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.

Tinospora cordifolia

Evidence Summary

Preclinical studies have shown increased lifespan, prevention of cancers, diabetes, and inflammation, but clinical evidence is very limited.

Neuroprotective Benefit: Only a few preclinical studies have tested Tinospora cordifolia for its neuroprotective benefits and mechanisms have not been clearly defined.

Aging and related health concerns: Preclinical data suggest lifespan extension and potential for treating diabetes and cancers, but clinical data are very limited.

Safety: Based on a few small clinical studies, Tinospora cordifolia is generally well-tolerated; reported adverse events include nasal pain and headache.

Availability: OTC	**Dose:** for allergic rhinitis (hay fever), 300 mg of aqueous stem extract is used 3 times daily, orally	**Chemical formula:** varies **MW:** varies
Half life: not well studied except berberine (3-4 hr)	**BBB:** berberine is penetrant—unknown for others	
Clinical trials: largest DBRCT included 75 patients with hay fever	**Observational studies:** none available	

What is it? Tinospora cordifolia (also known as guduchi or amrita) is a medicinal plant used in Ayurvedic medicine and is well-documented for its immunomodulatory properties. It has been researched most extensively for alleviating allergic rhinitis. A particular extract of Tinospora cordifolia (Tinofend, Verdure Sciences) appears to significantly decrease sneezing and nasal itching, discharge, and stuffy nose ([1]; WebMD.com). It is also being studied for potential benefits in diabetes, glucose metabolism, inflammation, and immune system support (examine.com).

Health benefits are attributed to various compounds present in Tinospora cordifolia, including epicatechin and arabinogalactan polysaccharide (antioxidants), quercetin and rutin (anti-cancer), berberine (cardioprotective), and immunomodulatory active components (11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, and syringin) [2].

Neuroprotective Benefit: Only a few preclinical studies have tested Tinospora cordifolia for its neuroprotective benefits and mechanisms have not been clearly defined.

Types of evidence:

- 0 meta-analysis or clinical trials
- 0 observational studies
- 3 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None available.

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

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
A few preclinical studies have tested Tinospora cordifolia for its potential neuroprotective benefits.

In sleep-deprived rats, 50% ethanolic extract of Tinospora cordifolia (140 mg/kg, orally) for 15 days significantly improved cognitive functions (e.g., novel object recognition and elevated plus maze) compared to vehicle-treated sleep-deprived animals [3]. Tinospora cordifolia pretreatment modulated the stress induced-expression of plasticity markers (PSA-NCAM, NCAM and GAP-43) along with proteins involved in synaptic plasticity (i.e., CamKII-α and calcineurin) in hippocampus and pyriform cortical regions of the brain. Interestingly, contrary to vehicle-treated animals, Tinospora cordifolia-treated animals showed downregulated expression of inflammatory markers such as CD11b/c, MHC-1 and cytokines along with inhibition of apoptotic markers. However, protein levels were measured based on immunohistochemistry/immunoblots and were not very quantitative.

In a rat model of drug (scopolamine)-induced amnesia, a combination of Tinospora cordifolia, Bacopa monnieri, and Evolvulus alsinoides (ethanolic extract; 200 mg/kg; orally) provided greater nootropic effects than any of the herbs alone or combinations of any two [4]. The full text for this study was not readily available, and therefore details of the methods and results could not be evaluated.

In primary cerebellar neuronal cultures exposed to neurotoxic insult (monosodium glutamate), pretreatment with butanol extract of Tinospora cordifolia normalized the stress-induced downregulation in the expression of neuronal markers (MAP-2, GAP-43, NF200) and an anti-apoptotic marker (Bcl-xL) [5]. Also, these cells showed enhanced expression of inflammatory (NF-κB, AP-1) and senescence markers (HSP70, Mortalin) as well as greater mitochondrial damage, but Tinospora cordifolia pretreatment was able to prevent these changes. Tinospora cordifolia treatment also promoted regeneration, migration, and plasticity of cerebellar neurons, which was otherwise significantly inhibited by glutamate treatment. A mass spectrometry analysis (UPLC-MS) revealed 8 peaks corresponding to magnoflorine, palmatine, norcoclaurine, cordifolioside A, oblongine,

tetrahydropalmatine, 11-hydroxy mustakone, and tinocoriside (which belong to alkaloids, glycosides and sesquiterpenoids).

APOE4 interactions: Unknown.

Aging and related health concerns: Preclinical data suggest lifespan extension and potential for treating diabetes and cancers, but clinical data are very limited.

Types of evidence:

- 2 clinical trials
- Numerous laboratory studies

Lifespan: POTENTIAL BENEFIT IN ANIMAL MODELS. No studies have examined whether Tinospora cordifolia is associated with enhanced lifespan in humans. In a small study of 15 pregnant cows, Tinospora cordifolia treatment (60 g/day for 45 days prepartum, 120 g/day for 45 days postpartum) improved reproductive performance by improving its immunity and reducing prepartum plasma progesterone concentrations [6]. Treatment reduced occurrence of reproductive disorders (e.g., uterine infections), helped resume cyclicity, increased calf body weight at birth, and improved calf survival. While this data may be relevant for dairy farmers (e.g., profitability), it is based on only 15 cows. It is not possible to extrapolate this data to what one might expect for human life expectancy.

Another study in drosophila flies reported that Tinospora cordifolia treatment (0.25, 0.5, or 0.7 g/100 mL, mixed with food) for 30 days significantly increased lifespan in both the treated flies and their offspring [7]. The lifespan of control groups ranged from 24-28 days, while the 0.25 g/100 mL treatment group had average survival days of 83-84 days in both males and females (199.4% increase). Higher doses also increased lifespan but not to the same extent (164.45% increase in 0.5 g dose and 94.72% increase in 0.7 g dose). The offspring also benefited from increased lifespan. The 0.25 g/100 mL treatment group had mean survival of 46 days (91% increase) compared to 24 days in control. Higher doses showed some lifespan extension but not as much as the 0.25 g/100 ml dose. Authors speculated that the lifespan extension observed in flies is due to the high antioxidative capacity of Tinospora cordifolia.

Cardiovascular: POTENTIAL BENEFIT. In a small placebo-controlled clinical study of 30 healthy volunteers subjected to cycle ergometer exercise (and other physical stressors), Tinospora cordifolia treatment (150 or 300 mg of aqueous extract) showed a significant increase in mean maximum speed

compared to placebo, as well as a significant decrease in mean systolic BP and heart rate (HR) on fixed workload exercise compared to placebo [8]. On day 14 and 28, Tinospora cordifolia (300 mg) showed a significant decrease in mean HR on the cold pressor test, compared to placebo. Based on these data, Tinospora cordifolia improved physical performance and suppressed over-activation of the sympathetic nervous system consistent with its purported adaptogenic property. In Ayurvedic literature, this herb is mentioned as an adaptogen (anti-stress activity).

In a rat model of myocardial infarction (induced by ischemia-reperfusion), Tinospora cordifolia pretreatment (250, 500, or 1,000 mg/kg, alcoholic extracts) for 7 days significantly reduced infarct size from 50.9 (% of left ventricle) in control animals to 34.5, 27.3, and 20.8 with 250, 500, and 1,000 mg/kg doses, respectively [9]. There was a dose-dependent decrease in oxidative stress (MDA levels) in the heart tissue and in the serum with Tinospora cordifolia treatment. It is unknown whether it is protective when treatment is initiated after an ischemic event.

Diabetes: POTENTIAL BENEFIT IN PRECLINICAL MODELS. No clinical trials have tested whether Tinospora cordifolia may prevent or treat diabetes. In a prospective randomized controlled study of 45 patients with diabetic foot ulcers, Tinospora cordifolia treatment for 4 weeks showed significantly better outcome with improvement in wound healing [10]. Reduced debridements and improved phagocytosis were statistically significant (but not corrected for multiple comparisons), indicating beneficial effects of immunomodulation for ulcer healing. No significant differences were seen in other measures including rate of change of ulcer area, rate of change of ulcer perimeter, change of depth, and change of wound score. Full text was unavailable and therefore specific details of the study design, formulation, and dose could not be evaluated.

Benefits have also been observed in rodent models. Oral treatment of Tinospora cordifolia (25-200 mg/kg) for 2-6 weeks in rat models of diabetes resulted in decreased blood glucose [11; 12], increased insulin secretion [11], and decreased oxidative stress (decreased TBARs, increased SOD, GPx, and GSH) [11; 13]. The treatment also inhibited gluconeogenesis and glycogenolysis (by inhibiting glucose 6-phosphatase and fructose 1,6-diphosphatase and restoring glycogen content in the liver) [11]. In one of the studies, Tinospora cordifolia was more effective than glibenclamide and as effective as insulin in reducing blood glucose (from 260 mg/100 mL to 89 mg/100 mL) [12]. In a rat model of diabetic neuropathy, Tinospora cordifolia treatment (100-400 mg/kg) for 2 weeks also prevented hyperalgesia (enhanced pain response) compared to the control group [14].

Cancers: POTENTIAL BENEFIT IN PRECLINICAL MODELS. No clinical studies have evaluated the effectiveness of Tinospora cordifolia in cancer patients. Numerous preclinical studies have been carried out.

In a mouse model of Dalton's lymphoma, Tinospora cordifolia treatment (alcoholic extract, i.p.) augmented basic functions of macrophages (e.g., phagocytosis, antigen presenting ability, secretion of IL-1, TNF, and RNI) while slowing tumor growth and increasing the lifespan of tumor-bearing hosts [15]. Full text was not available for review, so the doses used or the magnitude of benefit could not be assessed. In a follow-up study in the same model, Tinospora cordifolia treatment (alcoholic extract, 200 mg/kg, i.p.) injected 2 days post-tumor transplantation significantly enhanced the differentiation of tumor-associated macrophages to dendritic cells (in response to granulocyte/macrophage-colony-stimulating factor, IL-4, and TNF) [16]. These cells had enhanced tumor cytotoxicity and production of tumoricidal soluble molecules (e.g., TNF, IL-1, and NO). Thus, Tinospora cordifolia appears to have antitumor functions by promoting differentiation of tumor-associated macrophages into dendritic cells that exhibit enhanced tumor cytotoxicity and production of tumoricidal molecules.

In a mouse model of skin cancer, Tinospora cordifolia treatment (extract, orally) started 7 days before and continued for 7 days after carcinogenesis significantly reduced tumor weight and tumor incidence in comparison to control treatment [17]. In addition, Tinospora-treated mice subjected to carcinogenesis showed significant reduction in cumulative number of papillomas, tumor yield, and tumor burden, along with significant elevation of detoxifying enzymes and inhibition of lipid peroxidation in the liver and skin.

The rest of the evidence comes from cell culture studies. Tinospora cordifolia treatment inhibited proliferation of colon cancer cells [18], breast cancer cells [19], neuroblastoma cells [20], and oral squamous cell carcinoma [21]. In the colon cancer study, they identified a new clerodane furano diterpene glycoside which induced mitochondria-mediated apoptosis and autophagy in HCT116 cells [18]. Other mechanisms included increased intracellular reactive oxygen species [19], expression of pro-apoptotic genes [19], cell cycle arrest in G0/G1 phase [20; 21], and induction of senescence pathways (e.g., mortalin and Rel A subunit of NFkB; decreased anti-apoptotic marker Bcl-xl).

Safety: Based on a few small clinical studies, Tinospora cordifolia is generally well-tolerated; reported adverse events include nasal pain and headache.

Types of evidence:

- 1 double-blind randomized clinical trial in allergic rhinitis
- 2 laboratory studies

Clinical: In a double-blind randomized controlled trial, 75 allergic rhinitis patients received 300 mg of Tinospora cordifolia (water extract of stem containing more than 5% "bitter principles") or placebo 3 times a day for 8 weeks [1]. Out of 36 patients who were in the Tinospora cordifolia group, 2 complained of nasal pain and 1 had a headache, which were resolved with analgesics. None required discontinuation of treatment due to these adverse effects. Tinospora cordifolia was otherwise well tolerated.

Preclinical: In a mouse safety study, Tinospora cordifolia treatment (150, 200, and 250 mg/kg, orally) for 7 days did not display clastogenic or DNA damaging effects in bone marrow erythrocytes and peripheral blood lymphocytes, respectively [22]. An Ames test of up to 5000 mg/plate of Tinospora cordifolia did not exhibit any mutagenic effects in Salmonella typhimurium mutant strains. In a chromosome aberration assay, Tinospora cordifolia was not clastogenic to human peripheral blood lymphocytes up to a concentration of 3000 mg/ml.

In a rat liver microsome study, Tinospora cordifolia extract showed concentration-dependent inhibition of CYP3A4 (IC50=136.45 µg/ml), CYP2D6 (144.37), CYP2C9 (127.55), and CYP1A2 (141.82) [23]. However, Tinospora cordifolia extract as well as tinosporaside showed higher IC50 (µg/ml) values compared to known inhibitors, suggesting less interaction potential. These data suggest that Tinospora cordifolia or its constituents do not have significant herb-drug interactions relating to the inhibition of major CYP450 isozymes.

***Drug interactions*:** Based on WebMD.com, Tinospora cordifolia interacts with medications for diabetes (e.g., glimepiride, glyburide, insulin, pioglitazone, rosiglitazone, glipizide, etc.) and immunosuppressants (e.g., cyclosporine, azathioprine, basiliximab, corticosteroids, prednisone, tacrolimus, sirolimus, and others).

Sources and dosing: Tinospora cordifolia supplements are available OTC in the forms of capsules, powder, liquid extracts, or whole dried herbs. For allergic rhinitis (hay fever), 300 mg of aqueous stem extract used 3 times per day, orally, significantly decreased symptoms [1]. It is best to take Tinospora cordifolia with a meal.

In Ayurvedic medicine, Tinospora cordifolia is taken with ghee and ginger (referred to as Amrita Ghrita), at doses ranging from 10-15 g, once daily (Examine.com).

Research underway: No clinical trials are under way testing the effects of Tinospora cordifolia based on ClinicalTrials.gov.

Search terms: Tinospora cordifolia or Guduchi
Pubmed, Google:

- + cognitive, + memory, + Alzheimer's, + APOE, + apolipoprotein, + clinical trial, + meta-analysis, + Cochrane, + neuropathy, + cancer, + cardiovascular, + lifespan, + mortality, + adverse

Websites visited for Tinospora cordifolia or Guduchi:

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

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