

ENERGY + MIND COFFEE

white paper provided by Archmore Botanical Research Group, LLC

*A Javita
International
product*



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ENERGY + MIND COFFEE

a Javita International product

- Technical overview outlining the safety and efficacy of Energy + Mind Coffee, a dietary supplement designed to support healthy brain function and improve mental capacity and energy.*
- This technical white paper will include:
 - Formulation breakdown
 - Synopsis of health benefits associated with the proprietary ingredients
 - Efficacy
 - Cellular, animal, and human trials demonstrating benefits for brain support and mental energy
 - A review of any negative outcomes found in trials using these ingredients
 - Potential secondary health benefits outside the scope of mental wellness
 - Safety
 - In vitro and in vivo trials demonstrating the safety of ingredients in Energy + Mind Coffee at recommended levels
 - A review of any adverse events associated with these ingredients
 - Recommended guidelines for use
 - Dosing recommendations for brain support and mental energy
 - Potential adverse events and warnings

**These statements have not been evaluated by the Food and Drug Administration and are meant for research purposes only.*



Overview of Product

Ayurveda is a system of Hindu traditional medicine native to the Indian subcontinent that dates back over 3000 years. The origins of Ayurveda describe magical cures for disease, most including the use of herbal medicines, minerals or metal supplementation, surgical techniques, opium, and applications of oil by massages. Although considered magical or mystical at one time, many of these therapies have been intensively studied by modern science and observed to have specific mechanisms of action in the body, confirming their benefits. Two of these herbal remedies are among the most widely known in Ayurveda, and thus have the most scientific research behind them. They are *Bacopa monnieri* and *Centella asiatica*, also referred to as Gotu Kola. It was for these widely known and well-researched benefits that Javita utilized such powerful herbs when formulating Energy + Mind Coffee, a product designed to support brain function while improving mental energy and focus.

This white paper will walk through the history of use of these plants which lead scientists in pursuit of validation using modern research techniques. This paper will present and evaluate available research, from cellular to animal models and finally human clinical trials. A detailed description of the mechanisms by which these herbs work in the body will be discussed along with the outcomes of clinical trial. Safety will also be reviewed along with dosing recommendations for the benefits described for Energy + Mind Coffee. Any adverse events noted in clinical trials or potential negative outcomes from supplementation with these herbs will also be addressed. Finally, any potential warnings for this product will be addressed.



Formulation Overview and Breakdown

Energy + Mind Coffee was designed to bring additional mental health benefits to the average coffee drinker. Aside from being a blend of South American estate-grown Arabica and Robusta coffee beans, Energy + Mind Coffee contains two Ayurvedic herbal ingredients to stimulate the mind and provide neuroprotective benefits for brain support. These herbs are *Bacopa monnieri* and *Centella asiatica*, referred to in this paper as Gotu Kola. Together, these powerful nootropic herbs assist in improving focus and memory, reducing stress and anxiety, decreasing fatigue and depression, and preventing long-term cognitive decline.

- Formulation includes two key herbal ingredients for enhanced efficacy of the coffee
- *Bacopa Monnieri* provides bacopasides/ bacosides for neuroprotection which function in multiple ways:
 - Act as an antioxidant for enhanced memory and focus
 - Inhibit acetylcholinesterase for neuroprotection
 - Modulate neurotransmitters such as GABA, promoting well-being and reducing anxiety
- Gotu Kola contains triterpenoid compounds: asiaticoside, madecassoside, and madasiatic acid which:
 - Act as a specifically targeted antioxidant and anti-inflammatory in the brain, promoting neural health and improving memory and focus
 - Modulate β -amyloid peptide to improve cognitive decline associated with disease
 - Improve microcirculation for enhanced blood flow through cerebral tissues



Bacopa monnieri- Background Information

Bacopa monnieri is a creeping herb native to wetlands throughout southern India, but has been found throughout much of the world. Known in Ayurveda as Brahmi, *Bacopa monnieri* is a powerful herb used safely for over 3,000 years in this Hindu medicine. It is through this branch of medicine that Bacopa was first used as a neurological tonic and cognitive enhancer. However, it has since been studied more extensively through modern medical research for its nootropic effects and confirmed safe for use in humans.

Bacopa monnieri has been shown to provide mental health benefits for everyone undergoing the normal process of aging, for example, improvement in cognitive focus and memory. These benefits may also be reaped by those unconcerned with aging but simply looking to improve their retention of information. Research shows that *Bacopa monnieri* increases cerebral blood flow, thereby stimulating brain activity. This increased blood flow has also been shown to improve more serious conditions such as dementia [1]. This may be one mechanism by which this herb improves working memory and free recall, as noted in several human clinical trials. This benefit is seen in healthy elderly subjects but also in children with ADHD, where attention was markedly improved. These trials will be discussed later in this white paper.

In addition, the neuroprotective benefits of *Bacopa monnieri* have been shown in individuals with more severe disorders of the brain, i.e. Alzheimer's, epilepsy, Parkinson's disease, and schizophrenia. Much data point to Bacopa's antioxidative potential in the brain as the primary mechanism for neuroprotection. By protecting the brain from oxidative stress, many of these conditions may be prevented or symptoms reduced. Although these are severe conditions, the mechanisms by which Bacopa functions have been confirmed in healthy individuals as well, providing proof that the neuroprotective effects can be applied to all.

An unfortunate side effect of cognitive decline is anxiety or depression. *Bacopa monnieri* first addresses the memory decline itself, improving memory and retention of information through neuroprotection and antioxidation. But it has also been shown to reduce the associated anxiety and depression directly, a win-win for those taking Energy + Mind Coffee.

Bacopa monnieri has also been shown to inhibit acetylcholinesterase. As part of a complicated biochemical pathway, this inhibition has been used to treat neuropsychiatric symptoms of diseases like



Alzheimer's and Parkinson's, where apathy and dementia are common. This mechanism aids in reversing these conditions.

Epilepsy is another serious yet common condition that dramatically affects the brain and can have significant long term detrimental effects on cognitive functions. In epileptics, neurotransmission is altered mainly due to GABA receptors. *Bacopa monnieri* acts as a neurotransmitter modulator, specifically targeting GABA receptors, as documented in cellular and animal trials. It has been shown to improve neurotransmission to near control levels while also suppressing seizures in animal. This profound finding not only benefits the large numbers of individuals suffering from epilepsy, but can be applied to healthy individuals as well, for everyone has GABA receptors. By positively modulating these neurotransmitters, Bacopa may aid in alleviating depression and promote feelings of well-being due to the dopaminergic pathway that is dependent upon proper functioning of GABA receptors.

At the dosages used in Energy + Mind Coffee, *Bacopa monnieri* provides safe nootropic benefits, positively energizing the mind, improving feelings of well-being, and supporting neuroprotection through antioxidation for improved memory and focus.



Gotu kola- Background Information

Gotu kola, commonly referred to as or Asian pennywort or by its botanical name *Centella asiatica*, is a creeping plant that grows in low lying wetland areas of Asia and the Indian subcontinent. It is typically consumed raw by the people of Malaysia. For centuries Ayurvedic medicine has used Gotu kola for memory disorders as well as to slow down brain aging and help in regenerating neural tissues. Medhyarasayanas, as they are referred to in Ayurveda, represent herbal therapies that boost memory, restore cognitive deficits and improve mental functions. Both Gotu kola and *Bacopa monnieri* are considered Medhyarasayanas. After centuries of use, modern medicine has looked to Gotu kola as an origin for drug development, particularly in the areas of treating and preventing serious cognitive conditions, such as Alzheimer's disease and Parkinson's disease. Since two of the licensed drugs used for Alzheimer's are based on natural products, it is not surprising that research of natural remedies continues to persist. Modern medicine has identified several mechanisms of action for this herb, including decreasing oxidative stress and inflammation, preventing amyloid plaque formation (as seen in Alzheimer's disease), reducing anxiety and depression, and improving microcirculation [2].

As a brain tonic, research has shown the majority of benefits stem from Gotu kola's powerful antioxidant and anti-inflammatory properties. Numerous in vitro and in vivo trials demonstrate this. Several animal and human studies carry these conclusions a step further, citing that through antioxidation, Gotu kola improves memory and cognition. This is an interesting finding, as antioxidants are touted for their protective benefits throughout the body, preventing damage to critical tissues and prolonging longevity. It is astounding to learn that by protecting the delicate tissues and neurons of the brain, non-tangible functions such as memory and learning are directly benefited. A detailed analysis of these studies will follow in this white paper.

In addition to cognitive function and neuroprotection, Gotu kola is known for improving microcirculation. Microcirculation includes not just blood flow but also the health of the capillaries themselves, benefiting blood flow throughout the delicate tissues of critical organs. Gotu kola has been shown in multiple human clinical trials to improve microcirculation for those with venous insufficiency as well as healthy individuals.



When taken as a whole, the benefits of Gotu kola and their mechanisms of action demonstrate the power of this herbal ingredient: improving memory, concentration, and focus, while reducing depression and anxiety, particularly anxiety associated with cognitive stress. Through microcirculatory increases, as well as ATP-ase stimulatory activities, Gotu kola naturally increases mental energy. It also has a significantly long history of safe use as well as prolific number of trials with minimal adverse events, making this an exceptional herbal ingredient for Energy + Mind Coffee.



Formulation Efficacy- A Detailed Review of Available Studies

Research suggests multiple mechanisms by which *Bacopa monnieri* and Gotu Kola affect the brain and mental capacity. Outlined below are those conclusively defined in available peer reviewed literature. As these particular herbs have a significantly long history of use, some research will be categorized and summarized to reduce redundancies seen in trials. All research is cited should further reading be desired.

- *Bacopa Monieri*
 - Supports neuroprotection through antioxidation for improved cognitive function
 - Antioxidation leads to anti-inflammation, increased cerebral energy metabolism, and increased cerebral blood flow
 - Mechanism by which memory and focus are improved
 - Inhibits acetylcholinesterase which may aid in ameliorating neurodegenerative disorders associated with serious cognitive decline
- Gotu Kola
 - Potent antioxidant protecting memory from decline associated with oxidative stress
 - Decreases anxiety and depression particularly associated with mental stress
 - Improves microcirculation for improved mental energy and venous insufficiency

In addition to the nootropic benefits outlined above, these herbs have been shown to be affective in alleviating symptoms associated with serious cerebral disorders, namely epilepsy, Alzheimer's, Parkinson's disease, and schizophrenia. The particular mechanism by which *Bacopa monnieri* assists in this capacity is through neurotransmitter modulation, specifically with regards to GABA and dopamine, while Gotu kola mainly acts as an antioxidant providing similar outcomes.

Gotu kola also has significant secondary benefits, positively affecting diabetic symptoms, metabolic syndrome, fibroids, and topical wound healing abilities, which are outside the scope of this review.



Bacopa monnieri- Mechanisms of Action

Mechanism of Action: Neuroprotection Through Antioxidation

Bacopa monnieri has long been known as a nootropic, a product that improves one or more aspects of mental function. Much research in this area has been conducted confirming these effects. In recent years, scientists have proven repeatedly that Bacopa has significant antioxidant potential in the brain, assisting in the prevention of neurological damage caused by free radicals, aging, and disease [3].

In order to test the hypothesis that *Bacopa monnieri* protects the brain from oxidative stress, several neurotoxic compounds were selected and administered to animals under controlled conditions. Researchers selected three in particular in a series of trials. These compounds are acrylamide, known to cause neuropathy and associated neurological defects yet is widely used in multiple chemical and industrial applications; acrylamide, a manufacturing compound used in the production of paper, dyes, and wastewater treatment; and 3-nitropropionic acid, a mycotoxin, found in fungi and some foods like fermented products in Asia. In all studies, *Bacopa monnieri* showed neuroprotective properties, significantly protecting against oxidative damage caused by these toxic compounds [4, 5, 6, 7].

A follow up study tested Bacopa against paraquat, a toxic herbicide linked to the development of Parkinson's disease. This compound was used to induce oxidative stress and neurological damage in mice, who were supplemented with *Bacopa monnieri* or placebo. After 4 weeks, mice treated with Bacopa showed a significant reduction in oxidative markers in the brain. It was noted that the first 48 hours of exposure to paraquat showed the most significant oxidative stress in the control group, but Bacopa acted prophylactically, protecting the brain from this onslaught of oxidative stress. Therefore, it was reconfirmed that Bacopa may be an excellent preventative aid for neurological dysfunctions that may be a result of oxidative stress [8].

Although we are all bombarded with free radicals daily and undergo much oxidative stress through the natural process of aging, certain medical conditions and diseases exacerbate this stress and thus lead to more rapid cognitive decline. These conditions include diabetes, epilepsy, Alzheimer's, and Parkinson's disease to name a few. In a study using diabetic animals, researchers found that *B. monnieri* modulates antioxidant activity in the cerebrum, cerebellum, and midbrain, enhancing defense against damage caused by free radicals associated with diabetes [9].



Antioxidation in the brain can also lead to other significant benefits, such as anti-inflammation, and *B. monnieri* has been linked to this benefit as well. Supplementation with *B. monnieri* has been shown to protect against age-related cognitive disorders and complications associated with neuroinflammation [10].

Bacopa monnieri was found to have a particular active constituent called bacopaside 1. In animal studies, this compound was shown to increase antioxidant levels in the brain while simultaneously improving cerebral energy metabolism and blood flow. Researchers concluded that benefits play a role in protecting the brain against injury caused by cerebral ischemia, i.e. the restriction of blood supply to the brain [11]. For those not at risk for ischemia, an increase in cerebral energy metabolism and blood flow reap the benefits of enhanced mental energy due to the influx of oxygenated blood to this vital organ system.

Therefore, *Bacopa monnieri* functions as a powerful antioxidant, specifically targeting delicate tissues in the brain. By acting in this capacity, *B. monnieri* is able to protect the brain from oxidative stress and tissue damage that occur through the normal aging process but that also occur in higher frequency under disease conditions or injury. In addition, by improving cerebral energy metabolism and blood flow, neurological functions and mental energy are improved.

Mechanism of Action: Inhibits Acetylcholinesterase

Although the main mechanism by which *Bacopa monnieri* protects the brain is through antioxidation, a secondary mechanism is the suppression of acetylcholinesterase activity. Acetylcholinesterase (AChE) is a hydrolase that hydrolyzes (or breaks down through the addition of water) the neurotransmitter acetylcholine. Research has shown that by suppressing the activity of AChE, *B. monnieri* protects neurons from beta-amyloid-induced cell death. In addition to the reduction in oxidative stress, prolongs the life span of the neurons. [12]. In other words, *B. monnieri* assists in slowing down the aging process in the brain.

Mechanism of Action: Neurotransmitter Modulation (GABA)

Several studies have analyzed the affect of *Bacopa monnieri* on modulating GABA, the main neurotransmitter in the mammalian central nervous system. This neurotransmitter assists ions to cross



membranes, maintaining balance in synapses of the brain - when this balance is upset, negative outcomes occur, including depression, anxiety, and even seizures. Therefore, maintaining this balance is key. In conditions such as epilepsy, GABA receptors are greatly diminished, disrupting the balance and causing seizures on a regular basis. In multiple studies, epileptic models have been used to determine *B. monnieri's* effect on reversing this condition. Multiple studies have confirmed that *B. monnieri* significantly increases GABA receptors to control levels and thus has therapeutic applications for epilepsy management [13, 14]. This balance should also result in a reduction of anxiety and depression, as is noted in clinical trial [15, 16].



Bacopa monnieri: Efficacy in Trials

While reviewing the underlying mechanisms by which *Bacopa monnieri* works is enlightening, confirming these mechanisms in the body is more critical to understand its use in Energy + Mind Coffee. Bacopa has been shown to be a potent nootropic for centuries, while modern science has confirmed its positive benefits in the area of memory retention, delay in long term cognitive decline, improved focus and attention, and reduction of stress and anxiety.

Memory, Focus, Attention, and Delay in Cognitive Decline

The majority of Bacopa research has focused on memory, improving and retaining it while also preventing cognitive decline. These studies have demonstrated a wide gamut of benefits, some conducted in healthy individuals but the majority in those with compromised health, either from Alzheimer's, ADHD, or aging. In these severe cases, more pronounced results can be seen, and conclusions applied to healthy individuals as well.

Alzheimer's disease (AD) is a condition frequently studied in conjunction with *Bacopa monnieri* due to the positive outcomes this herb achieves- researchers have been searching for both symptom alleviation as well as prevention of this devastating disease. *B. monnieri* has been shown to increase expression of sodium- and potassium-ATPase which is diminished in AD conditions. This in turn reverses memory impairment and improves memory performance [17, 18, 19]. These results suggest the therapeutic potential of this powerful herb for preventing and possibly reversing cognitive decline. These sentiments have been echoed in multiple clinical trials involving Alzheimer's patients as well as animal models representing AD, where research showed improvement in memory and cognitive performance through supplementation of Bacopa monnieri. For example, the deleterious effects of AD may be portrayed as senile dementia. This dementia can be prevented or reversed with the treatment of bacosides, according to Rastogi et. Al [20]. Improving cerebral blood flow also seems to reverse or forestall dementia [21]. Although not completely convinced of its ability to prevent, Apetz et.al found, through their secondary research, this herb's ability to delay the onset of Alzheimer's disease, concluding that science may one day prove this herb a possible remedy for this condition [22].

Similar benefits may be applied to healthy individuals. In a 12-week study involving fifty-four (54) participants 65 or older, without clinical signs of dementia, *B. monnieri* improved delayed word recall



memory scores compared to placebo. They also noted that depression, anxiety, and heart rate all decreased in the treated group, while all parameters increased in the placebo group. This indicates that *Bacopa monnieri* improves memory recall and reduces stress and anxiety in aging individuals [23]. In a slightly larger trial involving sixty (60) healthy participants with a mean age of 62.62 years, a low and high dose of *B. monnieri* were compared. Both doses improved attention, cognitive processing, and working memory compared to placebo. This was measured by observing the reduced time interval between stimulation and response, indicating heightened attention. This trial demonstrates that even at a low dosage, Bacopa is a powerful cognitive enhancer in healthy individuals [24].

These same results are observed in healthy participants of younger age. In a large trial involving eighty-one (81) healthy adults of varying ages, researchers observed improved verbal learning, memory acquisition, and delayed recall memory when supplemented with extracts of *B. monnieri* [25]. A second cross-over design trial measured a high and low dosage of *B. monnieri* in younger participants. This study showed improved performance when faced with a cognitively demanding series of tests; results were seen for both low and high dosages and for individuals of all ages [26]. In a review of nine different trials using 518 healthy subjects, an improvement in cognition was seen across the board for *B. monnieri* compared to placebo. This also included a decrease in choice reaction time, a measurement of heightened cognitive performance [27]. These plentiful results demonstrate the benefits of *Bacopa monnieri* for improving memory and cognitive performance, protecting against age-related cognitive decline, and reversing some of the negative side effects of the aging process.

Reduces Stress and Anxiety

A beneficial side effect noted in these trials was the reduction of stress and anxiety when participants consumed *B. monnieri*. This benefit became a point of interest for further investigations. Researchers found that in addition to positive cognitive effects, this herb also reduces stress associated with multi-tasking while improving mood and reducing cortisol levels [28]. In two separate clinical trials, healthy participants were subjected to various activities with and without *B. monnieri* supplementation. Memory functions and anxiety levels were measured. Supplementation with this herb decreased anxiety and stress while improving retention of new information, while all parameters increased in the placebo groups [29, 30]. Both age-related and disease-induced cognitive decline have been linked to heightened anxiety. *Bacopa monnieri* improves and reverses the decline itself, but it also diminishes the associated



anxiety and stress [31]. It may be a beneficial supplement for those feeling stress and anxiety associated with normal age-related memory loss or mental anxiety.



Bacopa monnieri- A Review of Negative Outcomes From Clinical Trials

Research shows the immense positive benefits of *Bacopa monnieri*; however, it must be noted that some trials have reported a lack of benefit from this herb. In a meta-analysis of six studies using three different dosages of *Bacopa monnieri*, improved memory recall was indeed observed. However, analysts noted that there was little evidence of enhancement in any other cognitive domains using these six trials. They noted that this lack of result may be due to the inconsistent measures employed by studies across these particular cognitive domains. Loosely translated, the six trials did not have enough overlap in the points they measured to show statistically significant improvements. This has more to do with trial design than the efficacy of the herb itself. Therefore, the analysts urged for continued research using similar measuring points [32].

Finally in a trial involving seventy-six (76) healthy adults between the ages of 40-65 years, memory was positively affected by *B. monnieri* in terms of retention of new information. However, rate of learning was unaffected, as were tasks assessing attention, verbal and visual short-term memory, and the retrieval of pre-experimental knowledge. While this appears to be a lack of benefit from *B. monnieri*, researchers concluded that this herb does in fact decrease the rate of forgetting newly acquired information, as evidenced by these results [33]. In terms of students or professionals needing to retain new information, Bacopa seems to be the herb of choice.

Therefore, the immense clinical evidence and minimal lack of benefit results offer conclusive proof of the cognitive enhancing effects of *Bacopa monnieri* and justify its inclusion in Energy + Mind Coffee.



Gotu kola (*Centella asiatica*)-Mechanisms of Action

Mechanism of Action: Cognitive Improvement Through Antioxidation and Anti-Inflammation

Although not commonly known, antioxidation and cognitive function are directly correlated. In fact, there is a specific model used to test this close relation. It involves d-galactose induced neurotoxicity to measure age-related oxidative damage and memory impairment [34]. As inflicting neurotoxicity is not permitted on human subjects, animals must be used in these studies. Three separate animal studies demonstrate improved memory and increased retention of new information. Researchers in all three trials measured the antioxidative effects of Gotu kola and cited this as the reason for the benefit [35, 36, 37]. These same results are seen in dose-dependent studies where low, medium, and high doses of Gotu kola were tested to determine if increased dosages corresponded to increased cognitive function. A dose-dependent increase in cognitive behavior was observed, indicating that low doses of Gotu kola still improve cognitive function, but that higher doses have a more pronounced effect [38]. All doses used in this study correspond to those in Energy + Mind Coffee, with the higher doses relating to two-three cups of coffee per day.

In subjects with Parkinson's disease (PD) or Alzheimer's disease (AD), a high oxidative stress level is observed. Therefore, Gotu kola has been tested repeatedly in PD and AD animal models to determine if its antioxidative properties are strong enough to combat the symptoms and delay the onset of these devastating conditions. The neuroprotective benefits of this herb were observed, including improved locomotor dysfunction and protection of dopaminergic neurons through antioxidant activity [39]. This antioxidation also protects against mitochondrial damage, another classic symptom of PD [40]. In AD models, Gotu kola significantly attenuated memory impairment and oxidative damage [41].

Anti-inflammation is critical in the brain when a stroke or head injury has occurred. In these cases, levels of pro-inflammatory cytokines damage cerebral neurons, in many cases resulting in neuronal apoptosis, or cell death. By administering madecassoside from Gotu kola, researchers saw a significant reduction in neuronal apoptosis along with a reduction in the levels of the pro-inflammatory cytokines, confirming the neuroprotective effect of Gotu kola on damaged brain tissues [42]. Identical results were found when using the other major triterpenoid found in Gotu kola, asiaticoside [43].

Mechanism of Action: Modulates β -Amyloid Peptide



An increase in the β -amyloid peptide is associated with cognitive decline and disorders such as Parkinson's disease and Alzheimer's disease, as this peptide can form plaques in the extracellular matrix [44]. Extracts from Gotu kola have been shown to decrease levels of this peptide in the hippocampus of Alzheimer's animal models, which then positively impacts the amyloid cascade, modulating components of the oxidative stress response that have been implicated as a main cause of changes in Alzheimer's patients [45]. For those healthy individuals concerned with this condition, Gotu kola may be a beneficial preventative agent.

Mechanism of Action: Improves Microcirculation

Microcirculation is blood flow through the smallest of blood vessels that are present in the vasculature of organ tissues. This is different than blood flow to and from the organs themselves and is critical for the health of the tissues of vital organs such as the brain. Microcirculation is compromised due to diabetes, venous insufficiency, stroke, and other health conditions. Researchers have found that Gotu kola improves microcirculation and may assist in preventing the detrimental effects caused by this condition [46-50].

Mechanism of Action: Anxiolytic to Diminish Anxiety and Stress

Many herbs and herbal preparations are used for alleviating general anxiety and specific anxiety disorders. Much evidence supporting their use is circumstantial, thus a comprehensive review of the data has been conducted to determine which herbs truly contain anxiolytic properties. It has been determined that among these herbs, Gotu kola, along with herbs such as *Bacopa monnieri*, have shown significant anxiolytic effects. Gotu kola was found effective in treating healthy individuals with generalized anxiety, while Bacopa seemed to target those with cognitive decline, either due to the normal process of aging or disease [51]. A mechanism for this anxiolytic property is believed to be Gotu kola's ability to stimulate glutamic acid decarboxylase (GAD). This is a similar response in the body to stimulating GABA, both pathways reducing stress and promoting feelings of well-being. Extracts of Gotu kola were shown to stimulate GAD activity by over 40% at relatively low dosages [52]. These effects have been demonstrated in animals initially, where healthy non-stressed mice were subjected to acute stress in behavioral tests. In cases of both acute and chronic stress, improvement was seen in those mice supplemented with Gotu kola versus placebo. In addition there was a corresponding effect of Gotu



kola in relation to the amount of madecassoside and asiaticoside supplemented, indicating that it truly was the Gotu kola compounds providing the anti-anxiety benefits [53].



Gotu kola – Efficacy in Trials

While knowing the mechanisms of action is useful for understanding the role Gotu kola plays in the body, it is more critical to see these mechanisms in action. As this herb has been studied for centuries, there are several animal and human trials confirming the neurological benefits of Gotu kola.

Improved Memory and Focus

Much research confirms that the antioxidant and anti-inflammatory potential of Gotu kola is correlated to an improvement in memory and focus; therefore, it is most well-known for its ability to protect the brain from memory loss and improve retention and focus. Using a tiered dosing scenario, researchers determined that an increase in Gotu kola consumption was directly proportional to an increased retention of information and higher learning ability [54]. A similar study was conducted using only juvenile or young adult mice to determine the effects Gotu kola has on the developing brain. They saw significant improvement in cognitive performance, suggesting that Gotu kola can influence the neuronal morphology and promote higher brain function in youth [55].

An interesting study compared the benefits of meditative Yogic practices, well known for promoting concentration and learning, with Gotu kola supplementation in school-age children. After 3 months of intervention, it was interesting to note that the supplementation alone of Gotu kola had a marked improvement in short-term memory test and serial recall effects rather than Yogic practices or no intervention. They also noted that initial results were seen in the first couple of weeks, indicating that Gotu kola is quick to act in the body. The supplement was also very well tolerated by the children, with no reportable side effects, confirming its safe use at these levels even in young children [56].

Adults also reap the benefits of improved memory, recall, and focus. In a trial measuring doses ranging from 250mg to 750mg, Gotu kola was tested on adults for improving age-related cognitive decline. This is the normal decline as a result of aging and not a result of disease. All doses saw an improvement in mental function with the higher doses measurable improvements in working memory [57].

Anxiety and Depression

The anxiolytic actions of Gotu kola have been shown to be beneficial in animal models where animals were healthy and not exhibiting symptoms of cognitive decline. Researchers wanted to see if this stayed



true when healthy human participants with generalized anxiety disorder were supplemented with Gotu kola. Thirty-three (33) healthy males and females with an average age of 33 years were supplemented with Gotu kola orally for 60 days. Researchers observed a significant reduction in anxiety related disorders, reduced stress and depression, and an improved willingness for adjustment and cognition. These dramatic results confirm the anti-stress and anti-depression benefits of Gotu kola in healthy, young people [62].

However, it is not just the young that experience stress and depression and are in need of alleviation--it is also the elderly. Many studies have cited a reason for this age-related depression or anxiety is due to the cognitive decline most experience as a natural result of aging. Researchers tested the effects of varying doses of Gotu kola on twenty-eight (28) healthy elderly participants over 60 days. They, too, found an improvement in depression and overall mood, in addition to improved memory [63]. Therefore, it can be concluded that Gotu kola can alleviate symptoms of anxiety and depression associated with mental stress in most healthy individuals, young and old alike.

Microcirculation

In a double-blind placebo-controlled randomized study, patients suffering from venous hypertensive microangiopathy were supplemented with relatively low doses of Gotu kola (60-120mg daily). They were then tested for resting blood flow, venoarteriolar reflex, and the variation of flow related to a temperature increase. All tests showed significant improvement at both levels of Gotu kola treatment versus placebo with no side effects. This confirms the safe and successful use of Gotu kola for improving microcirculation [58]. In patients with venous hypertension, a condition of drastically reduced or compromised microcirculation, researchers tested varying doses of Gotu kola for their effect on capillary filtration rate, ankle circumference, and ankle edema versus normal subjects. The treated groups showed significant improvement over placebo with the best results appearing for a dose of 180mg/day. The placebo group showed no change at all. This again shows the microcirculatory benefits of Gotu kola at relatively moderate doses [59].

Microcirculation is compromised in diabetes. Therefore fifty (50) patients with diabetic microangiopathy were studied for the effects Gotu kola has on skin blood flow and venoarteriolar response. The latter was measured using transcutaneous measurements as well as capillary permeability evaluation, which is



the rate of ankle swelling. At a low dose of 60mg twice daily, there was a significant improvement in microcirculatory parameters in Gotu kola-treated patients versus placebo. It was concluded that Gotu kola protects against the deterioration of microcirculation due to diabetic microangiopathy [60]. These results were duplicated in a second study which also confirmed tolerability of the supplement, as there were neither dropouts nor side effects reported [61]. Again these improvements in microcirculation have a direct correlation to tissue health, including cerebral tissues, thereby improving neurological health and mental energy.

Secondary Benefits

While much of the anti-inflammatory effect targets neuronal tissues, it has been noted in clinical trials that oral supplementation with Gotu kola promotes anti-inflammation in joints with respect to arthritis, alleviating much of the negative conditions and discomfort. Some of this anti-inflammatory response was directly tied to the reduced expression of COX-2, demonstrating the potential future benefits of Gotu kola as an anti-arthritic therapy [64, 65].

Microcirculation may be compromised in healthy individuals when subjected to certain stressors, such as long flights or sitting for significant periods of time. In a study evaluating microcirculatory alterations associated with edema, passengers traveling for more than 3 hours by air were supplemented with Gotu kola 2 days prior to the flight, the day of the flight, and the day following the flight. The average age ranged from 30-50 years, and all individuals were considered healthy. Gotu kola significantly alleviated symptoms associated with edema due to its benefits on microcirculation and helped prevent all of the negative side effects associated with this stressor [66].



Safety

Energy + Mind Coffee was designed to be safe and effective for everyday consumption in healthy individuals. Targeting multiple functions of the brain, this coffee contains active herbal ingredients that have significantly long histories of use with minimal side effects. They have been used historically for improving mental capacity and protecting the brain from aging while imparting little to no harm in individuals. Modern testing techniques have confirmed the safety of these ingredients for oral use.

- Energy + Mind Coffee was designed such that a single cup daily could produce results, but that multiples cups would maintain the same safety parameters.
- All safety studies outlined below are relevant to the dosages recommended for Energy + Mind Coffee
- Adverse safety and toxicity trials are also reviewed



Bacopa monnieri- Safety

Bacopa monnieri represents an interesting case where a significantly long history of use deems it safe for human consumption. However, modern science dictates that certain safety criteria must be met in order to truly make this statement. Therefore researchers Neely, Walsh-Mason, et al. set out to design a multi-criteria decision analysis model to assess botanicals utilizing history of use data. After designing the model, they analyzed one of the oldest known botanical remedies: *Bacopa monnieri*. Following their unique scoring system, these researchers determined that the history of use scores for *Bacopa monnieri* fall within the target range and therefore does indeed qualify it for safe human consumption [67].

In addition, several dozen clinical trials, including trials on children, have been conducted [68]. The outcomes of these trials were discussed earlier in this white paper. However, it should be noted here that in most instances, no adverse events were reported with consumption of *Bacopa monnieri*, by adults or children, even at doses higher than those recommended with Energy + Mind Coffee [69, 70].

Adverse Events: A Review of Literature on Bacopa monnieri

Although *Bacopa monnieri* has a significantly long history of safe use and has been deemed safe for human consumption by modern science, there has been an instance of side effects in a clinical trial. In a study involving elderly individuals, 300 mg /day of *Bacopa monnieri* was supplemented for 12 weeks. Eighty one individuals completed the trial. Although memory parameters were improved over placebo, the Bacopa group noted minor gastrointestinal tract side effects. These included increased stool frequency, abdominal cramps, and nausea. These minor irritations were not severe enough for any of the 81 participants to discontinue to the trial [71].

In a separate single case study of a 64 year old female patient, hepatotoxicity was deemed a result of self-treatment with various Indian Ayurvedic herbal products for her vitiligo (loss of pigmentation in the skin). Patient was taking multiple tablets each with several Ayurvedic herbs, including one Brahmi tablet that may have contained *Bacopa monnieri* or *Eclipta alba*. Using the updated Council for International Organizations of Medical Science (CIOMS) scale for causality assessment, practitioners determined that the probable cause was a tablet containing *Psoralea corylifolia* leaves rather than the Brahmi tablet.

Therefore, hepatotoxicity from *Bacopa monnieri* has not been found [72].



In an animal study to determine the antifertility potential of *Bacopa monnieri* in male mice, researchers dosed animals with 250mg/kg body weight /day for 28 and 56 days. This is a dose several times higher than is used in healthy human subjects and particularly in Energy + Mind Coffee. At this high dosage, researchers were able to reduce motility, viability, morphology and number of spermatozoa, thereby reducing fertility. However, libido remained unaffected. After treatment withdrawal, all parameters recovered to control levels. Researchers concluded that at high doses, *Bacopa monnieri* may be an effective contraceptive in males, without producing apparent toxic effects. These results should not be seen even after consuming even multiple cups of Energy + Mind Coffee, due to the high dosage used in this animal study. Similar results have not been seen in any human clinical trials in the years since this publication [73].



Gotu kola- Safety

Gotu kola has a significantly long history of safe use in Ayurvedic medicine, a history with no known instances of toxicity at recommended levels [74, 75]. In fact, most of the studies showed relatively minimal side effects, mainly headache or minor stomach upset, and were extremely well tolerated by animals when administered orally. Several human clinical trials, including trials involving school age children, young adults, and the elderly, have been conducted with no reported side effects [76, 77, 78]. In clinical trials involving delicate cancerous tissues, Gotu kola was also shown to have a relative lack of systemic toxicity [79]. A toxic dose for asiaticoside from Gotu kola was not observed, even when animals were orally administered high doses of this single compound [80].

Adverse Events: A Review of Literature on Gotu Kola

There have been a handful of instances of contact dermatitis stemming from the topical use of the herb, but this is not seen when administered orally [81, 82]. Some research points to a sedative property of the herb at extremely high doses; these dosages are very difficult to achieve with the recommended consumption of Energy + Mind Coffee. However, care should be exercised if already taking anti-anxiety medication, as the sedative properties may be exacerbated [83].

In an animal trial, the antifertility action of Gotu kola was tested in male rats. Low, medium, and high doses of extract were fed to animals for 42 days. A decrease in serum testosterone levels was seen in all treatment groups as well as some degeneration of spermatogenic cells, including sperm count and motility. These are similar results to those seen with *Bacopa monnieri*; however, in that trial, all counts returned to normal upon discontinuation of the extract. This study did not carry the trial through to the same endpoint, thus returning counts to normal levels is not known for Gotu kola [84]. Similar findings have not been reported in more recent research, nor have these findings been reported in any human clinical trial.



Usage Guidelines

Mental stress, inability to focus, and trouble retaining new information are afflictions that trouble everyone at some time or another. Whether a university student studying for finals, or an adult forgetting the location of their keys, everyone has felt the stress associated with cognitive impairment. Energy + Mind Coffee was designed to improve focus and attention while enhancing memory and concentration. It will alleviate some of the anxiety and depression associated with mental stress and assist in bringing about an overall feeling of well-being. In terms of serious mental health conditions, such as Alzheimer's and Parkinson's, Energy + Mind Coffee may play a role in alleviating some of the more detrimental symptoms associated with these diseases.

Energy + Mind Coffee was formulated as a beverage that would enhance mental energy in addition to the benefits above. It is considered safe for human consumption at the recommended dose of 1-2 cups per day. As it does contain caffeine from the coffee itself, it should be taken with consideration of the total amount of caffeine one consumes from all sources.

Following the dosing instructions provided, one should experience the positive benefits as outlined in this white paper. Results will vary from individual to individual, as no two bodies act identically when faced with the same stimuli. However, the general results should include

- An improvement in focus and attention
- An increase in memory and concentration
- A reduction in stress and anxiety and overall improvement in mood

If taking anti-anxiety medication, high doses of Energy + Mind Coffee may compound the effects, causing a sedative-type effect. These results have not been seen with Energy + Mind Coffee, but are present in the literature regarding Gotu kola. Consult your healthcare professional if taking such medication.

As always, pregnant and nursing women as well as children should consult their health care professional before beginning any supplement program, particularly caffeine-containing products.

Should adverse effects be felt when consuming any new supplement, discontinue use and contact your healthcare professional immediately.



Citations

1. Kamkaew N, Norman Scholfield C, Ingkaninan K, Taepavaraprak N, Chootip K. Bacopa monnieri increases cerebral blood flow in rat independent of blood pressure. *Phytother Res.* 2013 Jan;27(1):135-8.
2. Orhan IE. Centella asiatica (L.) Urban: From Traditional Medicine to Modern Medicine with Neuroprotective Potential. *Evid Based Complement Alternat Med.* 2012;2012:946259.
3. Mukherjee S, Dugad S, Bhandare R, Pawar N, Jagtap S, Pawar PK, Kulkarni O. Evaluation of comparative free-radical quenching potential of Brahmi (Bacopa monnieri) and Mandookparni (Centella asiatica). *Ayu.* 2011 Apr;32(2):258-64.
4. Shinomol GK, Raghunath N, Bharath MM, Muralidhara. Prophylaxis with Bacopa monnieri attenuates acrylamide induced neurotoxicity and oxidative damage via elevated antioxidant function. *Cent Nerv Syst Agents Med Chem.* 2013 Mar;13(1):3-12.
5. Shinomol GK, Bharath MM, Muralidhara. Pretreatment with Bacopa monnieri extract offsets 3-nitropropionic acid induced mitochondrial oxidative stress and dysfunctions in the striatum of prepubertal mouse brain. *Can J Physiol Pharmacol.* 2012 May;90(5):595-606
6. Shinomol GK, Bharath MM, Muralidhara. Neuromodulatory propensity of Bacopa monnieri leaf extract against 3-nitropropionic acid-induced oxidative stress: in vitro and in vivo evidences. *Neurotox Res.* 2012 Aug;22(2):102-14.
7. Shinomol GK, Mythri RB, Srinivas Bharath MM, Muralidhara. Bacopa monnieri extract offsets rotenone-induced cytotoxicity in dopaminergic cells and oxidative impairments in mice brain. *Cell Mol Neurobiol.* 2012 Apr;32(3):455-65. doi: 10.1007/s10571-011-9776-0.
8. Hosamani R, Krishna G, Muralidhara. Standardized Bacopa monnieri extract ameliorates acute paraquat-induced oxidative stress, and neurotoxicity in prepubertal mice brain. *Nutr Neurosci.* 2014 Aug 25
9. Kapoor R, Srivastava S, Kakkar P. Bacopa monnieri modulates antioxidant responses in brain and kidney of diabetic rats. *Environ Toxicol Pharmacol.* 2009 Jan;27(1):62-9.
10. Rastogi M, Ojha RP, Devi BP, Aggarwal A, Agrawal A, Dubey GP. Amelioration of age associated neuroinflammation on long term bacosides treatment. *Neurochem Res.* 2012 Apr;37(4):869-74.
11. Liu X, Yue R, Zhang J, Shan L, Wang R, Zhang W. Neuroprotective effects of bacopaside I in ischemic brain injury. *Restor Neurol Neurosci.* 2013;31(2):109-23.
12. Limpeanchob N, Jaipan S, Rattanakaruna S, Phrompittayarat W, Ingkaninan K. Neuroprotective effect of Bacopa monnieri on beta-amyloid-induced cell death in primary cortical culture. *J Ethnopharmacol.* 2008 Oct 30;120(1):112-7.
13. Mathew J, Gangadharan G, Kuruvilla KP, Paulose CS. Behavioral deficit and decreased GABA receptor functional regulation in the hippocampus of epileptic rats: effect of Bacopa monnieri. *Neurochem Res.* 2011 Jan;36(1):7-16.
14. Mathew J, Balakrishnan S, Antony S, Abraham PM, Paulose CS. Decreased GABA receptor in the cerebral cortex of epileptic rats: effect of Bacopa monnieri and Bacoside-A. *J Biomed Sci.* 2012 Feb 24;19:25.
15. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood. *Phytother Res.* 2014 Apr;28(4):551-9.
16. Jadiya P, Khan A, Sammi SR, Kaur S, Mir SS, Nazir A. Anti-Parkinsonian effects of Bacopa monnieri: insights from transgenic and pharmacological Caenorhabditis elegans models of Parkinson's disease. *Biochem Biophys Res Commun.* 2011 Oct 7;413(4):605-10.
17. Zhang LN, Sun YJ, Pan S, Li JX, Qu YE, Li Y, Wang YL, Gao ZB. Na⁺-K⁺-ATPase, a potent neuroprotective modulator against Alzheimer disease. *Fundam Clin Pharmacol.* 2013 Feb;27(1):96-103.
18. Saini N, Singh D, Sandhir R. Neuroprotective effects of Bacopa monnieri in experimental model of dementia. *Neurochem Res.* 2012 Sep;37(9):1928-37.
19. Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of Bacopa monnieri in Alzheimer's disease model. *J Ethnopharmacol.* 2010 Jan 8;127(1):26-31.
20. Rastogi M, Ojha RP, Prabu PC, Devi BP, Agrawal A, Dubey GP. Prevention of age-associated neurodegeneration and promotion of healthy brain ageing in female Wistar rats by long term use of bacosides. *Biogerontology.* 2012 Apr;13(2):183-95.
21. Kamkaew N, Norman Scholfield C, Ingkaninan K, Taepavaraprak N, Chootip K. Bacopa monnieri increases cerebral blood flow in rat independent of blood pressure. *Phytother Res.* 2013 Jan;27(1):135-8.



22. Apetz N, Munch G, Govindaraghavan S, Gyengesi E1. Natural compounds and plant extracts as therapeutics against chronic inflammation in Alzheimer's disease--a translational perspective. *CNS Neurol Disord Drug Targets*. 2014;13(7):1175-91.
23. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *J Altern Complement Med*. 2008 Jul;14(6):707-13.
24. Peth-Nui T, Wattanathorn J, Muchimapura S, Tong-Un T, Piyavhatkul N, Rangseekajee P, Ingkaninan K, Vittaya-Areekul S. Effects of 12-Week Bacopa monnieri Consumption on Attention, Cognitive Processing, Working Memory, and Functions of Both Cholinergic and Monoaminergic Systems in Healthy Elderly Volunteers. *Evid Based Complement Alternat Med*. 2012;2012:606424.
25. Morgan A, Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. *J Altern Complement Med*. 2010 Jul;16(7):753-9.
26. Downey LA, Kean J, Nemeh F, Lau A, Poll A, Gregory R, Murray M, Rourke J, Patak B, Pase MP, Zangara A, Lomas J, Scholey A, Stough C. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of Bacopa monnieri (CDRI 08) on sustained cognitive performance. *Phytother Res*. 2013 Sep;27(9):1407-13.
27. Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, Limpeanchob N, Norman Scholfield C. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. *J Ethnopharmacol*. 2014;151(1):528-35.
28. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood. *Phytother Res*. 2014 Apr;28(4):551-9.
29. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effects of bacosides of Bacopa monnieri: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. *Phytother Res*. 2002 Nov;16(7):639-45.
30. Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (Bacopa monnieri) on human memory. *Neuropsychopharmacology*. 2002 Aug;27(2):279-81.
31. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, part 2: a review of clinical studies with supporting preclinical evidence. *CNS Drugs*. 2013 Apr;27(4):301-19.
32. Pase MP, Kean J, Sarris J, Neale C, Scholey AB, Stough C. The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. *J Altern Complement Med*. 2012 Jul;18(7):647-52.
33. Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (Bacopa monnieri) on human memory. *Neuropsychopharmacology*. 2002 Aug;27(2):279-81.
34. Kumar A, Prakash A, Dogra S. Centella asiatica Attenuates D-Galactose-Induced Cognitive Impairment, Oxidative and Mitochondrial Dysfunction in Mice. *Int J Alzheimers Dis*. 2011;2011:347569.
35. Nasir MN, Habsah M, Zamzuri I, Rammes G, Hasnan J, Abdullah J. Effects of asiatic acid on passive and active avoidance task in male Sprague-Dawley rats. *J Ethnopharmacol*. 2011 Mar 24;134(2):203-9.
36. Rao MK, Rao MS, Rao GS. Treatment with Centella asiatica (Linn) fresh leaf extract enhances learning ability and memory retention power in rats. *Neurosciences (Riyadh)*. 2007 Jul;12(3):236-41.
37. Rao SB, Chetana M, Uma Devi P. Centella asiatica treatment during postnatal period enhances learning and memory in mice. *Physiol Behav*. 2005 Nov 15;86(4):449-57.
38. Veerendra Kumar MH, Gupta YK. Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. *Clin Exp Pharmacol Physiol*. 2003 May-Jun;30(5-6):336-42.
39. Xu CL, Qu R, Zhang J, Li LF, Ma SP. Neuroprotective effects of madecassoside in early stage of Parkinson's disease induced by MPTP in rats. *Fitoterapia*. 2013 Oct;90:112-8.
40. Haleagrahara N, Ponnusamy K. Neuroprotective effect of Centella asiatica extract (CAE) on experimentally induced parkinsonism in aged Sprague-Dawley rats. *J Toxicol Sci*. 2010 Feb;35(1):41-7.
41. Kumar A, Dogra S, Prakash A. Neuroprotective Effects of Centella asiatica against Intracerebroventricular Colchicine-Induced Cognitive Impairment and Oxidative Stress. *Int J Alzheimers Dis*. 2009 Sep 13;2009.
42. Luo Y, Yang YP, Liu J, Li WH, Yang J, Sui X, Yuan X, Nie ZY, Liu YQ, Chen D, Lin SH, Wang YA. Neuroprotective effects of madecassoside against focal cerebral ischemia reperfusion injury in rats. *Brain Res*. 2014 May 27;1565:37-47.



43. Chen S, Yin ZJ, Jiang C, Ma ZQ, Fu Q, Qu R, Ma SP. Asiaticoside attenuates memory impairment induced by transient cerebral ischemia-reperfusion in mice through anti-inflammatory mechanism. *Pharmacol Biochem Behav.* 2014 Jul;122:7-15.
44. da Rocha MD, Viegas FP, Campos HC, Nicastro PC, Fossaluzza PC, Fraga CA, Barreiro EJ, Viegas C Jr. The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease. *CNS Neurol Disord Drug Targets.* 2011 Mar;10(2):251-70.
45. Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV. Centella asiatica extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model. *Phytother Res.* 2009 Jan;23(1):14-9.
46. De Sanctis MT, Belcaro G, Incandela L, Cesarone MR, Griffin M, Ippolito E, Cacchio M. Treatment of edema and increased capillary filtration in venous hypertension with total triterpenic fraction of Centella asiatica: a clinical, prospective, placebo-controlled, randomized, dose-ranging trial. *Angiology.* 2001 Oct;52 Suppl 2:S55-9.
47. Incandela L, Belcaro G, De Sanctis MT, Cesarone MR, Griffin M, Ippolito E, Bucci M, Cacchio M. Total triterpenic fraction of Centella asiatica in the treatment of venous hypertension: a clinical, prospective, randomized trial using a combined microcirculatory model. *Angiology.* 2001 Oct;52 Suppl 2:S61-7.
48. Cesarone MR, Incandela L, De Sanctis MT, Belcaro G, Bavera P, Bucci M, Ippolito E. Evaluation of treatment of diabetic microangiopathy with total triterpenic fraction of Centella asiatica: a clinical prospective randomized trial with a microcirculatory model. *Angiology.* 2001 Oct;52 Suppl 2:S49-54.
49. Cesarone MR, Belcaro G, Rulo A, Griffin M, Ricci A, Ippolito E, De Sanctis MT, Incandela L, Bavera P, Cacchio M, Bucci M. Microcirculatory effects of total triterpenic fraction of Centella asiatica in chronic venous hypertension: measurement by laser Doppler, TcPO₂-CO₂, and leg volumetry. *Angiology.* 2001 Oct;52 Suppl 2:S45-8.
50. Cesarone MR, Incandela L, De Sanctis MT, Belcaro G, Geroulakos G, Griffin M, Lennox A, Di Renzo AD, Cacchio M, Bucci M. Flight microangiopathy in medium- to long-distance flights: prevention of edema and microcirculation alterations with total triterpenic fraction of Centella asiatica. *Angiology.* 2001 Oct;52 Suppl 2:S33-7.
51. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, part 2: a review of clinical studies with supporting preclinical evidence. *CNS Drugs.* 2013 Apr;27(4):301-19.
52. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnason JT. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. *Can J Physiol Pharmacol.* 2007 Sep;85(9):933-42.
53. Wanasuntronwong A, Tantisira MH, Tantisira B, Watanabe H. Anxiolytic effects of standardized extract of Centella asiatica (ECa 233) after chronic immobilization stress in mice. *J Ethnopharmacol.* 2012 Sep 28;143(2):579-85.
54. Nasir MN, Habsah M, Zamzuri I, Rammes G, Hasnan J, Abdullah J. Effects of asiatic acid on passive and active avoidance task in male Sprague-Dawley rats. *J Ethnopharmacol.* 2011 Mar 24;134(2):203-9.
55. Rao SB, Chetana M, Uma Devi P. Centella asiatica treatment during postnatal period enhances learning and memory in mice. *Physiol Behav.* 2005 Nov 15;86(4):449-57.
56. Sarokte AS, Rao MV. Effects of Medhya Rasayana and Yogic practices in improvement of short-term memory among school-going children. *Ayu.* 2013 Oct;34(4):383-9.
57. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, Yimtae K, Sripanidkulchai B, Singkhoraard J. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica. *J Ethnopharmacol.* 2008 Mar 5;116(2):325-32.
58. Incandela L, Belcaro G, De Sanctis MT, Cesarone MR, Griffin M, Ippolito E, Bucci M, Cacchio M. Total triterpenic fraction of Centella asiatica in the treatment of venous hypertension: a clinical, prospective, randomized trial using a combined microcirculatory model. *Angiology.* 2001 Oct;52 Suppl 2:S61-7.
59. De Sanctis MT, Belcaro G, Incandela L, Cesarone MR, Griffin M, Ippolito E, Cacchio M. Treatment of edema and increased capillary filtration in venous hypertension with total triterpenic fraction of Centella asiatica: a clinical, prospective, placebo-controlled, randomized, dose-ranging trial. *Angiology.* 2001 Oct;52 Suppl 2:S55-9.
60. Cesarone MR, Incandela L, De Sanctis MT, Belcaro G, Bavera P, Bucci M, Ippolito E. Evaluation of treatment of diabetic microangiopathy with total triterpenic fraction of Centella asiatica: a clinical prospective randomized trial with a microcirculatory model. *Angiology.* 2001 Oct;52 Suppl 2:S49-54.
61. Cesarone MR, Belcaro G, Rulo A, Griffin M, Ricci A, Ippolito E, De Sanctis MT, Incandela L, Bavera P, Cacchio M, Bucci M. Microcirculatory effects of total triterpenic fraction of Centella asiatica in chronic venous hypertension: measurement by laser Doppler, TcPO₂-CO₂, and leg volumetry. *Angiology.* 2001 Oct;52 Suppl 2:S45-8.



62. Jana U, Sur TK, Maity LN, Debnath PK, Bhattacharyya D. A clinical study on the management of generalized anxiety disorder with *Centella asiatica*. *Nepal Med Coll J*. 2010 Mar;12(1):8-11.
63. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, Yimtae K, Sripanidkulchai B, Singkhoraard J. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of *Centella asiatica*. *J Ethnopharmacol*. 2008 Mar 5;116(2):325-32.
64. Sharma S, Gupta R, Thakur SC. Attenuation of Collagen Induced Arthritis by *Centella asiatica* Methanol Fraction via Modulation of Cytokines and Oxidative Stress. *Biomed Environ Sci*. 2014 Dec;27(12):926-38.
65. No author listed. Inhibitory action of asiaticoside on collagen-induced arthritis in mice. *Yao Xue Xue Bao*. 2007 Jul;42(7):698-703.
66. Cesarone MR, Incandela L, De Sanctis MT, Belcaro G, Geroulakos G, Griffin M, Lennox A, Di Renzo AD, Cacchio M, Bucci M. Flight microangiopathy in medium- to long-distance flights: prevention of edema and microcirculation alterations with total triterpenic fraction of *Centella asiatica*. *Angiology*. 2001 Oct;52 Suppl 2:S33-7.
67. Neely T, Walsh-Mason B, Russell P, Horst AV, O'Hagan S, Lahorkar P. A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use. *Toxicol Int*. 2011 Aug;18(Suppl 1):S20-9.
68. Dave UP, Dingankar SR, Saxena VS, Joseph JA, Bethapudi B, Agarwal A, Kudiganti V. An open-label study to elucidate the effects of standardized *Bacopa monnieri* extract in the management of symptoms of attention-deficit hyperactivity disorder in children. *Adv Mind Body Med*. 2014 Spring;28(2):10-5.
69. Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb *Bacopa monnieri*. *Rejuvenation Res*. 2013 Aug;16(4):313-26
70. Sarkar S, Mishra BR, Praharaj SK, Nizamie SH. Add-on effect of Brahmi in the management of schizophrenia. *J Ayurveda Integr Med*. 2012 Oct;3(4):223-5.
71. Morgan A and J Stevens. *J Altern Complement Med*. 2010 Jul;16(7):753-9. Does *Bacopa monnieri* improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial.
72. Teschke R and R Bahre. *Ann Hepatol*. 2009 Jul-Sep;8(3):258-66. Severe hepatotoxicity by Indian Ayurvedic herbal products: a structured causality assessment.
73. Singh A and SK Singh. Evaluation of antifertility potential of Brahmi in male mouse. *Contraception*. 2009 Jan;79(1):71-9.
74. Defillipo PP, Raposo AH, Fedoce AG, Ferreira AS, Polonini HC, Gattaz WF, Raposo NR. Inhibition of cPLA2 and sPLA2 activities in primary cultures of rat cortical neurons by *Centella asiatica* water extract. *Nat Prod Commun*. 2012 Jul;7(7):841-3.
75. Gohil KJ, Patel JA, Gajjar AK. Pharmacological Review on *Centella asiatica*: A Potential Herbal Cure-all. *Indian J Pharm Sci*. 2010 Sep;72(5):546-56.
76. Jana U, Sur TK, Maity LN, Debnath PK, Bhattacharyya D. A clinical study on the management of generalized anxiety disorder with *Centella asiatica*. *Nepal Med Coll J*. 2010 Mar;12(1):8-11.
77. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, Yimtae K, Sripanidkulchai B, Singkhoraard J. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of *Centella asiatica*. *J Ethnopharmacol*. 2008 Mar 5;116(2):325-32.
78. Sarokte AS, Rao MV2. Effects of Medhya Rasayana and Yogic practices in improvement of short-term memory among school-going children. *Ayu*. 2013 Oct;34(4):383-9.
79. Al-Saeedi FJ. Study of the cytotoxicity of asiaticoside on rats and tumour cells. *BMC Cancer*. 2014 Mar 25;14:220.
80. Kartnig T. Clinical applications of *Centella asiatica* (L.) Urb herbs spices and medicinal plants, nd ed. 2nd. Vol. 28. Rocklin, CA: Prima Publishing; 1988. pp. 146–73.
81. No author listed. Hepatotoxicity associated with the ingestion of *Centella asiatica*. *Rev Esp Enferm Dig*. 2005 Feb;97(2):115-24.
82. Gonzalo Garijo MA, Revenga Arranz F, Bobadilla González P. Allergic contact dermatitis due to *Centella asiatica*: a new case. *Allergol Immunopathol (Madr)*. 1996 May-Jun;24(3):132-4.
83. No author listed. *Centella*: Monographs for herbal medicinal products. 2007. available from: <http://www.mohp.gov.eg/Sec/Statistics/hplants.pdf>.
84. Yunianto I, Das S, Mat Noor M. Antispermato-genic and antifertility effect of Pegaga (*Centella asiatica* L) on the testis of male Sprague-Dawley rats. *Clin Ter*. 2010;161(3):235-9.

