral hypoperfusion is a key issue in many types of dementia and other brain conditions from mild cognitive impairment to stroke. Useful for treatment of cerebrovascular and memory disorders, vinpocetine protects nerves by increasing brain vascularization.<sup>66</sup>

Vinpocetine also strongly inhibits neuro-inflammation.<sup>66</sup> Found to be neuroprotective, providing anti-inflammatory and antioxidant activity, vinpocetine could be useful to support recovery from cerebrovascular conditions.



### Huperzine A

Huperzine A demonstrates neuroprotective qualities and exhibits anticholinesterase activity.<sup>71-73</sup> It is well-recognized for its potent acetylcholinesterase (AChE) inhibitory effect. Neuroprotective against hydrogen peroxide, beta-amyloid protein, glutamate, ischemia and apoptosis with ability to modulate oxidative stress, the therapeutic effects of Huperzine A are thought to be multi-faceted.<sup>70</sup>



### Tinofolin® (*Tinospora cardifolia*)

*Tinospora cordifolia* is a highly revered and extensively used herb in the Ayurvedic tradition. In classical Ayurvedic texts, it is described as a rejuvenator with the ability to encourage youthfulness, vitality, and longevity.<sup>74</sup> It is used in Ayurveda as a tonic associated with inflammation and allergies, neurological function, and glucose metabolism, and it is traditionally well-known for its anti-stress activity.<sup>75-76</sup>

*Tinospora cordifolia* is of significant interest to modern researchers. A variety of active compounds have been derived from the plant including alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides. Research suggests *Tinospora cordifolia* possesses memory and cognition

improving abilities. The efficiency of the plant was studied in human subjects to improve cognitive parameters. Healthy volunteers (n=30) of age 18-30 years received Tinofolin® (*Tinospora cordifolia* extract, 500 mg) or a matching placebo for 21 days in a double-blind, randomized, and placebo-controlled study. Learning and memory were assessed by subjecting the volunteers to a battery of psychological tests that aimed at studying visual memory, logical memory, verbal memory, attention span, and concentration. The results showed that the consumption of the extract augmented the verbal learning, and memory and logical memory (of immediate and short-term type) compared to placebo.<sup>77</sup> The mechanism of action has been predicted to be through modulation of neurotransmitter balance, resulting in a more active and receptive brain.

*For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please contact email info@naturaedu.com.*



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