FOCUSFUSION COCOA

white paper provided by Archmore Botanical Research Group, LLC

A Dollar Coffee Club product

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Archmore Botanical Research Group, LLC

FocusFusion Cocoa

a Dollar Coffee Club product

- A technical overview outlining the safety and efficacy of FocusFusion Cocoa, a dietary supplement designed to support healthy mental balance and improved memory and focus*
- This technical white paper will include:
    - Formulation breakdown
        - Synopsis of health benefits associated with the proprietary ingredients
    - Efficacy
        - Cellular, animal, and human trials demonstrating cognitive benefits
        - A review of any negative outcomes found in clinical trials using the proprietary ingredients
        - Potential secondary health benefits outside the scope of cognitive function and mood
    - Safety
        - In vitro and in vivo trials demonstrating safety of ingredients in FocusFusion Cocoa at recommended levels
        - A review of any adverse events associated with the ingestion of the proprietary ingredients
    - Recommended guidelines for use
        - Dosing recommendations for cognitive functions and mood
        - Potential adverse events and warnings

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

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Overview

With so many stimulatory products on the market claiming to enhance mental energy and improve focus, it is difficult to find a product to benefit the mind that does not contain a stimulant. However, a number of individuals choose not to include stimulants, such as caffeine, in their diet, be it for health, religious, or age reasons. Therefore, DCC developed a product with proven efficacy for cognitive improvement, without the use of caffeine. Using key botanicals that have thousands of years of historical safe use, DCC developed FocusFusion Cocoa.

Researching Ayurveda, a system of Hindu traditional medicine native to the Indian subcontinent that dates back over 3000 years, modern scientists confirmed the benefits of two herbs for cognitive function and health. They are *Bacopa monnieri* and *Centella asiatica*, referred to as Gotu Kola. It was for these widely known and well-researched benefits that DCC utilized such powerful herbs when formulating FocusFusion Cocoa. This product was designed to support brain function while improving mental energy and focus. By formulating with a cocoa base, DCC was able to develop a caffeine-free beverage safe for children and adults who wish to enhance their cognitive performance.

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 FocusFusion Cocoa. Any adverse events noted in clinical trials or potential negative outcomes from supplementation with these herbs will also be addressed. Finally, any warnings for this product will be addressed.

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Formulation Overview and Breakdown

FocusFusion Cocoa was designed as a caffeine-free alternative to the DCC's Energy + Mind Coffee, providing mental stimulation and cognitive health through the use of botanical ingredients. Designed with the health of children in mind, as well as those eliminating caffeine from their diet, FocusFusion Cocoa blends the brain-enhancing herbs, *Bacopa monnieri* and Gotu kola, with decadent European chocolate in a fat-free, gluten-free Kosher beverage. This beverage supports increased focus and attention, improved memory and concentration, and reduced anxiety for a more positive mood.

- 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
    - Modulate neurotransmitters such as GABA, promoting well-being and reducing anxiety
- Gotu Kola contains triterpernoid compounds: asiaticoside and madecassoside which:
    - Act as a specifically targeted antioxidant and anti-inflammatory in the brain, promoting neural health and improving memory and focus
    - Improve microcirculation for enhanced blood flow through cerebral tissues
- Chocolate itself contributes to the efficacy of the formula by:
    - Supplying natural compounds that alleviate anxiety
    - Provide natural antioxidant to support brain health

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***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 herbal product used safely for over 3,000 years in this Hindu medicine. It is through this branch of medicine that *Bacopa monnieri* was first used as a neurological tonic and cognitive enhancer but has since been studied more extensively through modern medical research for its nootropic effects and confirmed for safe 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 Focus Fusion Cocoa.

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 theses 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 FocusFusion Cocoa, *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.

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***Gotu kola*- Background Information**

Gotu kola, commonly referred to as or Asian pennywort or by its botanicals 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 identified several mechanisms of action for this herb, including decreasing oxidative stress and inflammation, 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 also improved. A detailed analysis of these studies will follow in this white paper.

A number of these clinical trials were performed on young, developing subjects, both animal and human, to determine their benefit for children and young adults. Children and young adults are constantly stressed mentally through the natural learning process, and in many cases, this may compounded by serious cognitive conditions like ADHD. Supplementation with Gotu Kola is seen to alleviate much of the stress and anxiety associated with learning in both healthy children as well as those afflicted with ADHD. It has also been shown to improve focus and attention in these individuals.

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 herb: 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, including trials specifically using young children as the participants. These results clearly demonstrate that Gotu kola is an exceptional herbal ingredient for FocusFusion Cocoa.

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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 improves memory, learning, and focus
        - Antioxidation leads to anti-inflammation, increased cerebral energy metabolism, and increased cerebral blood flow
    - Reduces anxiety and stress through neurotransmitter modulation
- *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 blood flow

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.

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***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* was shown to have neuroprotective properties, significantly protecting against oxidative damage caused by these 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].

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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: 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 [12, 13]. This balance should also result in a reduction of anxiety and depression, as is noted in clinical trial [14, 15].

***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 FocusFusion Cocoa. 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, and Attention

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 simply age. In these severe conditions, 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 [16, 17, 18]. 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 [19]. Improving cerebral blood flow also seems to reverse or forestall dementia [20]. 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 [21].

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* improve memory recall and reduces stress and anxiety in older individuals [22]. In a larger trial involving sixty (60) healthy participants with a slightly younger 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 [23].

Improved memory and attention is not just observed in trials involving older individuals; it has been documented in trials involving children, specifically those with ADHD. In a trial involving thirty-one (31) children between the ages of 6-12 years with ADHD onset before 7 years of age, treatment involved a relatively moderate dose of *B. monnieri* (as compared to FocusFusion Cocoa). Children were then tested for symptoms of ADHD. It was noted that *B. monnieri* significantly reduced symptoms of this disorder including restlessness, attention-deficit, learning problems, impulsivity, and psychiatric problems. Self-control was also significantly improved in these children; however, social problems remained unchanged. These results demonstrate the positive attention-modifying and cognitive benefits *B. monnieri* has on children with ADHD [24].

Similar results are observed in healthy participants of all ages and normal mental health status. 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 compared results from 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 heighted cognitive performance [27]. These plentiful results demonstrate the benefits of *Bacopa monnieri* for improving memory and cognitive performance for individuals of all ages, and improving attention and focus even in children afflicted with ADHD.

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 *B. monnieri* 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 while also diminishing 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 those experiencing stress while trying to learn and retain new information.

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***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 FocusFusion Cocoa.

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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 Goto 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 FocusFusion Cocoa, with the higher doses indicative of two-three cups of cocoa 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 even 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: 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 [44-48].

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 [49]. 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 [50]. These effects have been demonstrated in animals initially, where healthy non-stressed mice were subjected to acute stress via 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 [51].

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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 demonstrating the neurological benefits of Gotu kola.

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 [52]. 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 [53].

In a randomized, double-blind, placebo controlled trial involving 120 children newly diagnosed with ADHD, researchers tested the effects Gotu kola supplementation has on learning and attention. During this 4-month trial, they noticed a significant improvement in attention, cognition, and impulse control in the treated group, and no improvement in the placebo group. In addition, the supplement was well-tolerated, confirming its safe and beneficial use in children with ADHD [54].

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 [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].

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 its correlated 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 [61].

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 [62]. Therefore, it can be concluded that Gotu kola should alleviate symptoms of anxiety and depression associated with mental stress in most healthy individuals, children and adults 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 [57]. 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 [58].

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 [59]. These results were duplicated in a second study which also confirmed tolerability of the supplement, as there were neither dropouts nor side effects reported [60]. 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 [63, 64].

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 [65].

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Safety Overview

FocusFusion Cocoa was designed to be a safe and effective caffeine-free beverage for everyday consumption by healthy individuals including children. Targeting multiple functions of the brain, this beverage 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 on individuals. Modern testing techniques have confirmed the safety of these ingredients for oral use.

- FocusFusion Cocoa 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 Focus Fusion Cocoa
- Adverse safety and toxicity trials are also reviewed

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***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 [66].

In addition, several dozen clinical trials, including trials on children, have been conducted [67]. 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 FocusFusion Cocoa [68, 69].

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 irritation were not severe enough for any of the 81 participants to discontinue the trial [70].

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 [71].

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 FocusFusion Cocoa. 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 Focus Fusion Cocoa, 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 [72].

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***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 [73, 74]. 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 report of side effects [75, 76, 77]. In clinical trials involving delicate cancerous tissues, Gotu kola was also shown to have a relative lack of systemic toxicity [78]. A toxic dose for asiaticoside from Gotu kola was not observed, even when animals were orally administered high doses of this single compound [79].

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 [80, 81]. 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 FocusFusion Cocoa. However, care should be exercised if already taking anti-anxiety medication, as the sedative properties may be exacerbated [82].

In an animal trial, the antifertility action of Gotu kola was tested in male rats. A low, medium, and high dose of extract was 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 [83]. Similar findings have not been reported in more recent research, nor have these findings been reported in any human clinical trial.

Why Chocolate?

It is common knowledge that chocolate seems to make the majority of people happy, or so marketers would have you believe this a universal concept. Take Valentine's Day for instance- the act of giving chocolate symbolizes giving happiness. But there is a scientific explanation for this. Chocolate is derived from a plant called cacao, from which beans are harvested and processed to create what we know today as the yummy dark treat. Cocao beans contain natural compounds called methylxanthines and flavonols. These families of compounds are found in a variety of plants consumed by humans, yet are concentrated at such levels in chocolate to provide a relief from anxiety and depression and an overall feeling of well-being.

Methylxanthines include caffeine, theophylline, and theobromine. It seems counterintuitive to include methylxanthines in a caffeine-free formula; however, unlike coffee which also contains methylxanthines, the ratio of caffeine to other xanthines in chocolate is dramatically reduced, rendering it virtually caffeine-free. In studies comparing the effects of caffeinated coffee with chocolate, consumers noticed the effects of the coffee and the chocolate are not equal. This seems obvious, as one contains this stimulant at significantly higher concentrations than merely a minor naturally-occurring presence. Chocolate is far more enriched with theobromine than caffeine, and it is this compound that contributes most abundantly to its particular psychotropic benefits.

Methylxanthines act on adenosine receptors in the central nervous system, enhancing arousal, mood, and concentration levels. This draws the cravings people often feel in response to chocolate (and even coffee) as part of the reward pathway in the brain. In addition, the appeal of chocolate is further heightened by its smell. A study on honeybees rewarded with methylxanthines were three times as likely to remember a learned floral scent as were honeybees rewarded with sucrose alone [84]. This affect is modulated by these same adenosine receptors and the reward pathway.

The particular ratio of theobromine found in both milk and dark chocolate is directly proportional to the amount of psycho-stimulant recorded in the body. For example, dark chocolate is known to have a higher concentration of theobromine than milk chocolate. Both chocolates delivered improved cognitive performance and mood, yet dark chocolate had slightly higher results. When compared with white chocolate, which is not derived from cacao and thus contains no theobromine, both milk and dark chocolate outperformed in terms of enhancing mood and cognitive function [85].

While theobromine is toxic for a variety of mammals including dogs, its toxicity in humans is very low. There exists overwhelming evidence as to the safety of methylxanthines, particularly caffeine, and theobromine appears in research to be even safer for humans. Although some may claim to be "a chocoholic", there is no possibility to become chemically dependent upon this substance. Both the FDA and the International Olympic Committee have restricted amounts of caffeine recommended for human consumption and athletes, there have been no such limits imposed for theobromine, nor has it been put

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under as much scrutiny as caffeine. The oral lethal dose for theobromine is nearly 10-fold higher than that of caffeine, thus making it safe for the purposes of FocusFusion Cocoa [86].

By formulating FocusFusion Cocoa with the highest quality European chocolate, DCC has created a two-pronged product that heightens well-being through olfactory stimulation as well as chemically through adenosine receptors. It is via this pathway that anxiety is relieved, depression alleviated, and an overall feeling of well-being may be achieved with each sip of this delicious beverage.

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Usage Guidelines

Mental stress, inability to focus, and trouble retaining new information are afflictions that trouble everyone at some time or another, both students and adults alike. FocusFusion Cocoa 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.

FocusFusion Cocoa was formulated as a non-stimulatory beverage that would be safe for human consumption at the recommended dose of 1-2 cups per day. As it does not contain caffeine, it should be a safe and effective product for school-age children as well. In addition, it could be a highly effective supplement for those children demonstrating symptoms of ADHD. Consult with your healthcare provider before beginning any supplementation program for children with this condition, as medication interactions may as yet be unknown.

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

There are no stimulatory ingredients in this product, thus consuming it during the day or evening hours should have no difference in benefits. However, if taking anti-anxiety medication, high doses of Focus Fusion Cocoa may compound the effects, causing a sedative-type effect. These results have not been seen with FocusFusion Cocoa, but are referenced 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.

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

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