Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Bacopa Monnieri

Evidence Summary

Bacopa monnieri has long been thought to have cognitive benefits and anxiolytic effects. Preclinical and early clinical data suggest benefit, but larger, longer studies are needed to confirm this benefit.

Neuroprotective Benefit: Laboratory studies have identified possible mechanisms of action for broad neuroprotection in brain aging and some early clinical trials suggest that bacopa is somewhat nootropic, but larger, longer studies are needed.

Aging and related health concerns: Bacopa is thought to have anti-inflammatory and antioxidant properties and could have benefits for aging or age-related diseases. There is early evidence for potential use for mood disorders or cardiovascular health.

Safety: Bacopa is typically thought to be well-tolerated. Clinical trials suggest that gastrointestinal side effects are the most common adverse events. Longer, larger, more robust trials in different patient populations would help confirm the safety profile.

Availability: OTC	**Dose**: The ideal dose of bacopa has not yet been determined. Trials typically use between 200 and 600 mg per day, with most trials using approximately 300 mg.
Half-life: N/A	**BBB**: At least some compounds in bacopa are BBB penetrant
Clinical trials: Bacopa has been used in several small trials; the largest meta-analysis identified included 645 participants.	**Observational studies**: No observational studies of individuals using bacopa were identified.

What is it?

Bacopa monnieri, referred to in this report as bacopa, is an herb with a long history of use in Indian Ayurveda traditional medicine. It is also called brahmi, water hyssop, herb of grace, thyme-leafed gratiola, and Indian pennywort. It is worth noting that the term 'brahmi' can sometimes refer to different plants such as gotu kola. Bacopa is native to India, Indochina, Australia, and Sri Lanka. They contain a number of compounds including triterpenoid saponins, alkaloids, flavonoids, glycosides, phytochemicals, sapogenins, and other compounds (Walker & Pellegrini, 2023).

Ayurveda practitioners have claimed that bacopa can improve cognitive function, promote longevity, and help with a range of ailments including but not limited to anxiety, depression, chronic fatigue, insomnia, stomach ulcers, and asthma and bronchitis (Walker & Pellegrini, 2023). Bacopa has been tested in several clinical trials, primarily focused on cognitive performance, though it has also been tested for ADHD and other conditions (clinicaltrials.gov).

Neuroprotective Benefit: Laboratory studies have identified possible mechanisms of action for broad neuroprotection in brain aging and some early clinical trials suggest that bacopa is somewhat nootropic, but larger, longer studies are needed.

Types of evidence:

- 6 systematic reviews or meta-analyses

- 12 randomized controlled trials
- 3 clinical trials that were either non-randomized or open-label studies
- 2 reviews
- Numerous laboratory studies on possible mechanisms of action

Ayurvedic medicine has long used bacopa for memory improvement and as an anxiolytic, among other uses. Preclinical studies have suggested that bacopa may be neuroprotective through different mechanisms of action. There have been multiple clinical trials and systematic reviews of its effects on cognition. However, many of these trials have been small and may also have had methodological issues that have hampered a definitive clinical understanding. Moreover, the trials by and large use different doses, durations, and formulations including combination formulations of bacopa; test different populations; and use different assessments, which makes it difficult to compare results or synthesize all the work done into a comprehensive understanding. Ultimately, larger and more rigorous trials are required to determine whether bacopa does have a neuroprotective effect in humans, whether in healthy adults, patients with MCI, or patients with dementia.

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Studies in the laboratory suggest that bacopa has biological effects that might protect against brain aging and dementia although we don't yet know if these biological effects will produce clinically meaningful effects in humans (see the 'Mechanisms of action' section below).

No study identified examined whether bacopa can prevent dementia diagnosis or decline. Several clinical trials have been run in different patient populations to quantify the cognitive effects, if any, of the herb. A 2024 systematic review included a total of 22 clinical trials in various patient populations, ranging from children with symptoms of inattention and hyperactivity to healthy adults to adults with a neurodegenerative disease. The authors concluded that they found bacopa treatment to be promising, but also found that the trials varied widely on dose and duration and tended to be small and/or not rigorous, and that larger, more robust trials are needed to not just assess benefit but also appropriate dosing, frequency, and duration (Valotto Neto et al., 2024). A 2021 systematic review and meta-analysis assessed double-blinded RCTs testing formulations containing only bacopa and doses of at least 200 mg per day. They included 11 studies comprising 645 healthy adults. All but one study reported at least one statistically significant improvement on at least one neuropsychological measure in the bacopa group compared to placebo, and the studies thus concluded that there was a benefit of bacopa. However, in

the meta-analysis, no two studies found statistically significant changes across the same neuropsychological test. Furthermore, most studies only found one or two measures of memory to be significantly improved in the bacopa group, and those changes were small (Brimson et al., 2021).

While none of these studies are large or rigorous enough to draw firm conclusions, it is worth discussing the results thus far. Treatment for at least 3 months might be needed to see benefit (Stough et al., 2001; Nathan et al., 2001) although immediate benefits have been on a handful of cognitive tests in a couple small trials that have tested either bacopa alone or bacopa in combination with other herbs (Benson et al., 2014; Downey et al., 2013; Best et al., 2021). The latter also observed significant changes in cerebral hemodynamic responses, indicating changes in brain activation patterns, in the group who received the supplement that contained bacopa and two other herbs compared to those who received the placebo. In 6 to 9 trials that tested bacopa for 3 months or longer and were analyzed in meta-analyses (Pase et al., 2012; Kongkeaw et al., 2014), most cognitive scores were unaffected but some benefits have been occasionally observed in tests on memory and attention. One of the trials that reported modest benefits tested elderly people with memory impairment (MMSE scores of 24+). Other studies have reported that treating healthy middle aged or older adults, or adults with hypertension, with a supplement containing bacopa and other vitamins or herbs for two or three months resulted in significant improvements in certain cognitive domains in the group or a subgroup who received the supplement compared to the groups that received placebo. However, it is difficult to ascribe this benefit to bacopa alone as the supplement contained multiple ingredients (Giugliano et al., 2018; Crosta et al., 2020; Young et al., 2022). Not all studies have found benefit; an open label study of 320 mg of bacopa in 35 individuals did not find a difference in cognition or mood after 3 months of dosing (Keegan et al., 2023).

For patients with mild cognitive impairment, the evidence is also limited. One small trial reported that bacopa modestly improved scores on tests of attention and verbal memory when used for 3 months at 450 mg per day in elderly people with memory complaints but not dementia (Barbhaiya et al., 2008, listed in Kongkeaw et al., 2014). In a randomized controlled trial also from India, treatment of healthy older adults with a combination of three herb extracts including bacopa for 1 year reportedly improved some aspects of cognitive ability, depression, and reduced biochemical markers of inflammation and oxidative stress. It should be noted, though, that the group of healthy older adults had average MMSE scores of less than 20; how relevant this data is to cognitively intact adults is not clear (Sadhu et al., 2014). A 2024 study enrolled 62 patients with MCI and risk factors for dementia and randomized them to receive either 160 mg bacopa extract twice a day or matching placebo for 2 months. The authors first assessed individual cognitive domains; while many cognitive domains were unaffected, the authors did

report a significant difference in attention and language at the end of the 2-month study, with the intervention group performing better than the placebo group. When they assessed cognitive function using the Montreal Cognitive Assessment (MoCA), there was a significant improvement over time in both groups, as well as a significantly better average score in the intervention group compared to placebo. There was no change in sleep between groups (Delfan et al., 2024).

Human research to suggest benefits to patients with dementia:

A 2022 systematic review sought to assess the safety and efficacy of bacopa in patients with MCI or AD. The study included all randomized and quasi-randomized controlled trials that compared bacopa to placebo or cholinesterase inhibitor. The review ultimately assessed 5 studies comprising approximately 286 patients. The duration of these studies varied from 2 months to 12 months. Doses ranged from 125 mg to 500 mg daily of bacopa; some studies tested only bacopa, while others tested a combination product that contained bacopa and other extracts. The authors of the review were unable to meta-analyze the results. While each of the 5 trials reported at least one statistically significant difference between bacopa and the comparator group, all studies were also judged to be at high risk of bias. They rated the overall quality of evidence to be very low based on both the high risk of bias and the overall small sample sizes (Basheer et al., 2022). Another group attempted to perform a meta-analysis of bacopa in patients with AD, but was unable to given the dearth of studies that ran a double-blinded RCT of formulations of only bacopa in patients with AD (Brimson et al., 2021).

There are other studies that either didn't meet inclusion criteria for the above systematic review or were published after the review. A small pilot study of 20 patients with Parkinson's disease (PD) assigned individuals to receive 225 mg or 450 mg of bacopa daily or matching placebo; there were two placebo groups, one who received 1 pill daily to match the 225 mg bacopa group, and one who received 2 pills daily to match the 445 mg bacopa group. The dosing lasted for 90 days. The authors reported that there were no differences in PD symptoms, emotional function, or social function between groups at the end of the 90-day study. There was a larger percent increase in emotional function scores in the higher bacopa dose group (13.8% improvement) compared to the one and two pill placebo groups and lower dose bacopa group (5.38%, 2.22%, and 0.62%, respectively) but this was not said to be significant. The authors reported that there was a strong correlation found between quality of life and motor outcomes at 30 days with bacopa treatment, and a moderate correlation found for these outcomes at 60 and 90 days. The authors report that the study was non-randomized, and that patients were 'randomly selected and distributed among groups' as they attended doctor visits. It is unclear whether that could have biased results (Santos et al., 2023).

In an open-label, non-randomized, and uncontrolled study from India, patients with AD showed improved cognitive scores and subjective improvements in quality-of-life, irritability, and insomnia during 6 months of treatment with 600 mg per day of a bacopa extract (Goswami et al., 2011).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Bacopa is comprised of many different active compounds, several of which could have neuroprotective effects. These compounds include triterpenoid saponins such as different bacosides; these saponins are thought to be the main active compounds (Brimson et al., 2021; Walker & Pellegrini, 2023). Laboratory studies have identified several possible mechanisms of action by which bacopa could protect against dementia and cognitive aging. Bacopa is thought to have antioxidant and anti-inflammatory properties and may modulate different neurotransmitter systems such as the cholinergic system. Whether these biological effects can occur in humans has not yet been tested although one trial reported that treatment with a combination of three herb extracts including bacopa reduced biochemical markers of inflammation and oxidative stress (Sadhu et al., 2014). Another study tested bacopa in 35 cognitively healthy individuals for 3 months and found that over the 3 month period, there was a decrease in NF-κB phosphorylation, potentially suggesting an anti-inflammatory effect (Keegan et al., 2023). In laboratory studies in cell culture and rodents, bacopa protected against oxidative stress or inflammation (including Priyanka et al., 2013; Singh et al., 2012; Dwivedi et al., 2013; Williams et al., 2014). The effects on oxidative stress may occur by activating Nrf2 via Keap1 expression, thereby upregulating glutathione and preserving cellular redox homeostasis (Singh et al., 2012; Dwivedi et al., 2013). Bacopa reduced amyloid beta levels in one rodent study (Holcolmb et al., 2006) and protected against cell death caused by amyloid beta in a cell culture study (Limpeanchob et al., 2008). Bacopa may modulate tau phosphorylation in cell models (reviewed in Fatima et al., 2022). Bacopa treatment for three months was also reported in one study to protect against brain aging in rats as measured by lipofuscin accumulation, glutathione levels and glutathione reductase activity, and changes in some neurotransmitter levels (Rastogi et al., 2012).

APOE4 interactions:

No research is available on whether or not the effects of bacopa differ in people with and without the APOE4 risk factor for Alzheimer's disease.

Aging and related health concerns: Bacopa is thought to have anti-inflammatory and antioxidant properties and could have benefits for aging or age-related diseases. There is early evidence for potential use for mood disorders or cardiovascular health.

Types of evidence:

- 3 RCTs
- Numerous laboratory studies

Anti-Inflammation, Aging, and Longevity: MOSTLY PRECLINICAL SUGGESTION OF BENEFIT, BUT SOME CLINICAL EVIDENCE SUPPORT
In traditional Ayurveda, bacopa has been claimed to promote longevity and protect against various aspects of aging. Very little research has been done in either humans or laboratory models to verify these effects, but anti-inflammatory and antioxidant effects are possible.

In one randomized trial that included healthy elderly individuals and patients with AD, a combination of three herbs including bacopa taken for 1 year reportedly reduced biochemical markers of inflammation such as homocysteine, CRP, and TNFα, and reduced markers of oxidative stress like decreased TBARS, glutathione peroxidase, and superoxide dismutase with increased glutathione GSH. The herb extracts used were bacopa (whole plant extract), hippophae rhamnoides (leaves & fruit), dioscorea bulbifera (bulbils) (Sadhu et al., 2014). The only functional outcomes in the trial related to cognitive ability and depression but the biochemical effects might yield broad benefits in aging and related diseases.

A handful of laboratory studies support the idea that bacopa can protect against age-related oxidative stress and inflammation, possibly by activating Nrf2 (see mechanisms of action discussion above). In *C. elegans*, one study reported that an aqueous extract of bacopa could upregulate a stress-associated gene that can promote longevity during stress conditions (*hsp-16.2*) and increase lifespan during exposure to stress (thermal or oxidative stress) but not in standard laboratory conditions (Phulara et al., 2015). In aged rats, bacopa treatment for 3 months led to a dose-dependent reduction of the brain's lipofuscin, a putative biomarker of aging probably due to accumulated oxidation of fatty acids (Rastogi et al., 2012). The study didn't evaluate lipofuscin build-up in other areas of the body although a separate mouse study reported less lipofuscin accumulation in the prostate (Kalamade et al., 2008). Bacopa was also reported to protect against other biochemical markers of aging like pro-inflammatory cytokine levels and iNOS expression and protect against age-related changes to behavior like immobility during tail suspension (a model of depression) and total activity in a closed field (Rastogi et al., 2012).

Cardiovascular Health: EARLY CLINICAL EVIDENCE OF POTENTIAL BENEFIT

The research is also very preliminary for cardiovascular health but bacopa was reported to reduce stress and/or salivary cortisol levels in one clinical trial (Benson et al., 2014). A 4-week study of a nutraceutical called AkP05 that contains bacopa and other ingredients was found to reduce systolic blood pressure and improve endothelial function compared to placebo (n=45), and improve indices on a cardiopulmonary exercise test in patients receiving bacopa as compared to a diuretic (n=24); all patients in both parts of the study had hypertension, were receiving antihypertensives and had stable but unsatisfactory blood pressure (Carrizzo et al., 2020). It is impossible to say whether these results were due to bacopa or another ingredient. Some early rodent studies suggest that bacopa could reduce blood pressure (Kamkaew et al., 2011), protect against high cholesterol (Kamesh & Sumathi, 2012), or protect against the heart against ischemia-reperfusion injury, with increased heart muscle expression of antioxidants and heat-shock protein 72 in healthy rats (Mohanty et al., 2010).

Historically, bacopa has been used as an anxiolytic or for its calming effects. It has been clinically explored for effects on conditions such as depression or anxiety and some studies have suggested a benefit for patients with these conditions, though the results have been mixed and also complicated by some studies using multi-ingredient formulations while others use bacopa alone (reviewed in Brimson et al., 2021).

Preclinically, a couple laboratory studies hint at possible benefits for arthritis (Vijayan et al., 2011, Viji et al., 2010) and cancer (Peng et al., 2010, Janani et al., 2010, Kalamade et al., 2008). However, the laboratory work is very preliminary, tends to rely on the oxidative or inflammatory pathways, and have never been tested in humans in a trial or observational study.

Safety: Bacopa is typically thought to be well-tolerated. Clinical trials suggest that gastrointestinal side effects are the most common adverse events. Longer, larger, more robust trials in different patient populations would help confirm the safety profile.

Types of evidence:

- 3 systematic reviews and/or meta-analyses
- 1 open-label study
- 1 professional resource

- Biochemical data on bacopa accumulation of mercury and other metals

Bacopa has been used for centuries in traditional Indian medicine. In clinical trials, the use of bacopa extracts for three months in healthy adults has been safe and well-tolerated with no serious adverse events; occasional gastrointestinal discomfort like nausea, increased stools or diarrhea, and abdominal cramps, as well as dry mouth or flu-like symptoms, have been reported (Kongkeaw et al., 2014; Brimson et al., 2021). Systematic reviews have also identified reports of headache and drowsiness or fatigue, but these were uncommon (Basheer et al., 2022). The extracts of bacopa used in these trials varied. The doses averaged around 300 mg/day but ranged from 250 to 600 mg/day. In one trial, adverse events like heart palpitations, muscular fatigue, and the frequency of urination were more common in people given bacopa instead of placebo but the difference between the groups was not statistically significant (Stough et al., 2001). One open label study of 35 individuals utilized a 320 mg dose of bacopa for 3 months. They reported that 11% of the participants discontinued the trial due to gastrointestinal events; 22% of the remaining participants reported an adverse event, though none were reported by more than one individual and only one (fatigue) was thought to potentially be due to bacopa. There were no serious adverse events and no clinically significant changes in basic labs (Keegan et al., 2023). The larger and more robust trials that would be needed to establish efficacy would also have a benefit of confirming the safety profile of bacopa and also could shed more light onto whether specific patient populations or particular herb-drug interactions have unique safety signals.

Bacopa may also worsen certain conditions, including bradycardia, gastrointestinal obstruction, peptic ulcers, pulmonary conditions such as asthma, or urogenital tract obstruction; patients with these conditions should talk to their doctor before taking bacopa (Walker & Pellegrini, 2023).

Some sources of bacopa might be unsafe. The plant is known to accumulate toxins like mercury and has even been promoted as a tool to clean up the environment. So, depending on where the plant is grown, its extracts might contain mercury, lead, and other heavy metals (Srikanth Lavu et al., 2013). In 2008, a random evaluation of Ayurveda supplements sold online concluded that roughly 20% of Ayurveda supplements manufactured in either the United States or India contained lead, mercury, or arsenic (Saper et al., 2008).

Drug interactions:

Drug interactions with bacopa are generally not well studied or understood. Bacopa is thought to affect the cholinergic, serotonin, and dopaminergic systems; as such, it may interact with anticholinergic drugs or acetylcholinesterase inhibitors. There may be a risk of either greater side effects from cholinergic drugs or less benefit from their anticholinergic medications (Walker & Pellegrini, 2023; Examine.com). One animal study also reported that bacopa might affect levels of thyroid hormones so people who take thyroid medication should be particularly careful (Kar et al., 2002). An *in vitro* study found that bacopa may inhibit certain P450 enzymes; bacopa could therefore affect levels of drugs that are metabolized by those enzymes (Ramasamy et al., 2014). As with any supplement or medication, it is important to discuss your complete supplement and medication list to identify any potential interactions.

Research underway:

There are two ongoing studies that involve bacopa.

NCT04927338 is an ongoing study of approximately 170 veterans who have Gulf War Illness, which is a disorder that affects multiple organ systems including memory and cognition difficulties. The study will randomize participants to either 300 mg daily of bacopa from BacoMind® or matching placebo; dosing will last for 12 weeks. The primary outcome is the change in assessment of verbal learning and memory; secondary outcome measures include changes in blood biomarkers such as brain-derived neurotrophic factor (BDNF), safety, and overall health status. This trial is scheduled to end in fall of 2025.

NCT06523218 aims to enroll 50 healthy adults ages 50 to 75 and randomize them to either a supplement known as 1MD Nutrition MindMD® or matching placebo. The supplement contains 600 mg of bacopa from Bacognize, among other ingredients. Dosing will last for 3 months. The primary outcome is cognitive function and memory. This trial began in spring of 2024 and was estimated to end in summer of 2024.

Search terms:
Pubmed, Google: bacopa, Ayurveda

- amyloid, tau, cognitive, dementia, Alzheimer, oxidative, telomere, autophagy, mitochondria, lifespan, mortality, arthritis, cancer, cardiovascular, mercury

Websites visited for bacopa:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- Labdoor.com
- ConsumerLab.com

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