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Article *in* Australian Journal of HerbalMedicine · January 2011

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Volume 23 • Issue 4 • **2011**

Australian Journal of Medical Herbalism

A publication of the National Herbalists Association of Australia

Australian Journal of Medical Herbalism **2011** 23(4)

Tinospora cordifolia: role in depression, cognition and memory

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Tinospora cordifolia is known as an adaptogen or rejuvenator and is traditionally used in Ayurvedic medicine. It has immunomodulatory, antioxidant, antihyperglycemic, anti-inflammatory, antiulcer, antispasmodic and other properties. Recent evidence from animal and human studies underscores the potential antistress properties of *Tinospora cordifolia*. The antistress action has been shown to be beneficial in depression and in improving cognition and memory. The most likely antidepressant mechanisms involve inhibiting reuptake of amines in the brain. Improved levels of norepinephrine (NE), serotonin (5-hydroxytryptamine or 5-HT), and dopamine (DA), and decreased levels of gamma-aminobutyric acid (GABA) have been demonstrated. Inhibiting the breakdown of amines, particularly norepinehphrine and serotonin has also been demonstrated. GABA-B receptor antagonism and G-protein mediated signallling have been suggested as additional underlying mechanisms. Central antioxidant and protective properties play an important role in improving cognition, concentration and memory. *Tinospora cordifolia* has also been shown to be beneficial in improving cerebral ischemia. Prevention of oxidative stress injury and regulation of cytokines are possible mechanisms involved in these beneficial effects. *Tinospora cordifolia* works synergistically with many herbal preparations, which makes it an important component of polyherbal formulations. Lack of evidence for serious toxicity presents *Tinospora cordifolia* as one of the unique herbal medicines in management of depression, Alzheimer's disease and attention deficit hyperactivity disorder. Further work on elucidation of mechanisms, selectivity of action and drug interactions with other herbal substances will be helpful in determining the current status of *Tinospora cordifolia* as a psychopharmacological agent.

Key words: *Tinospora cordifolia*, gulvel, antistress, depression, cognition, memory, Alzheimer's disease

Introduction

Tinospora cordifolia (Willd) (Miers ex Hook F & Thoms) is also known as *Cocculus cordifolius* Dec, *Menispermum cordifolium* Willd, and *Tinospora glabra* (N Brum) Merr. It is a deciduous, fleshy, robust climber from the family Menispermaceae. It is also commonly known by the name gulvel and throughout the present article will be referred to as *Tinospora cordifolia* or gulvel.

Its Hindi name *giloya* refers to a heavenly elixir used to stay off the aging and to stay young forever. The Sanskrit name *guduchi* means one that protects the body from illnesses, providing the description of rejuvenator or adaptogen (Kennedy 2009). It is found in India, China, Myanmar, Sri Lanka, Thailand, Philippines, Indonesia, Malaysia, Borneo, Vietnam, Bangladesh, North Africa, West Africa and South Africa (Pendse 1981, Jain 2010, Mia 2009, Singh SS 2003). Its stem, root, leaves, fruits, and seeds have been used however maximum activities are ascribed to its stem and root. The tribes that have been traditionally using gulvel include Garo from Bangladesh (Mia 2009) and Gond, Tagin, Korkus and Baiga from different areas in India (Tambekar 2009, Acharya 2011, Goswami 2009, Sinha 2004). It is traditionally used in polyherbal formulations in India and China (Gupta 2010).

Ayurvedic pharmacodynamics

Ayurveda describes the taste of *Tinospora cordifolia* as bitter, pungent and astringent (Pendse 1981). Ayurvedic pharmacodynamic properties for Rasa are *tikta* (bitter) and *kashaya* (astringent); for Guna are *laghu* and *snigdha* (light and oily); for Virya it is considered *ushna* (hot); and for Vipaka it is *madhura* (sweet). It has been called *tridosha-shamak*, which means useful for alleviating all three doshas (Kafa, Vata and Pitta) (Singh SS 2003).

Constituents

Tinosporine, tinosporaside, cordifolide, cordifol, and hepatacosanol are important constituents of gulvel (Ninivaggi 2001). Barberine and palmatine are major alkaloids found in the stem. Glucosides are 18-norclerodane glucoside and sesquiterpenes tinocordioside, tinocordifolioside, tinocordifolin, tinosponone, and cordioside, cordifolisides and syringene (Verma 2011, Pendse 1981). The stem contains immunologically active substances arabinogalactan and (1, 4)-alpha-D-glucan (Chintalwar 1999, Nair 2006).

Gulvel contains high fibre (15.9%), sufficient protein (4.5%-11.2%), sufficient carbohydrate (61.66%) and low fat (3.1%). Its nutritive value is 292.54 calories per 100 g. It has high potassium (0.845%), high chromium (0.006%), sufficient iron (0.28%) and sufficient calcium

(0.131%) all important in various regulatory functions (Nile 2009).

Evidences of actions

Extensive work on *Tinospora cordifolia* through animal and human studies has established its immunomodulatory activity (Bapat 1995, Nagarkatti 1994, Manjrekar 2000, Thatte 1994, Nair 2004, Thatte 1992). It has antioxidant and protective effects (Jain 2010, Manjusha 2011, Kumar 2000, Robak 1998). Due to these effects as well as the antihyperglycemic activity, it has been found useful in management of diabetes mellitus (Raghunathan 1969, Grover 2000, Grover 2002, Nagaraja 2007). It has protective effects against hepatic and splenic injury (Bishayi 2002, Singh RK 2005). These effects along with the antioxidant and immunomodulatory properties have established its usefulness in obstructive jaundice (Rege 1993, 1989) and malaria (Singh RK 2005).

Tinospora cordifolia was shown to produce lethal effects to HeLa cells (Jagetia 1998). In mouse macrophages it was shown to produce modulation of chemotaxis, interlukin-1 (IL-1), and tumor necrosis factor (Dhuley 1997). Thus immunomodulation was shown to be involved in its antineoplastic activity (Singh N 2005). Gulvel was found to be useful in amelioration of cyclophosphamide induced toxicity (Mathew 1997, Thatte 1987) and in preventing hepatotoxicity due to antituberculosis medications (Adhvaryu 2008, Panchabhai 2008). Due to its immunomodulatory actions it has been found to be useful in preventing chronic, recurrent (especially ear, nose and throat) and other infections (Lumba 1983). In animal studies as well as in clinical trials it has been shown to be useful in joint inflammations including rheumatoid arthritis due to some of the above properties and its anti-inflammatory effect (Gulati 1982, Gulati 1980). It has antiulcer actions (Bafna 2005, Sarma 1995b), antispasmodic actions (Kamble 2008, Lather 2011), and has been shown to be useful in dissolving urinary calculi (Rai 1967).

Recent evidence indicates that *Tinospora cordifolia* has antistress action. The important implications involve an antidepressant effect, improvement in cognition, concentration and memory, and improvement in cerebral ischemia. The following is an account of psychoneurological effects of *Tinospora cordifolia*.

General actions contributing to psycho-neurological effects

Tinospora cordifolia has been considered a *rasayana* or a substance useful as a rejuvenator or restorative, and is hence classed as an adaptogen. This action has been correlated with its antioxidant properties that protect against stress (Kennedy 2009, Winston 2007, Palpu 2008). Prophylactic benefits of *Tinospora cordifolia* have been shown in a middle cerebral artery occlusion model of stroke in rats. The benefits have been ascribed to its potential for preventing oxidative stress injury and regulation of cytokine levels and growth factors in the blood of angiogenesis induced animals (Chaudhary 2003). It has found a place in traditional herbal medicine due to the beneficial effects in conditions of cerebral ischemia (Gupta 2010). *Tinospora cordifolia* is often used in combination with other agents in Ayurvedic formulations. The rationale is based on the Ayurveda process of *shodhan-vidhi* which means a substance is used to help the actions of other substances in a combination. This synergistic effect of gulvel has supportive evidence from modern pharmacological studies (Kamble 2008, Lather 2011). Such a substance may also help to counter the unwanted effects of other substances in the combination. Modern pharmacology describes this as reparative drug interaction under the category of clinically desirable drug interactions (Caranasos 1985). Thus apart from its own activities, *Tinospora cordifolia* becomes an important constituent of polyherbal formulations for additive or synergistic effects (Palpu 2008). Central antioxidant properties have been shown to be involved in various neuropsychopharmacological effects including enhancement of memory (Palpu 2008).

Stress and depression

Tinospora cordifolia is claimed to be useful in maintaining healthy brain function and in stress management (Mentalife 2011). The root of gulvel is traditionally used for its antistress activity (Singh J 2003). Its antistress activity was confirmed by its effects on brain neurotransmitters in stressed rats (Sarma 1995a, Patil 1997). The supportive evidence is in terms of normalisation of stress induced biochemical changes in norepinephrine, dopamine and 5-hydroxytryptamine in experimental rat models and improved levels of 5-hydroxyindoleacetic acid (5-HIAA) (a metabolite of 5-HT) in mice with ethanolic roots extracts (Singh J 2003).

Tinospora cordifolia is one of the components of polyherbal formulations such as Chaihu-Shugan-San, EuMil, Mentot, Siotone, Catuama, Banxia-houpu, Kami-shoyo-san and Sho-ju-sen prescribed for mild to moderate cases of depressive disorders. The extracts have been shown to have antidepressant effects on learned helplessness in mice and rat models of depression (Dhingra 2006).

Depressive disorders are characterised by decreased brain levels of monoamines including NE, 5-HT) and DA. Established modern antidepressants act by inhibiting reuptake or breakdown of one and/or more of these amines and increasing their levels at postsynaptic receptors. Tricyclic antidepressants (TCAs) (e.g. imipramine, amitriptyline) nonspecifically inhibit the reuptake of brain amines. However TCAs also block dopaminergic D2, histaminergic H1 and muscarinic receptors. These additional actions are responsible for a large number of adverse effects of TCAs. Monoamine oxidase inhibitors (MAO-I) (e.g. phenelzine, isocarboxazid, tranylcypromine) potentiate brain amine levels by

inhibiting the breakdown of brain amines. However they produce severe adverse effects. Concurrent use of foods that are rich in amines can also seriously enhance the amine levels leading to profound sympathetic stimulation. Hence too many dietary restrictions are necessary while using monoamine oxidase inhibitors. The newer amine reuptake inhibitors include selective serotonin reuptake inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine). These are amongst the best tolerated and commonly used class of antidepressants. SSRIs selectively inhibit reuptake of serotonin and contribute in raising the brain levels of serotonin, and their use is associated with comparatively fewer incidences of adverse effects. Newer antidepressants also include SSNRIs (Harvey 2009).

The antidepressant activity of *Tinospora cordifolia* was shown in Swiss albino mice by the tail suppression test and forced swim test on oral administration of its petroleum ether extract in the doses of 50, 100 and 200 mg/kg. The efficacy of its antidepressant activity was comparable to 15 mg/kg of imipramine (a TCA) and 20 mg/kg of sertraline (an SSRI). The dose of 50 mg/kg showed the most potent effect with no change in locomotor function. The antidepressant-like effect of gulvel was significantly reversed on tail suppression test by pretreatment of Swiss young albino mice with prazosin (an alpha-1 adrenoceptor antagonist), sulpiride (a selective dopamine D2-receptor antagonist), p-chlorophenylalanine (PCPA - a serotonin synthesis inhibitor) and baclofen (GABA-B agonist). The extract reduced the mouse whole brain monoamine oxidase (MAO-A and MAO-B) activities resulting in increased levels of brain monoamines. Inhibition of metabolism of monoamines, particularly serotonin and noradrenaline was also demonstrated (Dhingra 2006, Dhingra 2008).

Thus the mechanism of the antistress and antidepressant activities of *Tinospora cordifolia* most likely relates to increased levels of norepinephrine, dopamine and serotonin, and decreased level of gamma-aminobutyric acid (GABA), resulting from interaction with alpha-1 adrenergic, dopaminergic (D2), serotonergic and GABA-B receptors (Dhingra 2006, Dhingra 2008). Potentiation of brain monoamines by inhibition of the enzyme monoamine oxidase is another suggested mechanism (Dhingra 2006, Dhingra 2008). GABA-B receptor antagonism has been recently suggested as a basis for development of novel antidepressants (Mombereau 2004). Barberine, an alkaloid in gulvel, has been reported to have antidepressant effects. The mechanism seems to involve l-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway (Kulkarni 2007). Thus barberine is likely to be an active component in the antidepressant effect of gulvel.

Cognition

Tinospora cordifolia is classed as a *medhya rasayana* (learning and memory enhancer) and used for *bhrama* (vertigo) in Ayurveda (Singh SS 2003). Its memory enhancing effect has been claimed in different traditional systems of medicine. Ayurveda describes three aspects of mental ability with reference to learning and memory, being *dhi* (learning), *dhuti* (retention) and *smriti* (recall). Gulvel has found a place in traditional herbal medicine as a neuropsychopharmacological agent for enhancing memory and improving learning (Dua 2009).

The effect of a polyherbal formulation containing *Tinospora cordifolia* on aluminium induced cognitive deficits and cognition in aged wistar rats was studied in a one trial step through passive avoidance task. The *Tinospora cordifolia* containing formulation was found to significantly prolong the shortened latency of step through induced by aluminium administration. It significantly improved retention of learning in aged rats confirming the enhancement of learning and memory by *Tinospora cordifolia* in aluminium treated and aged rats. Gulvel was shown to enhance cognition and memory in normal rats and to reverse cyclosporine induced memory deficit. Alcoholic and aqueous extracts produced a decrease in learning scores in Hebb-William maze and retention memory. Histopathological examination showed that gulvel protected against the neurodegenerative changes produced by cyclosporine in the hippocampus of cyclosporine treated rats (Agarwal 2002).

The pure aqueous root extract of gulvel showed enhanced verbal learning in a 21 day randomised double blind placebo controlled study (Bairy 2004). Significant response to gulvel was reported in children with a moderate degree of behavioral disorders and mental deficit, with improvement in intelligence quotient levels (Singh SS 2003).

Memory and concentration

Improvement in memory and concentration by *Tinospora cordifolia* has been mentioned in Chinese, Western and Ayurvedic herbal medicine (Tillotson 2001). *Tinospora cordifolia* has found a place in natural and herbal treatments of attention deficit hyperactivity disorder (ADHD) (Burton 2011).

Tinospora cordifolia is used in the form of a tablet of a polyherbal formulation for general improvement of memory function. The formulation also contains *Celastrus paniculata, Bacopa monnieri, Convolvulus pluricaulis, Withania somnifera* and *Centella asiatica.* The root extract of *Tinospora cordifolia* was found to have a normalising effect against stress induced changes in norepinephrine, dopamine, 5-hydroxytryptamine and 5-hydroxyindole acetic acid levels (Ayurvedic medicine 2011). In a 21 day randomised double blind placebo controlled study, pure aqueous root extract of gulvel enhanced logical memory (Bairy 2004).

Recent evidence indicates the potential benefits of gulvel along with other herbal products in Alzheimer's disease. Alzheimer's disease affects 5% to 6% of older

people with a slow, gradual onset and worsening severity with advancing age. In the early course it is characterised particularly by recent or short term memory deficits with significant loss of intellectual abilities severe enough to interfere with social or occupational functioning. Microscopic brain tissue changes are senile or neuritic plaques (chemical deposits consisting of degenerating nerve cells combined with a β amyloid) and neurofibrillary tangles (malformation within nerve cells). The plaques found in the brain appear to be made, in part, from protein molecules (amyloid precursor protein, APP) that normally are essential components of the brain. Other abnormal anatomical and chemical changes include nerve cell degeneration in the nucleus basalis of Meynert and reduced levels of the neurotransmitter acetylcholine. Researchers have discovered a protein which has been named Alzheimer's disease associated protein (ADAP), in the autopsied brains of Alzheimer's patients (Palpu 2008).

Studies have shown that herbal formulations have the properties that can improve memory and function as a brain tonic in conditions of senile and presenile dementia. The basis of action has been thought to be the central antioxidant properties. One such synergistic formulation is comprised of alcoholic extracts/juice of stems of *Tinospora cordifolia*, leaves of *Centella asiatica*, roots of *Withania somnifera*, seeds of *Mucuna pruriens* and rhizomes of *Curcuma longa*, mixed in the ratio ranging from 1:0.5:1:1:2 and 1:1:1:1:2 by weight balance. These substances were found to produce enhancement in the catalase, superoxide dismutase and glutathione peroxidase in frontal cortex as well as striatum of rats. The formulation was used in the doses ranging from 100-200 mg/kg. The various tests performed included passive avoidance test (step down test) in rats, transfer latency in intracerebroventricular streptozotocin treated rats, the streptozotocin induced oxidative stress markers in various regions of brain and the Elevated Plus-Maze Behavioural Test, which is a predictable and reliable procedure for studying cognition in Alzheimer's disease and to study the effect of drug responses to senile dementia (Palpu 2008). This formulation was devoid of toxicity in rats and did not produce change in organ body weight at different doses of 100, 200 and 400 mg/kg. Lack of evidence of toxicity suggests a better place for this combination than the available therapies.

This novel polyherbal formulation is used in human beings as an emulsion or as soft gelatin capsules. It has been shown to improve memory, help in recall of thoughts, produced symptomatic improvement and helped to improve the general health (Palpu 2008). Modern pharmacological substances used in Alzheimer's disease include anticholinesterase agents (rivastigmine, galantamine and donepezil) which concentrate acetylcholine by inhibiting its breakdown, and memantine, the antagonist N-methyl D-aspartate (NMDA) type of glutamate receptor which serves a protective function against neurodegeneration (Harvey 2009). *Tinospora cordifolia* has been shown to exert protective effects against neuronal degeneration. Its role in cholinergic mechanisms is yet to be clearly understood and exploring this may further enlighten its currently known beneficial neuroprotective effects in Alzheimer's disease.

Summary

Tinospora cordifolia (gulvel) is extensively studied and used in Ayurvedic medicine. Its established immunomodulatory, antioxidant, protective and other properties have shown it has a place in the management of diabetes mellitus, obstructive jaundice, cancers, rheumatoid arthritis, hepatic or splenic injury by infectious agents or drugs, cyclosphosphamide and anti-tuberculosis drug toxicity, chronic ear, nose, throat and other infections, and many other conditions. *Tinospora cordifolia* has also been shown to have antistress activity in terms of prevention of oxidative stress injury. Its antistress activity led researchers to explore the potential of gulvel in the management of depression. It was shown to potentiate levels of brain amines including norepinephrine, serotonin and dopamine, mostly by inhibiting the reuptake mechanisms of these amines and/or inhibiting amine breakdown, in particular of norepinephrine and serotonin. It was shown to decrease the levels of GABA by a probable action on GABA-B receptors. Another possible mechanism involves l-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway. Barberine, an important alkaloid present in gulvel was shown to have antidepressant activity. It is notable that there is no evidence of serious toxicity with *Tinospora cordifolia*. There remains a further scope for searching its relative selectivity in potentiation of the three amines (norepinephrine, serotonin and dopamine), and in establishing the role of GABA-B receptor and G-protein mediated signalling in depressive disorders.

Central antioxidant properties are thought to be a key mechanism in improving cognition, concentration and memory, which provides potential benefits in Alzheimer's disease and attention deficit hyperactivity disorder. *Tinospora cordifolia* has also been shown to be beneficial in improving cerebral ischemia by possible mechanisms of preventing oxidative stress injury and cytokine regulation.

Lack of evidence of serious toxicity with *Tinospora cordifolia* remarkably differentiates it from currently available treatment options. *Tinospora cordifolia* works synergistically with other substances which makes it an important component of polyherbal formulations used for many conditions. There is a potential scope for searching and establishing the mechanisms of interactions of *Tinospora cordifolia* with other herbal extracts. Detailed pharmacokinetic, pharmacodynamic and human studies

will help to further elaborate the present status of *Tinospora cordifolia* as a psychopharmacological agent in the disorders of mood, cognition and memory.

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Volume 23 • Issue 4 • **2011**

Australian Journal of Medical Herbalism