



*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.*

## Centella asiatica (Gotu kola)

### Evidence Summary

Improvements in a few cognitive functions, venous insufficiency, microangiopathy, and atherosclerosis have been observed in people. A few cases of hepatotoxicity and contact dermatitis have been reported.

**Neuroprotective Benefit:** Some clinical studies suggest modest benefit in a few cognitive functions, though a meta-analysis failed to show statistically significant differences. In preclinical studies, it reduced oxidative stress, A $\beta$  levels, and apoptosis, while promoting dendritic growth and mitochondrial health.

**Aging and related health concerns:** Some clinical studies suggest benefit of *Centella asiatica* in patients with venous insufficiency, microangiopathy, atherosclerosis, and wound healing, though full texts were inaccessible for many of the studies.

**Safety:** Numerous clinical trials have tested *Centella asiatica* with mostly mild adverse events (GI discomfort, headache, rash), though 3 cases of hepatotoxicity have been reported.

<b>Availability:</b> OTC	<b>Dose:</b> extracts at 30-90 mg/day; crude form at 1.5-4.0 g/day ( <a href="#">Drugs.com</a> )	<b>Chemical formula:</b> C <sub>30</sub> H <sub>48</sub> O <sub>5</sub> (e.g., Asiatic acid) <b>MW:</b> 488.70 (e.g., Asiatic acid)
<b>Half life:</b> 2-4 hrs, depends on chemical	<b>BBB:</b> Asiatic acid is bbb-penetrant	
<b>Clinical trials:</b> meta-analysis of 11 RCTs, of which 5 RCTs (including a total of 215 subjects) tested <i>Centella asiatica</i> alone	<b>Observational studies:</b> none	

**What is it?** *Centella asiatica* (Gotu kola) is an herbal medicine that is used in Ayurveda and Traditional Chinese medicine. It is also known as Asiatic pennywort, Indian pennywort, Jal Brahmi, Mandookaparni, and Tsubokusa (in Japanese). *Centella asiatica* is most commonly known as a cognitive enhancing supplement that is often compared to or called with the same name as Bacopa monnieri (e.g., Brahmi can refer to Bacopa alone or the combination of both Bacopa and *Centella asiatica*)([Examine.com](#)). *Centella asiatica* is thought to activate MAP kinases, which increase levels of the neurotrophic factor BDNF.

Aside from its cognitive enhancing effects, it is also known for its ability to promote wound healing. In preclinical studies, *Centella asiatica* inhibits enzymes that break down collagen while increasing collagen synthesis, thus increasing wound healing rate ([Examine.com](#)). In clinical settings, *Centella asiatica* has been used to treat venous insufficiency, a condition where valves in the vein do not function properly and blood pools in the veins of one's legs [1]. Other studies have explored the effects of *Centella asiatica* in alleviating anxiety, depression, diabetes, rheumatoid arthritis, and fever ([Examine.com](#); [WebMD.com](#)).

The main bioactive compounds in *Centella asiatica* are triterpenoid structures called Asiatic acid (up to 1% of dry weight) and madecassic acid (up to 1% of dry weight). *Centella asiatica* also contains many other compounds including glucose-bound forms of triterpenoids (e.g., asiaticoside, madecassoside), other triterpenoids, rosmarinic acid, ginsenosides, apigenin, rutin, quercetin, vitamin C, beta-carotene, anthocyanins (up to 37.6 mg/100g), and minerals including iron, potassium, copper, zinc, calcium, sodium, manganese, magnesium, and cobalt ([Examine.com](#)).



**Neuroprotective Benefit:** Some clinical studies suggest modest benefit in a few cognitive functions, though a meta-analysis failed to show statistically significant differences. In preclinical studies, it reduced oxidative stress, A $\beta$  levels, and apoptosis, while promoting dendritic growth and mitochondrial health.

*Types of evidence:*

- 1 meta-analysis of 11 RCTs testing *Centella asiatica* alone or a combination of supplements
- 1 clinical trial in patients with vascular cognitive impairment
- 0 observational studies
- Numerous laboratory studies

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

A 2017 meta-analysis of 11 randomized controlled trials analyzed whether *Centella asiatica* affects cognitive function in healthy people as well as in patient populations [2]. Five RCTs tested *Centella asiatica* alone and 6 RCTs tested a combination including *Centella asiatica*. No significant differences were observed between *Centella asiatica* and placebo on any cognitive domain. However, *Centella asiatica* was associated with improved mood based on self-reported alert scores and lower self-reported anger scores at 1 hour after treatment. Current evidence does not support *Centella asiatica* alone on overall cognitive function. Also, no significant differences were observed for mood or QoL.

In a double-blind randomized controlled trial of 28 healthy elderly, *Centella asiatica* treatment (750 mg/day) for 2 months enhanced working memory and increased a component of event-related potential (N100 amplitude) [3]. *Centella asiatica* decreased reaction time while increased % accuracy of working memory, which suggested increased speed and quality of working memory. However, significant changes in reaction times and % accuracy were observed in some of the tests, not all. Because there were 12 tests of cognitive functions measured at 4 different time points (pre-dose, 1 hr post-dose, 1 month, and 2 months), some of the significant findings may have been due to chance. Improvements of self-rated mood were also found following the *Centella asiatica* treatment. However, the precise mechanism(s) underlying these effects still require further investigation. Alert factor and calm factor significantly increased after 1 and 2 months of *Centella asiatica* treatment compared to placebo.

In an exploratory clinical study of 99 patients with post-stroke vascular cognitive impairment, treatment with *Centella asiatica* extract (750 or 1,000 mg/day) for 6 weeks resulted in improved MoCA-Indonesia scores, though this improvement was also seen in the control group receiving 3 mg/day of folic acid [4].

No differences were seen between the treatment groups, suggesting that the improvements were due to natural recovery from stroke. However, delayed recall memory was significantly improved in patients treated with *Centella asiatica* compared to folic acid. No group effects were seen in other cognitive functions, including executive function, naming, attention, language, abstraction, or orientation.

Human research to suggest benefits to patients with dementia:

None available.

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

There are many components to *Centella asiatica*, of which Asiatic acid has been the most studied in preclinical models. Asiatic acid does cross the blood-brain-barrier and displays antioxidant and neuroprotective effects [5]. Other studies have used extracts of *Centella asiatica* or other components (e.g., asiaticoside).

**Alzheimer's models:** In a mouse model of Alzheimer's (Tg2576 mice), orally administered water extract of *Centella asiatica* attenuated A $\beta$ -associated behavioral abnormalities [6]. *In vitro*, the extract protected SH-SY5Y cells and MC65 human neuroblastoma cells from toxicity induced by exogenously added and endogenously generated A $\beta$ , respectively. The extract prevented intracellular  $\beta$ -amyloid aggregate formation in MC65 cells. The extract did not show anticholinesterase activity or protect neurons from oxidative damage and glutamate toxicity.

In a different mouse model of Alzheimer's disease (PS/APP mice), *Centella asiatica* extract treatment (2.5 g/kg/day) for 8 months starting at 2 months of age (prior to amyloid deposition) significantly decreased levels of A $\beta$ -40 and -42 [7]. The extract also functioned as an antioxidant *in vitro*, scavenging free radicals, reducing lipid peroxidation, and protecting against DNA damage.

In neurons from Alzheimer's mice (Tg2576 mice), water extract from *Centella asiatica* prevented the diminished outgrowth of dendrites and loss of spines caused by A $\beta$  exposure [8]. In wild-type mouse neurons, the same extract increased dendritic arborization and spine densities.

In a cell culture model of Alzheimer's (SH-SY5Y cells), asiatic acid treatment prevented aluminium maltolate-induced cell death, attenuated rotenone-induced reactive oxygen species, and prevented apoptosis and mitochondrial membrane dysfunction [5].



**Parkinson's models:** In a mouse model of Parkinson's (MPTP), Asiatic acid (100 mg/kg) significantly attenuated motor abnormalities, dopamine depletion, and the diminished expressions of neurotrophic factors and their receptor TrkB [9]. Asiatic acid activated the PI3K/Akt/mTOR signaling pathway associated with neuroprotection. In a cell culture model of Parkinson's (SH-SY5Y cells exposed to rotenone), Asiatic acid prevented the overproduction of reactive oxygen species, mitochondrial dysfunction, and apoptosis [10].

**Cognitive dysfunction models:** In a rat model of cognitive decline (subjected to aluminum), *Centella asiatica* treatment (150 and 300 mg/kg/day) significantly improved memory performance, decreased caspase-3, decreased the activity of an enzyme that degrades the neurotransmitter acetylcholine (acetylcholinesterase), and reversed mitochondrial deficits [11].

In a rat model of cognitive decline (streptozotocin injection), *Centella asiatica* treatment (100-300 mg/kg) showed a dose-dependent improvement in cognitive behavior [12]. A significant decrease in oxidative stress (MDA levels) and an increase in antioxidant defense (glutathione and catalase levels) were observed in rats treated with 200 and 300 mg/kg *Centella asiatica*.

In neonatal mice exposed to glutamate, oral administration of Asiatic acid (100 mg/kg) significantly attenuated cognitive deficits in the Morris water maze test, decreased oxidative stress (lipid peroxidation) and restored antioxidant activity (glutathione and SOD) in the hippocampus and cortex to levels comparable to controls [13]. Asiatic acid (50 and 100 mg/kg) also attenuated neuronal damage in hippocampal CA1 and CA3 regions.

**Aging model:** In a senescence-accelerated mouse model (SAMP8), asiaticoside (20, 40, and 80 mg/kg/day) markedly reduced A $\beta$  by inhibiting expression of APP, BACE1, and cathepsin B (lysosomal enzyme), and promoting expression of neprilysin (amyloid-degrading peptidase) and insulin degrading enzyme [14]. Asiaticoside also increased plasticity-related proteins (e.g., PSD95, pNR1, pCaMKII, pPKA, pCREB, and BDNF). It also increased levels of acetylcholine, and decreased activity of AChE (enzyme that degrades acetylcholine), and prevented learning and memory decline by scavenging free radicals and upregulating antioxidant enzymes.

**APOE4 interactions:** Unknown.

**Aging and related health concerns:** Some clinical studies suggest benefit of *Centella asiatica* in patients with venous insufficiency, microangiopathy, atherosclerosis, and wound healing, though full texts were inaccessible for many of the studies.

*Types of evidence:*

- 1 Cochrane meta-analysis in 53 RCTs of various treatments for venous insufficiency
- 4 randomized controlled trials, 1 testing wound healing in diabetic wound patients, 1 in venous hypertensive microangiopathy, and 2 in diabetic microangiopathy/neuropathy
- 1 controlled clinical trial in patients with stenosing atherosclerotic plaques
- Numerous laboratory studies

**Venous insufficiency:** POTENTIAL BENEFIT. In a 2016 Cochrane systematic review of 53 randomized controlled trials testing various treatments for venous insufficiency, 2 trials tested *Centella asiatica* [1]. In one study, two 10 mg tablets of *Centella asiatica* were taken 3 times per day (60 mg/day) for 30 days and the other study used two 30 mg tablets twice daily (120 mg/day) for 56 days. One study showed non-significant effects when compared to placebo while the other study showed favorable results for *Centella asiatica* in the dichotomous variable global assessment by the subject. Both studies are from the 80's and the outcome measures used were crude.

**Microangiopathy and/or neuropathy:** POTENTIAL BENEFIT. There have been several placebo-controlled clinical studies in patients with microangiopathy (and/or neuropathy), but the studies are from 2001 and the full text was not accessible for any of them. One study reported that treatment with the triterpenic fraction of *Centella asiatica* (60-120 mg/day) in people with venous hypertensive microangiopathy significantly improved transcutaneous PO<sub>2</sub>-PCO<sub>2</sub> measurements and subjective scores of symptoms [15]. The other study, also by the same authors, reported that treatment with the triterpenic fraction (120 mg/day) for 12 months in patients with diabetic microangiopathy, neuropathy, and edema, resulted in decreased resting flow, edema, and swelling. Based on how the abstract is written, the changes were from baseline and not directly compared to the placebo group. In another study in 50 patients with diabetic microangiopathy, the same treatment for 6 months significantly improved microcirculatory parameters, including resting flow and venoarteriolar response. This study suggests that the triterpenic fraction may be useful in treating diabetic microangiopathy by improving microcirculation and decreasing capillary permeability.

**Atherosclerosis:** POTENTIAL BENEFIT. In a controlled trial of 391 patients with stenosing atherosclerotic plaques (50-60% in at least one carotid or common femoral bifurcation), treatment with Pycnogenol®



alone (pine bark extract, 100 mg/day) or a combination of Pycnogenol® and *Centella asiatica* (100 mg/day) significantly lowered the rate of progression of ultrasound arterial score in comparison to controls (no supplements, just lifestyle recommendations) [16]. They also found that the combination treatment was more beneficial than Pycnogenol® alone. There was a reduction in progression of plaques (measured by maximum plaque thickness, plaque length, and echogenicity) in both supplement groups with significantly better effects obtained by the combination compared to Pycnogenol® alone. The occurrence of anginal events was less than 3% in the two supplement groups in comparison with 6.25% in controls, with the lowest incidence observed in the combination group. The occurrence of myocardial infarctions was significantly lower for the combination group. Minor transient ischemic attacks were also significantly less frequent with the supplements with the best results observed in the combination group. Minor events requiring hospital admission were seen in 16.4% of control subjects, 8.9% of subjects taking Pycnogenol® alone, and only 3.3% of subjects receiving the combination treatment. At 4 years, oxidative stress levels in both supplement groups were significantly lower than those in controls. The full text was not accessible for this study, so it is unclear what mechanisms underlie these benefits, or the scientific rationale for this combination therapy.

In a preclinical study of human umbilical vein endothelial cells exposed to oxidized LDL-induced inflammation, asiaticoside (glucose-bound form of Asiatic acid) treatment reduced endothelial hyper-permeability and expression of vascular cell adhesion molecule-1 (VCAM-1) by 10% and 35%, respectively [17]. Asiaticoside may inhibit the augmentation of endothelial permeability and prevent early events of atherosclerosis.

**Wound healing:** POTENTIAL BENEFIT. In a randomized controlled trial of 200 diabetic wound patients, asiaticoside treatment (300 mg/day) significantly increased wound contraction (normal healing process) compared to the placebo group, though greater formation of granulation tissue was observed in the placebo group [18]. The authors note that *Centella asiatica* extract may shorten the course of diabetic wound healing, though the full text was not accessible, and the data could not be evaluated.

In preclinical studies, *Centella asiatica* inhibits enzymes that break down collagen while increasing collagen synthesis, thus increasing wound healing rate ([Examine.com](http://Examine.com)).

**Cerebral ischemia:** BENEFIT IN PRECLINICAL STUDIES. No studies have tested *Centella asiatica* in people with cerebral ischemia. In a mouse model of focal cerebral ischemia, Asiatic acid (75 mg/kg) significantly reduced infarct volume by 60% on day 1 and by 26% on day 7 post-ischemia [19]. The treatment also improved neurological outcome at 24 hours post-ischemia. There was an inverted U-shaped dose effect



such that 75 mg/kg was most neuroprotective, while lower (30 mg/kg) and higher (165 mg/kg) doses did not decrease infarct volume significantly. Neuroprotective properties of asiatic acid might be mediated in part through decreased blood-brain barrier permeability and reduced mitochondrial injury.

**Safety:** Numerous clinical trials have tested *Centella asiatica* with mostly mild adverse events (GI discomfort, headache, rash), though 3 cases of hepatotoxicity have been reported.

*Types of evidence:*

- 1 Cochrane meta-analysis in 53 RCTs of various treatments for venous insufficiency
- 1 meta-analysis of 11 RCTs testing *Centella asiatica* alone or a combination of supplements
- 1 RCT testing asiaticoside treatment for wound healing in diabetic wound patients
- 1 clinical trial in patients with vascular cognitive impairment
- 1 case report of 3 patients with hepatotoxicity

Numerous clinical studies have examined the adverse effects of *Centella asiatica* or its components.

**Meta-analyses:** In a Cochrane systematic review of 53 RCTs in patients with venous insufficiency, only 2 RCTs tested *Centella asiatica* specifically, of which 1 study reported information on adverse events [1]. In this study, 31% of participants in the *Centella asiatica* group (19/61) experienced adverse events and 27.3% (9/33) in the placebo group. Two participants who took *Centella asiatica* (120 mg) withdrew - one because of gastric colic and the other because of absence of nerve activity—it is unknown whether these events were related to *Centella asiatica*. One participant taking placebo withdrew from the study because of cyanosis of the extremities.

In a meta-analysis of 11 randomized controlled trials testing the effects of *Centella asiatica* on cognitive function, 5 RCTs tested *Centella asiatica* alone and 6 RCTs tested a combination including *Centella asiatica* [2]. No adverse effects were reported in any studies looking at *Centella asiatica* alone. However, for studies testing *Centella asiatica*-containing combination therapies, 4 studies reported mild adverse events. Two studies reported adverse event rates comparable to the placebo rate, while the other 2 studies reported lower rates of adverse events for *Centella asiatica*-containing products. Common adverse events were gastrointestinal discomfort, flatulence, nausea, headache, decreased appetite, sedation, and rash. Hepatotoxicity, which has been reported in one previous case report (described below) [20], was not observed in any of the included RCTs.





**Other clinical trials:** In a randomized controlled trial of 200 patients with diabetes, treatment with extracted asiaticoside (component of *Centella asiatica*; 100 mg, 3 times daily) did not result in serious adverse events, though the full text was not accessible and the milder adverse events could not be evaluated [18].

In an exploratory clinical study of 99 patients with post-stroke vascular cognitive impairment, 750 or 1,000 mg/day of *Centella asiatica* extract for 6 weeks did not result in significantly greater or severe adverse events compared to control (3 mg/day of folate) [4]. One patient discontinued therapy due to an allergic reaction. No treatment effects were observed on liver enzymes (though see below for case studies on hepatotoxicity). In the 1,000 mg *Centella asiatica* group, 1 patient experienced constipation and 1 patient experienced itchiness. In the 750 mg group, 1 patient had abdominal bloating. In the folate group, 1 patient had heartburn and 1 had nausea.

**Case report of hepatotoxicity:** A study reported 3 cases of hepatotoxicity associated with ingestion of *Centella asiatica* [20]. Three women (ages 49, 52, and 61) developed jaundice after taking *Centella asiatica* for 20-60 days. All 3 women were ingesting *Centella asiatica* tablets (of unknown dosage) to lose weight. ALT levels went up to 324-1694 U/L (normal levels range from 7-56 U/L), ALP levels to 472-503 U/L (normal levels range from 44-147 IU/L), and bilirubin levels to 4.23-19.89 mg/dl (normal levels range from 0.1-1.2 mg/dl). Diagnoses were: granulomatous hepatitis with marked necrosis and apoptosis; chronic hepatitis with cirrhotic transformation and intense necroinflammatory activity; and granulomatous hepatitis. All patients improved after discontinuation of *Centella asiatica* and treatment with ursodeoxycholic acid (UDCA) at 10 mg/kg/day. The first patient took *Centella asiatica* again, resulting in recurrence of damage. The second patient had taken this herb a year before for 6 months with similar symptoms. Based on liver biopsies of these patients, the authors suspected that the damage produced by *Centella asiatica* is via induction of apoptosis through alteration of liver cell membranes, leading to hepatic lesions. Based on other studies reporting few and mild adverse events, it is not clear whether the hepatotoxicity is associated with a specific brand (not noted in this case report) or higher dose (also not included). *Centella asiatica* probably should not be used in people with liver disease.

**Drug interactions:** Drug interactions are not well-documented, though theoretically, *Centella asiatica* may interact with antiepileptics (e.g., phenytoin, valproate, and gabapentin) ([Drugs.com](#)).

In some clinical trials, contact dermatitis has been documented ([Drugs.com](#)).

**Sources and dosing:** *Centella asiatica* is available OTC and comes in the forms of whole herbs, powder, capsules, or liquid extracts. Although dose ranges noted in [Drugs.com](https://www.drugs.com) were 30-90 mg/day for extracts and 1.5-4.0 g/day for the crude form, much higher doses have been used in clinical studies. For example, doses used in patients with vascular cognitive impairment were 750 mg and 1000 mg of extract per day [4]. No studies have directly compared different formulations or brands of *Centella asiatica* and no information was found on Labdoor or ConsumerLab.

A review on recent updates on the neuroprotective potential of *Centella asiatica* noted that the extraction method, biochemical profile and dosage information of the extract need to be standardized to enhance the economic value of this traditional herb and to accelerate the incorporation of *Centella asiatica* extracts into modern medicine [21].

In a rodent study, aqueous extract, methanolic extract, and chloroform extract of *Centella asiatica* were compared and only the aqueous extract of the whole plant (200 or 300 mg/kg for 14 days) showed an improvement in learning and memory [22]. The aqueous extract at these doses also decreased brain levels of oxidative stress (MDA) and increased antioxidant defense (glutathione).

**Research underway:** Only one clinical trial on ClinicalTrials.gov is currently testing *Centella asiatica*. It is a clinical trial in breast cancer patients and they are testing the effects of herbal creams (cucumber, *Centella asiatica*, thunbergia, or placebo) on reduction of radiation-induced dermatitis ([NCT02922244](https://clinicaltrials.gov/ct2/show/study/NCT02922244)). It is scheduled to be completed in October 2018.

#### Search terms:

Pubmed, Google: Gotu kola, *Centella asiatica*

- + cognitive, + Alzheimer's, + dementia, + APOE, + meta-analysis, blood-brain barrier, + clinical trial, + cardiovascular, + diabetes, + inflammation, + atherosclerosis, + lifespan, + observational

Websites visited for gotu kola, *Centella asiatica*, or asiatic acid:

- [Clinicaltrials.gov](https://clinicaltrials.gov) (14, but only 1 ongoing)
- [Examine.com](https://www.examine.com)
- [Treato.com](https://www.treato.com)
- DrugAge (0)
- Geroprotectors (0)
- [Drugs.com](https://www.drugs.com)
- [WebMD.com](https://www.webmd.com)



- Labdoor.com (0)
- [ConsumerLab.com](http://ConsumerLab.com)
- Cafepharma (0)

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