Tinospora cordifolia (Willd.) Miers ex Hook. F. & Thoms (Menispermaceae)

(**Syns.**: *T. sinensis* (Lour.) Merr.; *T. cordifolia* (D.C.) Miers, *T. cordifolia* (Willd.) Miers.; *Cocculus cordifolius* (Willd.) DC.; *Menispermum cordifolium* Willd.)

Abstract

A large, perennial, deciduous, climbing herbaceous vine, that is distributed throughout India, Myanmar, Sri Lanka and China. In *Ayurveda*, it is mentioned as *rasayan* and is traditionally used for the treatment of asthma, chronic cough, to improve immune system, as a general tonic, antiperiodic in fevers, antispasmodic, anti-inflammatory, antiarthritic and antidiabetic agent, and is also credited with aphrodisiac property. Fresh plant is said to be more efficient than the dried one. It is taken with milk in rheumatism, acidity of the urine and dyspepsia. The stem of this very bitter herbaceous vine is used medicinally in *Unani* medicine as a bitter tonic, astringent, stomachic, anthelmintic, blood purifier, diuretic, and antipyretic for all types of fevers, including tuberculous fever. Water extracted from fresh plant is more potent. It is also used for chronic diarrhea, and in diseases, such as syphilis, and leprosy. In the Philippines and Malaysia, this is the most popular medicinal plant, and is considered a universal medicine. Its aqueous extract is used as a remedy for stomach trouble, indigestion and diarrhea. A preparation with coconut oil is considered an effective cure for rheumatism and for flatulence in children. Various constituents, such as alkaloids, diterpenoid lactones, cardiac glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides have been reported from the plant. The yield and physicochemical profile of the starchy material extracted from stem used in *Ayurvedic* preparations vary due to the plant stem size, collection time, season and maturity of the plant. Total alkaloidal contents are a bit higher in rainy and spring seasons. Aqueous, alcohol and chloroform extracts exerted significant hypoglycemic and antihyperglycemic effects in normal and diabetic animals. Aqueous extract significantly stimulates glucose uptake in 3T3-L1 adipocytes, comparable to insulin and greater than pioglitazone. Aqueous extract also prevented hyperalgesia of diabetic neuropathy, and inhibited aldose reductase. Ethanol extract of aerial parts offered significant neuroprotection against 6-OHDA-induced Parkinson's disease-like lesions in rat model, and decreased locomotor activity but did not affect amphetamine-induced hyperactivity in mice.

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Keywords
Gilo · Giloe · Guduchi · Guduchi-kräutertee · Gulancha tinospora · Gulbel · Guricha · Jivantika · Makabúhaí · Xin ye qing niu dan

Vernaculars: **Urd.**: Giloe; **Hin.**: Giloe, Guduchi, Gulach, Gulancha, Guruch; **San.**: Amurta, Bhishakpriya, Chinnaruha, Giloy, Guduchi, Jivantika, Nirjara, Pittaghni, Soma-valli; **Ben.**: Gadancha, Giloe, Gulach, Gulancha, Palo (extract); **Guj.**: Galo; **Mal.**: Amrita, Amruthu, Chitramruta; **Mar.**: Gharol, Guduchi, Gulavel, Guloe; **Tam.**: Amirthavalli, Kunali, Seenthil kodi, Shindilakodi, Shindil-shakkarai (extract); **Tel.**: Guluchi, Guricha, Manapala, Tippa-teega, Tippa-tige-satu (extract), Tippatege-veru (root); **Ara.**: Gilo; **Chi.**: 心叶青牛胆, Xin ye qing niu dan; **Eng.**: Gulancha tinospora, Heartleaf moonseed; **Fre.**: Guduchi, Tinofolin; **Ger.**: Guduchi-kräutertee; **Nep.**: Gurjo; **Per.**: Gulbel; **Tag.**: Makabúhaí; **Tha.**: Ching cha chali.

Description: It is a large, glabrous, perennial, deciduous, climbing herbaceous vine of weak and fleshy stem spreading on trees of *Mangifera indica* and *Azadirachta indica*. It is distributed throughout India, Myanmar, Sri Lanka and China. Fresh stem has a green succulent bark, covered by a thin brown epidermis, which peels off in flakes. It is studded with warty prominences, and gives off roots here and there, and branches bearing smooth heart-shaped leaves, and bunches of red berries. When dry it shrinks very much, and the bark separates from the wood, and becomes of a dull-brown color; the latter consists of a number of wedge-shaped bundles; the taste is very bitter, the odor is not in any way peculiar.[XL] Flowers are typically greenish-yellow, and the flowering season extends from summer to winter; male flowers are clustered, while the female flowers are solitary [99]. According to Narkhede et al. [51], *T. sinensis* closely resembles the description of *guduchi* in *Ayurvedic* literature rather than the commonly available *T. cordifolia*, but may be used as a substitute for *T. sinensis*; *T. cordifolia* growing on *Azadirachta indica* is called *Neem-guduchi* and has better immunomodulatory potential (Figs. 1 and 2).

Actions and Uses: In *Ayurveda*, it (temperament, cold and dry) is mentioned as *rasayan* and is traditionally used for the treatment of asthma, chronic cough, to improve immune system, as a general tonic, antiperiodic in fevers, antispasmodic, anti-inflammatory, antiarthritic and antidiabetic agent, and is also credited with aphrodisiac property [73, 98]. Fresh plant is said to be more efficient than the dried one. It is taken with milk in rheumatism, acidity of the urine and dyspepsia. It is said that if the stem is placed upon a bush in the open air, will retain its vitality through the hot season, and when the rains start, put forth leaves and long whipcord-like roots, which soon reach the ground, hence the Sanskrit synonym *Chinnaruha*, or growing when cut.[XL] The stem (temperament, hot 1° and dry 1°) of this very bitter herbaceous vine is used medicinally in *Unani* medicine as a bitter tonic, astringent, stomachic, anthelmintic, blood purifier, diuretic, and antipyretic for all types of fevers, including tuberculous fever. Water extracted from fresh plant is more potent. It is also used for chronic diarrhea, and in diseases, such as syphilis, and leprosy.[LXXVII] It is also described as alterative, and demulcent, and used in dyspepsia, secondary syphilis,

Fig. 1 *Tinospora cordifolia*, Plant, Tmd, WikimediaCommons, https://commons.wikimedia.org/wiki/File:Tinospora_cordifolia.jpg

Fig. 2 *Tinospora cordifolia*, Fruits, Vinayaraj, WikimediaCommons; ShareAlike 4.0 International CC BY-SA 4.0, https://commons.wikimedia.org/wiki/File:Tinospora_cordifolia_fruits_03.JPG; https://creativecommons.org/licenses/by-sa/4.0/deed.en

rheumatism, skin diseases (such as impetigo), jaundice, debility caused by repeated attacks of fever,[LXXXI,CV] urinary disorders, diabetes and anemia [8]. Water extract is used as a febrifuge and is referred to as 'Indian quinine.'[CV] Whole plant pounded with water is used for spermatorrhea and gonorrhea.[CXVII] In Ramgiri, Koraput district of Orissa (India), tribals orally administer 8 g starch obtained from stem, mixed in water

with equal quantity of sugar, daily for seven days to treat jaundice [24]. The Boxa tribe of Nainital district (India), use stem decoction bath in postdelivery fever [84]. It is also considered antihepatotoxic, antistress, immunomodulatory, and antioxidant [52]. In the Philippines and Malaysia, this is the most popular medicinal plant, and is considered a universal medicine. The aqueous extract is used as a remedy for stomach trouble, indigestion and diarrhea. A preparation with coconut oil is considered an effective cure for rheumatism and for flatulence in children.[CXVII]

Phytoconstituents: Various constituents, such as alkaloids, diterpenoid lactones, cardiac glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides have been reported from the plant [47, 99]. The yield and physicochemical profile of the starchy material extracted from stem used in *Ayurvedic* preparations vary due to the plant stem size, collection time, season and maturity of the plant. Total alkaloidal contents are a bit higher in rainy and spring seasons [79]. Ethanol leaf extract showed the presence of steroids, anthraquinones, flavonoids, cardiac glycosides, tannins and phenolics [94]. Seven compounds, 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, magnoflorine, cordifolioside A, tinocordiside, and syringin, with immunomodulatory activity were isolated, and the activity is assumed to be due to their synergistic effect [80]. Bala et al. [8] also isolated jatrorrhizine, palmatine, and yangambin from stem. The isoquinoline alkaloids, jatrorrhizine, palmatine and magnoflorine demonstrated significant inhibitory activity against aldose reductase isolated from male rats [56]. A novel sulfur-containing clerodane diterpene glycoside, cordifolide A, and two diterpene glycosides, cordifolides B and C were also isolated from the stem [53]. Ahmad et al. [4] isolated tinosporafuranol, tinosporafurandiol, tinosporaclerodanol, and tinosporaclerodanoid, along with β-sitosterol from stem bark. Two aporphine alkaloids (Tinoscorside A and B), a clerodane diterpene, tinoscorside C and a phenylpropanoid, tinoscorside D were isolated from methanol extract of aerial parts [100], while four clerodane furanoditerpene glucosides (Amritosides A, B, C and D) [46], three norditerpene furanglycosides, cordifolisides A, B and C [16], and two diterpinoid furonolactones, tinosporide [92] and columbin [93] were isolated from the stem. An immunologically active arabinogalactan with polyclonal mitogenic activity against B-cells was also reported from the stem [13]. Several other immunomodulating compounds have been reported from the plant. Syringin and cordiol inhibit *in vitro* immunohaemolysis of antibody-coated sheep erythrocytes by guinea pig serum; while cordioside, cordiofolioside A and cordiol activate macrophages [36]. A polysaccharide from stem is composed of glucose (98%), xylose (0.8%), arabinose (0.5%), galactose (0.3%), rhamnose (0.2%) and mannose (0.2%) [30]. Jatrorrhizine is also reported from the root of the plant [74].

Pharmacology: Aqueous, alcohol and chloroform extracts exerted significant hypoglycemic and antihyperglycemic effects in normal and diabetic animals [19, 21, 37, 39, 48, 58, 103]. Aqueous extract also prevented hyperalgesia of diabetic neuropathy, and *in vitro* inhibited aldose reductase [49]. Overexpression of angiogenic and inflammatory mediators, markers of diabetic retinopathy, was inhibited, retinal oxidative stress reduced and antioxidant enzyme levels of diabetic rats was

restored [3]. Treatment of diabetic animals also prevents polyuria and reduces urinary albumin [20], rise in insulin, TGs and glucose-insulin index, improves antioxidant status [66, 67, 71], inhibits α-glucosidase [14], and significantly prevents cataract formation [3, 65]. Oral administration of an α-glucosidase inhibitor constituent, saponarin, to maltose-fed rats produced hypoglycemic activity in doses of 20–80 mg/kg, comparable to 100–200 mg/kg of acarbose [76]. The isoquinoline alkaloid rich fraction of the stem and three alkaloids viz., palmatine, jatrorrhizine and magnoflorine significantly decreased FBG, and increased serum insulin level in glucose-fed rats [55]. Aqueous and ethanol root extracts also significantly reduced serum and tissue cholesterol, phospholipids, FFAs, and glucose of diabetic rats [60, 61, 90], and ethanol extract also improved antioxidant status [59, 62]. The plant is an immunostimulator [5, 40, 50, 81, 89, 91, 101]; the aqueous extract improved cellular immunity and significantly reduced rats' mortality following cholestasis and *E. coli* infection [69]; and the ethanol extract improved phagocytic function without affecting humoral or cell-mediated immune system [6], protected against CP-induced myelosuppression and leucopenia [44, 95], and against gamma radiation exposure [18, 52, 85]. Activation of macrophages by the extract [75] leads to increase in GM-CSF, resulting in leucocytosis and improved neutrophil function [96]. Various extracts exhibit analgesic and anti-inflammatory activities [17, 25, 57]. In a mouse model of asthma, hydroalcohol extract protected against oxidative stress, proinflammatory cytokines release and redox signaling, and reduced airway hyperresponsiveness [98].

Ethanol extract of aerial parts offered significant neuroprotection against 6-OHDA-induced Parkinson's disease-like lesions in rat model [41], and decreased locomotor activity but did not affect amphetamine-induced hyperactivity in mice [31]. Methanol stem extract significantly inhibited *in vitro* AChE [102], and petroleum ether extract at a relatively low dose produced significant antidepressant-like effect in mice, comparable to imipramine and sertraline, without significantly affecting locomotor functions and reducing activities of MAOs of whole brain [15]. Pretreatment with ethanol extract of whole plant reduced the infarct size and lipid peroxide levels of serum and heart tissue in surgically-induced myocardial I/R injury in rats [63], and normalized calcium chloride-induced cardiac arrhythmia in rats, comparable to verapamil [77]. Aqueous extracts of stem and leaves also reversed hematological changes in lead-treated mice [82]. Pretreatment with stem and leaves extracts protects from lead nitrate-hepatotoxicity, increased activities of antioxidant enzymes [83], CCl_4-liver damage [9], and whole plant powder protected against antitubercular drugs-hepatotoxicity [1, 54]. Ethanol extract of stems and leaves also showed antioxidant activity and decreased LPO in NDEA-induced liver cancer in rats [32], in diabetic rats [88], and CP-induced toxicity in mice [45].

Exposure of HeLa cells to methanol, aqueous, methylene chloride and dichloromethane extracts caused significant dose-dependent increase in cell killing [27, 28]. Dichloromethane extract increased tumor-free survival of mice transplanted with Ehrlich ascites carcinoma, with optimum effect when the extract was administered within five days of tumor inoculation [29, 64]. Hydroethanol extract also increased survival time and decreased peritoneal ascitic fluid content of Dalton's lymphoma ascites in Swiss mice [2], due to augmentation of function of macrophages [86].

Significant reduction by the extract in cumulative number, tumor yield, tumor burden, and tumor weight, along with significant elevation of phase II detoxifying enzymes, and inhibition of LPO was reported in skin carcinogenesis model [12]. The extract also inhibits melanoma cell-induced capillary formation in animals [42]; octacosanol has been identified as the antiangiogenic compound [97]. A polysaccharide fraction produced 72% inhibition in metastases formation of melanoma cells in the lungs of syngeneic C57BL/6 mice [43].

Sequential petroleum ether, chloroform, ethyl acetate, acetone, and ethanol extracts exhibited activity against Pseudomonas spp., while acetone, ethanol and aqueous extracts were active against *K. pneumonia*; Proteus spp. were inhibited by petroleum ether and benzene extracts, and *E. coli* was susceptible to ethyl acetate and acetone extracts [47]. Ethanol extract was inhibitory against *E. coli*, *P. vulgaris*, *E. faecalis*, *S. typhi*, *S. aureus* and *S. marcesenses* [33], and clinical isolates of MRSA and carbapenemase-producing *K. pneumoniae* [10]. Oral administration of methanol extract of stem to male rats for 60-days significantly decreased weight of testes, epididymis, seminal vesicle and ventral prostate, significantly reduced sperm motility and density, and serum testosterone levels, resulting in complete infertility [23]. A standardized aqueous extract reversed effects of cisplatin on gastric emptying, normalized intestinal hypermotility and the phagocytic function irrespective to the direction of change, complying to the definition of an adaptogen [70]. Ethanol and aqueous extracts of stem-bark produced dose-dependent antidiarrheal effect, and gastric antiulcer activity in rats [38].

Clinical Studies: In thirty Indian patients with malignant obstructive jaundice, addition of aqueous extract to conventional treatment with vitamin K, antibiotics and biliary drainage in half of the patients normalized the neutrophils phagocytic activity, completely resolved clinical signs of septicemia, and improved postoperative survival to near complete, compared to the control group with 40% survival rate [68]. Supplementation with aqueous extract to chronic asymptomatic moderate alcohol drinker with no chronic liver disease was still significantly protective against alcohol-induced damage [78]. Addition of aqueous extract as adjunct to chloroquine in partially/slow responding three Indian patients with malarial splenomegaly significantly regressed spleen size by two-third after six-months of treatment [87]. Sixty percent HIV positive Indian participants treated with a standardized aqueous extract for six-months reported relief from various symptoms compared to 20% in the placebo group of a double-blind RCT [35]. In a double-blinded RCT of patients with allergic rhinitis, eight-weeks treatment with the extract was effective in completely relieving sneezing in 83% and in more than two-thirds from nasal discharge and nasal obstruction, compared to those treated with placebo, who showed no relief in more than 80% patients [7, 22]. Topical application of a *T. cordifolia* lotion was comparably effective with permethrin in scabies-infected pediatric patients [11].

Mechanism of Action: Aqueous extract significantly stimulates glucose uptake in 3T3-L1 adipocytes, comparable to insulin and greater than pioglitazone [34]. Dichloromethane extract of stem *in vitro* inhibited 100% of α-glucosidase, 75% of

salivary amylase and 83% pancreatic amylase [14]. Anti-inflammatory effect in rat adjuvant-induced arthritis is mediated via reduction of proinflammatory cytokines [72].

Human A/Es, Allergy and Toxicity: Commonly reported adverse effects of a standardized aqueous extract in HIV positive patients were anorexia, nausea, vomiting and weakness [35].

Animal Toxicity: Oral LD50 of ethanol extract in mice is reported to be 2,650 mg (range 2,209–3,091 mg/kg). Oral doses of hexane- and chloroform-soluble extracts of the stem produced no significant toxic or adverse effects in rabbits up to the highest dose of 1,600 mg/kg [26].

Commentary: Significant protective and therapeutic effects of the aqueous extract on liver, spleen and HIV have been documented in RCTs, that should be further investigated in larger clinical trials and diverse patient populations to firmly validate its therapeutic efficiency. Other significant effects observed in animal studies also need further exploration in systematic clinical trials.

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