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.

Shankhpushpi

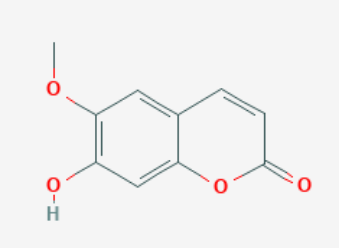
Evidence Summary

Used in Ayurvedic medicine for enhancing cognitive functions, slowing brain aging, and treating hypertension, diabetes, and other conditions. It has antioxidant and anti-inflammatory effects.

Neuroprotective Benefit: Although data from well-controlled, rigorously designed clinical trials are currently lacking, many preclinical studies suggest pro-cognitive, antioxidative, and anti-inflammatory effects with shankhpushpi treatments.

Aging and related health concerns: Shankhpushpi has been used for hypertension, diabetes, hyperlipidemia, and other conditions. It also extends lifespan in a fly model of Alzheimer's disease.

Safety: Shankhpushpi has been widely used in Ayurvedic medicine and is generally safe when used in line with recommendations, though it may have mild hypotensive effects. It also interacts with the anti-seizure medication phenytoin.

Availability: OTC.	**Dose**: Not established. One clinical study used a dose of 500 mg twice daily with milk.	**Chemical formula: N**umerous compounds, e.g., scopletin is $C_{10}H_8O_4$ **MW**: Numerous compounds, e.g. scopoletin is 192.17  Source: PubChem
Half life: Numerous compounds; varies.	**BBB**: Some compounds are likely penetrant.	
Clinical trials: A trial evaluating memory included 102 healthy volunteers.	**Observational studies**: None.	

What is it? Shankhpushpi (*Convolvulus pluricaulis*) is a perennial plant native to India and has been used in Ayurvedic medicine for enhancing memory and cognitive function (Farooqui et al., 2018). Shankhpushpi is also used for stress, anxiety, mental fatigue, neuroprotection, insomnia, diabetes, infections, pain relief, and immune system modulation (Balkrishna et al., 2020). Various formulations are also used to treat nervous disorders, such as insanity, epilepsy, hysteria, and psycho-neurosis. Shankhpushpi's calming effect is thought to be mediated in part by regulation of stress hormone production (e.g., adrenaline and cortisol). This medicinal herb contains many bioactive phytoconstituents that are responsible for nootropic and other activities, such as alkaloids (convolamine, convosine, convoline, convolidine, convolvine, confoline, evolvine, phyllabine, subhirsine, sankhpuspine), flavonoids (kaempferol, quercetin), and coumarins (ayapanin, scopolin, scopoletin). These compounds are thought to contribute to its nootropic and memory enhancing properties, along with some other pharmacological activities. Sedative activity is thought to be mediated by convolamine and scopoletin, which act as GABA-A agonists. It is also believed that a paste prepared from its roots and flowers act as anti-aging agents (Adams et al., 2007).

Neuroprotective Benefit: Although data from well-controlled, rigorously designed clinical trials are currently lacking, many preclinical studies suggest pro-cognitive, antioxidative, and anti-inflammatory effects with shankhpushpi treatments.

Types of evidence:

- 2 open-label clinical studies
- 2 reviews
- Numerous laboratory studies

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

In an open-label clinical study of 102 young (ages 16-25) healthy volunteers, shankhpushpi supplementation for 2 months (500 mg tablets, twice daily after food with milk) was compared with a yoga intervention: Satvavajaya Chikitsa adopted in form of yogic procedures such as Asana (sitting posture with breathing techniques), Pranayama (regulating breath), and chanting (Amin and Sharma, 2015). The yoga intervention group showed statistically significant improvement in verbal retention for similar pair, verbal retention for dissimilar pair, and visual immediate tests. The shankhpushpi intervention group showed significant improvement in auditory delayed, visual delayed, auditory recognition and visual recognition tests. Thus, the yoga practice appeared to improve immediate recollection in terms of short-term memory, while Shankhpushpi appeared to improve long-term memory. The authors suggest several mechanisms of action: increased neuropeptide synthesis, anti-stress activity, anti-depressant activity (via its interaction with adrenergic, dopaminergic and serotonergic systems), nootropic effects of flavonoids, anxiolytic activities, and anti-acetylcholinesterase activities. However, since this was a behavioral intervention compared with a supplement intervention, there was no true control group, and therefore, further studies are needed to validate these findings and understand the precise molecular mechanisms of potential neuroprotective action.

In an open-label study of 90 school children, a 3-month treatment of Ayurvedic medicine including *Centella asiatica*, yashtimadhu, guduchi, and shankhpushpi (dose of 2 g) twice daily with milk was compared with a control group or a group that practiced yoga (Asanas Pranayama)(Sarokte and Rao, 2013). Among the three groups, the Ayurvedic medicine group showed significant improvements in short-term memory and serial recall. The yoga practice group showed significant improvements in subjective and objective parameters in the mini-mental status scale. The authors suggest that the phytonutrients in shankhapusphi (convolidine, convolvine, convolvidine, convoline, confoline, phyllabine, subhirsine, and scopoline) may help to stimulate the brain and to increase the ability to

concentrate. Shankhpushpi is also known to reduce anxiety and stress by controlling the production of stress hormones, adrenaline and cortisol. Because the Ayurvedic medicine intervention included many plant products, it is not possible to attribute the benefit to any specific plant.

Human research to suggest benefits to patients with dementia:
None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Numerous studies have examined the neuroprotective benefits of shankhpushpi in rodents and in cell culture models. In normal rats, Shankhpushpi extract treatment (500 mg/kg) improved memory, increased synaptic plasticity (as measured by enhanced long-term potentiation), and reduced synaptic depression (long-term depression)(Das et al., 2020). In this study, an *ex-vivo* study of a single compound, scopoletin, present in shankhpushpi could exert similar increases in synaptic plasticity.

Shankhpushpi contains polyphenols, flavonoids, and vitamin E that act as scavengers of reactive oxygen species and also reduce lipid peroxidation (Balkrishna et al., 2020).

Cognitive impairment models: In a rat model of cognitive impairment (induced by scopolamine injection), oral treatment of shankhpushpi extract (150 mg/kg) prevented the increase in tau and Aβ peptides as well as histopathological changes in the cerebral cortex (Bihaqi et al., 2012). In a related study in rats, pretreatment with an aqueous extract of shankhpushpi (150 mg/kg) significantly reduced scopolamine-induced cognitive deficits, as measured by transfer latency in the elevated plus maze and improved spatial memory performance on the Morris water maze (Bihaqi et al., 2011). In the cortex and hippocampus, the extract treatment significantly inhibited acetylcholinesterase (AChE) activity by 46% in the cerebral cortex and by 56% in the hippocampus. The extract also increased antioxidant defense (SOD, glutathione reductase, reduced glutathione) within the cortex and hippocampus, while lowering lipid peroxidation (MDA levels) and protein carbonyl levels.

In a mouse model of cognitive impairment (induced by scopolamine), shankhpushpi extract treatment showed nootropic and anxiolytic activity (Malik et al., 2011). Different shankhpushpi plants were compared and the *Convolvulus pluricaulis* extract showed maximum nootropic and anxiolytic activity at 100 mg/kg dose, whereas the *Evolvulus alsinoides* extract and *Clitoria ternatea* extract showed maximum memory-enhancing and anxiolytic activity at 200 and 100 mg/kg doses, respectively. All 3 plants showed central nervous system depressant action at higher dose levels.

In a rat model of neurotoxicity (induced by aluminum injection), daily administration of shankhpushpi aqueous extract (150 mg/kg) for 3 months decreased the elevated enzymatic activity of acetylcholinesterase and also inhibited the decline in Na(+)/K(+)ATPase activity (Bihaqi et al., 2009). The extract treatment also prevented the accumulation of lipid and protein damage as well as changes in the levels of endogenous antioxidant enzymes. Oral administration of shankhpushpi extract preserved the mRNA levels of muscarinic acetylcholine receptor 1 (M1 receptor), choline acetyl transferase (ChAT) and Nerve Growth Factor-Tyrosine kinase A receptor (NGF-TrkA). It also ameliorated the upregulated protein expression of cyclin dependent kinase5 (Cdk5), which is implicated in neurodegeneration and induced by aluminium.

Alzheimer's models: In a Drosophila fly model of Alzhiemer's disease (human tau-induced neurotoxicity), an aqueous extract of shankhpushpi significantly decreased the level of tau protein, enhanced the activities of antioxidant enzymes (catalase and SOD), and ameliorated tau-induced oxidative stress (Kizhakke et al., 2019).

In mouse neuroblastoma cells expressing the Swedish Alzheimer's mutation (N2a-SweAPP cells), ethanol extract of shankhpushpi inhibited Aβ generation (Liu et al., 2012). However, the extract did not have any effect on the amyloid precursor protein (APP) levels. The authors speculate that the extract of shankhpushpi leaves did not reduce Aβ through APP modulation, but through some other pathway, such as by enhancing the activity of amyloid-degrading enzymes, e.g., insulin-degrading enzymes or neprilysin.

In cell culture (SHSY5Y cells), pretreatment with an ethanolic extract of shankhpushpi resulted in 50% cell survival against H_2O_2 challenge for 24 hours and it also decreased the leakage of lactate dehydrogenase (Rachitha et al., 2018). Shankhpushpi pretreatment also restored and regulated antioxidant (catalase, SOD) and apoptosis (p53 and caspase 3) markers and inhibited reactive oxygen species generation and depolarization of the mitochondrial membrane.

Other *in vitro* studies have shown that the syrup of shankhpushpi strongly inhibited Aβ40 and methionine Aβ40 fibrillation compared to extracts of other herbs (Witter et al., 2018). However, inhibition was affected by age and storage conditions of shankhpushpi; after three months of storage, the inhibition efficiency was reduced or disappeared completely.

Huntington's disease models: In a rat model of Huntington's disease (systemic injection of 3-nitropropionic acid, a mitochondrial complex II inhibitor that induces striatal toxicity and motor

impairment), motor deficits and oxidative damage are seen, but these effects are largely prevented with a methanolic extract of shankhpushpi (Kaur et al., 2016). Extract pretreatment (20 mg/kg) significantly attenuated the loss in body weight and improved locomotor activity, grip strength, and gait abnormalities. It also decreased oxidative stress markers (malondialdehyde and nitrite levels) and restored antioxidant defense (SOD and reduced GSH enzyme activity) in the striatum and cortex. Of the different compounds present in shankhpushpi, treatment with scopoletin alone also improved body weight, locomotor activity, rotarod performance, and balance beam walk, while attenuating oxidative damage (measured by lipid peroxidation, nitrite, SOD, and GSH levels). A similar study also reported that ethyl acetate and butanol fractions of shankhpushpi extract significantly attenuated Huntington's-like symptoms induced by 3-nitroproprionic acid, including locomotor activity, grip strength, memory, body weight, and oxidative defense (Malik et al., 2015).

Ischemia models: In a rat model of cerebral ischemia reperfusion injury (bilateral common carotid artery occlusion), chloroform and ethanol extract of shankhpushpi showed neuroprotective activity by significantly decreasing lipid peroxidation, and increasing antioxidant defense (superoxide dismutase, catalase, glutathione, and total thiol) (Shalavadi et al., 2019). Cerebral infarction area was reduced, blood brain barrier disruption was ameliorated, and histopathlogy was improved.

Stress models: In a rat model of chronic mild stress, treatment with a methanolic extract of shankhpushpi (50 and 100 mg/kg) for one week significantly ameliorated stress responses, as measured by increased sucrose preference index, reduced immobility time in the forced swim test, and increased the number of squares crossed and the number of rearing in the open field test (Gupta and Fernandes, 2019). Moreover, elevated levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α and liver damage biomarkers (ALT, AST) were significantly reversed by shankhpushpi treatment (50 and 100 mg/kg) or the antidepressant fluoxetine. Also, a one-week treatment of shankhpushpi (50 and 100 mg/kg) restored serotonin and noradrenaline levels in the hippocampus as well as in the prefrontal cortex of the chronically stressed rats.

APOE4 interactions: Unknown.

Aging and related health concerns: Shankhpushpi has been used for hypertension, diabetes, hyperlipidemia, and other conditions. It also extends lifespan in a fly model of Alzheimer's disease.

Types of evidence:

- 1 open-label clinical study in type 2 diabetes mellitus
- 1 observational study in people with hypertension
- 1 review
- Several laboratory studies

In Ayurvedic medicine, shankhapusphi has been used for anti-diabetic, anti-hyperlipidemic, anti-hypertensive, anti-microbial, anti-platelet aggregation, anti-ulcer, cardioprotective, and hepatoprotective properties (Balkrishna et al., 2020).

Hypertension: DECREASES BLOOD PRESSURE
In a small observational study of 40 patients with hypertension, a Brahmyadi Churna formulation that included shankhpushpi (along with Brahmi, Jatamansi, Jyotishmati, Vacha, and Ashwagandha) taken with milk for 1 month markedly improved blood pressure in 19 participants (systolic by 30–40 mmHg and diastolic by up to ≤15 mmHg), moderately improved blood pressure in 14 participants (systolic by 20–29 mmHg and diastolic by 11–14 mmHg), mildly improved blood pressure in 5 participants (systolic by 10–19 mmHg and diastolic by 5–10 mmHg), and showed no improvement in 2 individuals (Ali et al., 2015).

Inflammation: MAY REDUCE CYTOKINE MEDIATORS BASED ON PRECLINICAL STUDIES
No published studies have examined the effects of shankhpushpi in people with inflammatory conditions. However, hydroxy-cinnamic acid is a phenyl-propanoid compound found in shankhpushpi and it is known to downregulate cytokine mediators such as IL-8, MCP-1, and ICAM-1 (Balkrishna et al., 2020). In rats, oral administration of the ethanolic extract of shankhapusphi leaves (800 mg/Kg) showed significant inhibition of Carrageenan-induced paw edema (Agarwal et al., 2014).

Lifespan: EXTENDED IN A FLY MODEL OF AD
In a drosophila fly model of Alzhiemer's disease (human tau-induced neurotoxicity), an aqueous extract of shankhpushpi significantly offset the shortened lifespan and decreased tau protein levels (Kizhakke et al., 2019). Shankhpushpi treatment also enhanced the activities of antioxidant enzymes (catalase and SOD), ameliorated the tau-induced oxidative stress, and restored acetylcholinesterase activity. Mean life span of tauopathy flies was 46.25 ± 0.479 days, control flies was 76.25 ± 1.315 days, and tauopathy flies

reared on 0.01% and 0.02% shankhpushpi supplement was 51.63 ± 0.239 and 57.75 ± 0.323 days respectively.

Metabolic problems and hyperlipidemia: POTENTIAL BENEFIT IN T2DM, LDL
In an open-label clinical study of 68 patients with type 2 diabetes mellitus, 34 patients received a herb-mineral compound (containing Shuddha Shilajatu, Shuddha Guggulu, Vijayasara Ghana, Saptarangi Ghana, and Triphala Ghana) at 3 gm/day in three divided doses with luke-warm water before meals for 8 weeks and 34 patients received shankhpushpi at a dose of 1.5 g/day in three divided doses for 8 weeks along with the herb-mineral compound (Patel et al., 2012). In the herb-mineral compound group, serum triglyceride and VLDL were significantly decreased. In the group receiving both the herb-mineral compound with shankhapusphi, serum cholesterol and LDL were significantly decreased, and blood sugar levels were significantly lowered. In the group receiving both herb-mineral compound with shankhapusphi, 32.35% patients markedly improved, 58.82% moderately improved, 8.82% improved, and 0% remained unchanged with regards to overall symptoms. Because of the numerous biomarkers and subjective symptoms evaluated, and the lack of control for multiple comparisons, further studies are needed to validate these findings.

Anti-diabetic activities of shankhpushpi might be attributed to the presence of tropane alkaloids which are known as potent inhibitors of α-glucosidases and R-galactosidases (Balkrishna et al., 2020). The polyphenols in shankhpushpi act as reactive oxygen species quenchers, which in turn may ameliorate oxidative stress that is increased as a result of diabetes.

Pain: POTENTIAL PAIN RELIEF IN RODENT MODELS
In rats, treatment with an ethanolic extract of shankhpushpi (750 mg/kg) showed statistically significant analgesic activity as compared to standard analgesics like morphine sulphate, when tested in the hot plate test and tail-flick assay (Agarwal et al., 2014). Analgesic activity is attributed to flavonoids, volatile oils, alkaloids, polyphenols, and organic acids that together prevent the formation of cyclooxygenase enzyme and prostaglandins.

Sleep: POTENTIAL BENEFIT IN MICE
In mice, treatment with ethanolic and aqueous extracts of shankhpushpi significantly increased sleeping time, while the chloroform extract failed to show benefit (Siddiqui et al., 2011). Sedative activity is thought to be mediated by convolamine and scopoletin, which act as GABA-A agonists (Balkrishna et al., 2020).

Safety: Shankhpushpi has been widely used in Ayurvedic medicine and is generally safe when used in line with recommendations, though it may have mild hypotensive effects. It also interacts with the anti-seizure medication phenytoin.

Types of evidence:

- 2 reviews
- 1 laboratory studies

Shankhpushpi has been used for many years as part of Ayurvedic medicine and is generally thought to be safe when taken at common recommended doses. Shankhpushpi does have a mild hypotensive effect, so people suffering from low blood pressure, or those taking anti-hypertensive medications should consult with their healthcare providers before taking it.

In a review of the phytochemistry and medicinal properties of shankhpushpi, rats did not experience toxicity or behavioral changes up to the dose of 5,000 mg/kg of ethanolic or aqueous extract (Balkrishna et al., 2020). Histopathological examination did not reveal any aberrations or degeneration of neurons in the brain. Furthermore, no inflammation was observed in the heart or liver.

Drug interactions: Based on a review of herb-drug interactions, the Ayurvedic syrup shankhpushpi can decrease concentrations of phenytoin, leading to decreased control of seizure (Fugh-Berman, 2000). In two patients with seizure who were also taking shankhpushpi, there was an unexpected loss of seizure control and reduction in plasma phenytoin levels. In a study in rats, a single dose of shankhpushpi and phenytoin coadministration did not have any effect on plasma phenytoin levels but decreased the antiepileptic activity of phenytoin significantly (Dandekar et al., 1992). On multiple-dose coadministration, shankhpushpi reduced not only the antiepileptic activity of phenytoin but also lowered plasma phenytoin levels. Shankhpushpi alone also showed significant antiepileptic activity compared to placebo.

Sources and dosing: Shankhpushpi is available over-the-counter as a supplement. Shankhapusphi can come in tablet/capsule form, powder, juice, oil, and decoction. For tablets/capsules, 1 or 2 are typically taken twice a day with milk (preferably after meals)(netmeds.com). For powder, a typical dose is a 1/4 or 1/2 teaspoon infused in lukewarm milk taken twice a day. For shankhpushpi juice (Kashayam), 2-4 teaspoons are mixed with water and taken once or twice a day. For syrup, 20 ml are taken twice a day with water after meals.

Shankhpushpi is extensively used in pharmaceutical, cosmetic, and nutraceutical industries in India (Balkrishna et al., 2020). In the pharmaceutical industry, various extracts, syrups, and tablets are produced for targeting neurodegenerative diseases, hypertension, hypercholesterolemia, and gastric ulcers. In the cosmetic industry, shankhpushpi is used as a tonic for rejuvenating the skin and hair. Additionally, food grade shankhpushpi powder and syrups are also available as nootropic supplements in India.

One clinical study used a shankhpushpi dose of 500 mg twice daily with milk (Amin and Sharma, 2015).

Research underway: No clinical trials testing Shankhpushpi are currently ongoing, based on ClinicalTrials.gov.

Search terms:
Pubmed, Google: Shankhpushpi, *Convolvulos pluricaulis*

Websites visited for Shankhpushpi:

- Clinicaltrials.gov (0)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem (0)
- DrugBank.ca (0)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

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