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Tinospora Cordifolia (Guduchi): An Updated Pharmacognostic, Phytochemical and Mechanistic Pharmacological Perspective with Emphasis on Standardization and Safety

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ABSTRACT: Guduchi is one of the most highly valued and common herbs in Ayurvedic medicine. It has a rich history in the Indian sub-continent where it has been used and written about for thousands of years it is considered one of the best Rasayana and is usual in its potent versatility. The last decade has seen a global upsurge in the use of traditional medicine and complementary and alternative medicines in both developed and developing countries. Various forms of traditional, complementary and alternative medicines are playing a progressively more important role in health care globally and therefore their safety, efficacy, and quality control are important concerns today. Tinospora cordifolia (Willd.) Miers. (Amruthavalli or Guduci), is one of the most versatile rejuvenative herbs widely used as a traditional medicine. It is mentioned in various classical texts of Indian Medicinal Systems and is cultivated throughout the Indian subcontinent and China. The therapeutic efficacy makes for its extensive usage in various systems of medicine. Pre-clinical and clinical pharmacological studies affirm the importance of this herb. The notable and important medicinal properties reported are anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities. Tinospora cordifolia (TC) contain various chemical constituents belonging to different classes such as alkaloids, diterpenoid lactones, glycosides and steroids.

INTRODUCTION:

Tinospora cordifolia (TC) is one of the most versatile rejuvenating, glabrous, succulent, woody, deciduous climbing shrub found throughout India, especially tropical part of India and also in certain parts of China. It is described as 'the one who protects

the body against disease'.[1] In Hindi, the plant is commonly known as *Giloe* [2] which is a Hindu mythological term that refers to the heavenly elixir that has saved celestial beings from old age and kept them eternally young. In Ayurveda, it is designated as Rasayana drug recommended to enhance general body resistance, promote longevity and as antistress and adaptogen. [3,4]. A variety of active components derived from plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides has been isolated from the different parts of the plant body, including root, stem, and whole plant .Recently the plant is of great interest to researchers across the globe because of its reported medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulator and anti-neoplastic activities[5].

Distribution: It is indigenous to areas of India, Myanmar, Sri Lanka, China, Thailand, Philippines, Indonesia, Malaysia, Borneo, Vietnam, Bangladesh, North Africa, West Africa, and South Africa. [6-9] This herb is found throughout tropical asia ascending to a height of 300 mts.

Origin and Habitat: TC is a native plant from tropical and subtropical regions of India. Also, known to be found in Far East, primarily in rainforests. It prefers wide range of soil, acid to alkaline and it needs moderate level of soil moisture. The herb has a long history in use by practitioners of Ayurvedic medicine (the traditional medicine of India), since 2000 B.C. known by its practitioners to treat convalescence from severe illness.[10]

The Family: TC belongs to the family Menispermaceae[11-13] which consists of about 70 genera and 450 species that are found in tropical lowland regions. They are generally climbing or twining, rarely shrubs. This family is a rich source of alkaloid and terpenes (14)

The Genus: The genus *Tinospora* Miers (Menispermaceae) has about 32 species distributed in tropical Africa, Madagascar, Asia to Australia and the Pacific Islands. [15-17] In India, the genus is represented by four species; two species, TC (Thunb.) Miers and *T. sinensis* (Lour.) Merr., are known to occur in South India and other two *T. crispa* (L.) Hook.f. & Thomson and *T. glabra* (Burm.f.) Merr., are reported from Northeast India and the Andaman Islands [18].

Synonyms: Avyatha, Amrta, Amrtavalli, Kundali, Guduchi, Giloe, Guducika, Gundra, Cakrangi, Cakralaksana, Candrahasa, Jivantika, Jvara nagini, Jvarari, Tantrika, Deva nirmita, Dhara, Naga kanyaka, Naga kumarika, Bhisakpriya, Mandali, Madhupariii, Rasayani, Vatsadani, Vayastha, Vara, Visalya, syama, Surakrta, Soma, Soma valli etc.[19]

Names in different language (Vernacular Names)

Arabic - Gilo

Assamese - Amarlata

Bengali - Gadancha, Guluncha, Giloe

Chinese - K'uan chu Hsing

English – Tinospora

French - Culancha

Gujarati - Gado, Galo, Gulo

Hindi - Giloe, Gulbel, Gurcha

Kannada – Arnryta balli, Ugani

Kashmiri - Gilo

Malayalam - Amrytu, Sittamrytu

Marathi - Ambarvel, Giroli, Gulvel

Nepali - Garjo

Oriya - Gulancha

Persian - Gulbel

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Punjabi – Gilo, Batindu, Gibogularich

Sanskrit - Amrita, Guduchi

Sikkim - Gurjo

Tamil - Amridavalli, Niraidarudian

Telugu - Guduchi, Iruluchi

Urdu – Guruch[20-22]

Nutritive Composition of *Tinospora cordifolia*:

TC 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%), important in various regulatory functions [23].

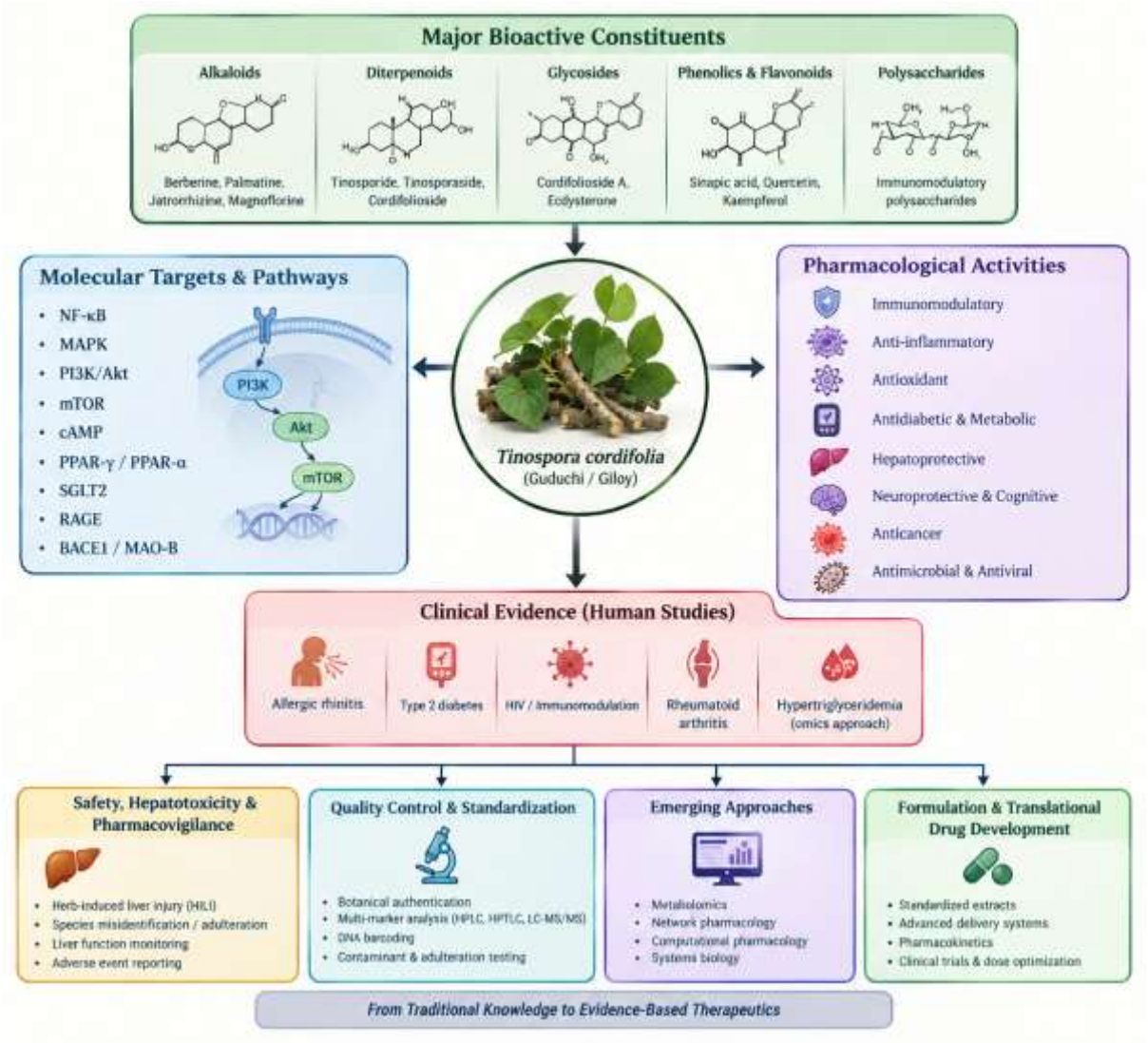

Figure 1. Integrated phytopharmacological framework linking major phytoconstituents of Tinospora cordifolia with molecular targets, pharmacological effects and translational considerations.

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MACROSCOPIC STUDY

TC is a glabrous climbing shrub with a succulent stem and papery bark that is creamy white to grey in color. It bears heart-shaped leaves. Leaves are simple, alternate exstipulate, long petioles upto 15cm long, roundish, pulvinate, both at the base and apex with the basal one longer and twisted partially and half way round. Lamina broadly ovate or ovate coridate, 10-12 cm long and 8-15cm broad. The yellow flowers are axillary and long-stalked racemes. The fruit is pea-sized, subglobose drupe and red colored on maturity. Flowers can be seen in June, while fruits occur in November. Guduchi is found in deciduous and dry forests throughout India [24].

Stem: Stem is characterized by the presence of bicollateral vascular bundles surrounded by pericycle fibers. The cork arises in the sub-epidermal layers and give rise to 2-3 layers of cork. Starch is present throughout the parenchyma of the stem [25-26] Fibrous and the transverse section exhibits wedge shaped wood bundles, containing large yellowish wood with radially arranged wedge shaped wood bundles, containing large vessels, separated by narrow medullary rays.[27]

Bark: creamy white to grey brown, warty, deeply left spirally, the space in between being spotted with large rosette like lenticels. [28-29]

Root: succulent with long filiform fleshy aerial roots from the branches. The aerial root is characterized by tetra-to penta-arch primary structure. The cortex is divided into outer thick-walled zone representing the velamen and inner parenchyma zone containing secretory canals. Starch is presnt throughout the parenchyma of the aerial root. The starch grains are oval or elliptical in shape, mostly simple but sometimes as compound grains of 2 to 5 components with faintly marked concentric striation and central hilum appearing like a point [30,31].

Leaves: simple, alternate, estipulate, cordate, long petioles up to 15 cm long, roundish, pulvinate. Both at the base and apex with basal one longer and twisted partially and half way round.[30]

Lamina: ovate or ovate cordate, 10-20 cm long, 8-15 cm broad, 7 nerved and deeply cordate base, membranous, whitish tomentose with prominent reticulum beneath.[31]

Flowers: unisexual, small on separate plants and appearing when plant is leafless, greenish yellow on axillary and terminal racemes. Male flower clustered and female usually solitary. Flowers grow during summer. [27-30]

Sepals: 6, free in two series of three each, the outer one are smaller than the inner.[30]

Petals: 6, free smaller than sepals, obovate and membranous.[31]

Fruits: aggregates of 1-3 ovoid smooth drupelet on thick stalk with sub terminal style scars, Scarlet or orange red color. Fruits grow during winter. [27,30]

Seeds: white, bean shaped, curved.[31]

Microscopy of *Tinospora cordifolia*

Leaves of *Tinospora cordifolia*

Stem of *Tinospora cordifolia*

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Aerial root of *Tinospora cordifolia*

Fruits, Flowers of *Tinospora cordifolia*

Seeds of *Tinospora cordifolia*

MICROSCOPICAL CHARACTERISTICS

Transverse section of TC stem shows cork, cortex and vasculature.

T.S of stem shows outer-most layer of cork, differentiating into outer zone of thick-walled brownish and compressed cells, inner zone of thin walled colorless, tangentially arranged 3-4 rows of cells, cork broken at some places due to opening of lenticels, followed by 5 or more rows of secondary cortex of which the cells of outer rows smaller than the inner one, just within the opening of lenticels, groups of sclereids consisting of 2-10 cells found in secondary cortex region, outer zone of cortex consists of 3-5 rows of irregularly arranged, tangentially elongated chlorenchymatous cells, cortical cells situated towards inner side, polygonal in shape and filled with plenty of starch grains, simple, ovoid, or irregularly ovoid-elliptical, occasionally compound of 2-4 components, several secretory cells, found scattered in the cortex, pericyclic fibers lignified with wide lumen and pointed ends, associated with a large number of crystal fibers containing a single prism in each chamber, vascular zone composed of 10-12 or more wedge-shaped strips of xylem, externally surrounded by semi-circular strips of phloem, alternating, with wide medullary rays, phloem consists of sieve tube, companion cells and phloem parenchyma of polygonal or tangentially elongated cells, some of them contain crystals of calcium oxalate, cambium composed of one to two layers of tangentially elongated cells in each vascular bundle, xylem consists of vessels, tracheids, parenchyma and fibers, in primary xylem, vessels comparatively narrow devoid of tyloses, secondary xylem elements thick-walled, lignified, vessels cylindrical in shape bearing bordered pits on their walls some large vessels possess several tyloses and often contain transverse septa, medullary rays 15-20 or more cells wide containing rounded, hemispherical, oblong, ovoid, with faintly marked concentric striations and central hilum appearing like a point, starch grains of 5.5-11.20 μ in diameter and 6-11.28 μ in length, pith composed of large, thin-walled cells mostly containing starch grains.

Cork: Older stem comprises of an outer zone of thick-walled brownish compressed cells and an inner zone of thin walled colorless, tangentially arranged cells. The cork tissue is broken at some places due to lenticels.

Cortex: Cortex is multilayered, outer few layers are made up of irregular, chlorenchymatous cells while cells of inner cortex is made up of polygonal cells that contain starch grains which are simple and ovoid. Many secretory cells are found scattered in the cortex. Pericycle shows the presence of fibers.

Vascular Bundles: TC shows anomalous secondary growth resulting in the formation of 10 to 12 wedged shaped external

xylem which is surrounded by semi –circular strip of phloem alternating with medullary rays. Phloem cells contain calcium oxalate crystals. Presence of two layered cambium. Xylem consists of vessels, tracheids, xylem parenchyma and fibres. Pith is parenchymatous which contain starch grains.[32]

Ayurvedic Properties:

Rasa : Tikta, Katu

Guna : Laghu, Snigdha

Veerya : Ushna

Vipaka : Madhura

Prabhava : Tridoshahara

Parts used: Stem, Root, Leaves [27]

Substitutes and Adulterants

The commonest species of Tinospora with which TC is likely to be substituted or adulterated are T. sinensis (Lour.) Merr. and T. crispa (Linn.) Miers ex Hook. f. and Th. The extract of Guduchi (Guduchi Satva) is adulterated with powder/flour of potato/sweet potato/ arrowroot/banana.[33]

Phytochemistry

The plant mainly contains alkaloids, glycosides, steroids, sesquiterpenoid, aliphatic compound,

essential oils, mixture of fatty acids and polysaccharides.

A variety of constituents has been isolated from TC plant and their structures were well elucidated. They belong to different classes such as alkaloids, diterpenoid lactones, glycosides, sesquiterpenoid, aliphatic compounds, phenolics, polysaccharides, steroids like tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furanolactone tinosporidine, columbin and β-sitosterol. Leaves of the plant are rich in protein (11.2%) and are fairly rich in calcium and phosphorus [34]

Three major groups of compounds; protoberberine alkaloids, terpenoids and polysaccharides are considered as putative active constituents of TC.[35]

Table 1:- Chemical constituents of *Tinospora cardifolia*

Type of chemical	Active principles	Parts in which present.
Alkaloids	Berberine, Palmatine, Tembetarine, Magnoflorine Choline, Tinosporin, Isocolumbin, Palmatine, Tetrahydropalmatine, Magnoflorine	Stem and root
Glycosides	18-norclerodane glucoside, Furanoid diterpene glucoside, Tinocordiside, Tinocordifolioside, Cordioside, Cordifolioside A, Cordifolioside B, Syringin, Syringin-apiosylglycoside, Palmatosides C,	Stem
Diterpenoid lactones	Palmatosides F, Cordifoliside A, Cordiofoliside B,	Whole plant
Steroids	Cordifoliside C, Cordifoliside D, Cordifoliside E Furanolactone, Clerodane derivatives, Tinosporon,	Stem and aerial part
Sesquiterpenoid	Tinosporides, Jateorine, Columbin	Stem, whole plant and root
Aliphatic compound	β -sitosterol, δ-sitosterol, 20 β-	
Miscellaneous compound	Hydroxy ecdysone. Ecdysterone , Makisterone A, Giloinsterol Tinocordifolin. Octacosanol, Heptacosanol ,	

	Nonacosan-15-one 3, (α,4-di hydroxy-3-methoxy-benzyl)-4-(4- Compounds hydroxy-3-methoxy-benzyl)- tetrahydrofuran. Jatrorrhizine. Tinosporidine, Cordifol, Cordifelone, N-trans-feruloyl tyramine as diacetate, Giloin, Giloinin, Tinosporic acid.	

Ethnobotanical, Folk and Tribal Uses

There are over 400 different tribal and other ethnic groups in India. Each tribal group has its own tradition, folk language, beliefs and knowledge about the use of natural resources as medicines.[29] TC finds a special mention for its use in tribal or folk medicine in different parts of the country. Almost all the parts of the plant are documented to be useful in ethno botanical surveys conducted by ethno botanists.[36-37] In folk and tribal medicine, whole plant, powdered root and stem bark, decoction of root and stem, juice of the root, juice or paste of the leaves, and stem of the TC are being used to treat various ailments viz. fever, jaundice, diarrhoea, dysentery, general debility, cough, asthma, leucorrhea, skin diseases, fractures, eye disorders, bites of poisonous insects, venomous snake etc. Ethnobotanical uses of TC are given in **Table 2**

Table 2:- Ethnobotanical uses of *Tinospora cordifolia*

S.No.	Plant part	Ethnobotanical uses
1.	Leaves	The leaves are beaten with honey and applied to ulcers and also treatment of gout and erysipelas (bacterial skin infection)
2.	Stem	The stem is bitter stomachic, stimulates bile secretion, diuretic, enriches the blood, cures jaundice, useful in skin diseases, The **juice** is useful in diabetes, vaginal and urethral discharges low fevers and enlarged spleen (20) **(Stem as an infusion)** used to drunk as a vermifuge, jaundice, against intestinal worms (**Stem as decoction**) used for washing sore eyes and syphilitic sores, antipyretic, antimalarial **Starch (statue)** obtained from stem used for chronic diarrhoea and some form of obstinate chronic dysentery, deal with intestinal problems and improve digestion (39)
3.	Root	The root is powerful emetic and used for visceral obstruction; its watery extract is used in leprosy.
4.	Stem + Root	Combination with other drugs as an antidote to snake bite and scorpion sting. (40-42)
5.	Bark	Anti-allergic, Anti-spasmodic, Anti-pyretic, Anti-leprotic (43-45)
6.	Fruit	Dried and powdered fruit, mixed with ghee or honey, is used as a tonic and also in the treatment of jaundice and rheumatism
7.	Whole plant	The whole plant is used in scabies in swine, diarrhoea and stomach trouble
	NS	Urinary diseases, syphilis, skin diseases, bronchitis (46)
	NS	Promote longevity and increase body's resistance (47) Stimulate the immune system (48-50)

NS = not specify

Bioactive Constituents and Their Molecular Targets

The pharmacological diversity of *Tinospora cordifolia* is associated with its chemically complex profile comprising alkaloids, diterpenoid lactones, glycosides, steroids, phenolics, terpenoids, polysaccharides and other secondary metabolites. Among these, alkaloids such as berberine, palmatine, jatrorrhizine and magnoflorine, together with diterpenoids such as tinosporide, tinosporaside and cordifolioside derivatives, have received considerable pharmacological attention. [38-40] Polysaccharide-rich fractions and phenolic constituents may additionally contribute to the antioxidant and immunomodulatory properties of the plant. [39,40]

The biological effects of *T. cordifolia* appear to involve modulation of multiple molecular targets rather than interaction with a single pharmacological target. Berberine and related protoberberine alkaloids have been associated with regulation of inflammatory mediators, oxidative stress and metabolic signaling, whereas diterpenoid and glycosidic constituents have been investigated for immunomodulatory, antioxidant and anti-inflammatory effects.[40-42] In experimental systems, the pharmacological activity of *T. cordifolia* has been linked with signaling pathways involving nuclear factor-kappa B (NF-ϰB), mitogen-activated protein kinases (MAPK), phosphoinositide-3-kinase/protein kinase B (PI3K/Akt), cyclic AMP (cAMP), mammalian target of rapamycin (mTOR) and apoptosis-related pathways.[42,44] However, these associations should be interpreted cautiously because many molecular-target predictions are derived from network pharmacology, molecular docking or in-vitro studies and require experimental validation.

Recent metabolomic and network-pharmacology research has further expanded the molecular landscape of *T. cordifolia*. An LC–MS/MS-based study identified 1186 metabolites and mapped their potential interactions with 591 human proteins, with enrichment of cAMP, mTOR, MAPK and PI3K/Akt signaling pathways as well as cholinergic, dopaminergic, serotonergic and glutamatergic pathways. BACE1 and monoamine oxidase-B (MAO-B) were proposed as potential targets relevant to neuroprotection and Alzheimer's disease.[43] These findings demonstrate that the therapeutic effects of *T. cordifolia* may arise from multi-component and multi-target interactions, providing a mechanistic framework for understanding its traditional use while highlighting the need for target-specific experimental and clinical validation.

PHARMACOLOGICAL ACTIVITIES: MECHANISTIC AND EVIDENCE-BASED UPDATE

Immunomodulatory and Anti-inflammatory Activity

Immunomodulation remains one of the most extensively investigated pharmacological properties of *T. cordifolia*. Experimental studies indicate that extracts and isolated constituents can influence macrophage activity, cytokine production and other components of innate and adaptive immune responses. Recent phytochemical investigations have also identified new constituents with immunomodulatory activity in macrophage-based experimental systems.[44] The anti-inflammatory activity of *T. cordifolia* is associated with modulation of inflammatory mediators and signalling pathways including NF-ϰB and MAPK, which regulate the expression of cytokines and other inflammatory mediators.[42]Nevertheless, the immunomodulatory effects are highly dependent on extract composition, dose and experimental model, and therefore cannot automatically be extrapolated to clinical efficacy.

Antioxidant Activity

The antioxidant activity of *T. cordifolia* has been demonstrated using both chemical and biological models and is generally attributed to its phenolic compounds, flavonoids, alkaloids and other redox-active constituents. The proposed mechanisms include direct scavenging of reactive oxygen species, reduction of lipid peroxidation and modulation of endogenous antioxidant defence systems. [39,40] The antioxidant response may contribute indirectly to the hepatoprotective, anti-inflammatory and neuroprotective effects reported for the plant. However, antioxidant activity observed in chemical assays should not be considered equivalent to therapeutic antioxidant efficacy in humans.

Antidiabetic and Metabolic Activity

Antidiabetic activity is another extensively investigated property of *T. cordifolia*. Preclinical studies have reported reductions in blood glucose and improvements in biochemical parameters following administration of *T. cordifolia* extracts. Proposed mechanisms include modulation of glucose metabolism, oxidative stress and inflammatory pathways. More recent computational studies have investigated interactions of *T. cordifolia* constituents with targets including peroxisome proliferator-

activated receptor-γ (PPAR-γ), PPAR-α, sodium-glucose cotransporter-2 (SGLT2) and receptor for advanced glycation end products (RAGE), providing hypotheses for its metabolic effects.[45] Such findings are promising but remain predominantly mechanistic or computational and require validation through controlled human studies.

Hepatoprotective Activity

The hepatoprotective potential of *T. cordifolia* has been investigated primarily in experimental models of chemically induced hepatic injury. Extracts have been reported to reduce biochemical indicators of liver injury and oxidative stress and to preserve hepatic architecture. Alkaloids including berberine, palmatine and jatrorrhizine, together with phenolic compounds such as sinapic acid, have been proposed as contributors to hepatoprotective activity.[46] The proposed mechanisms include reduction of oxidative stress, inhibition of lipid peroxidation, modulation of inflammatory responses and promotion of hepatic cellular recovery. However, the interpretation of hepatoprotective evidence must be considered alongside emerging reports of herb-induced liver injury, discussed separately in Section 9.

Neuroprotective and Cognitive Effects

The neuroprotective potential of *T. cordifolia* has received increasing attention. Experimental investigations suggest that its constituents may influence oxidative stress, neuroinflammation, cholinergic signalling and neuronal survival. A recent metabolomics and network-pharmacology study identified 1186 metabolites and predicted interactions with 591 human proteins, with enrichment of cAMP, mTOR, MAPK and PI3K/Akt pathways. BACE1 and MAO-B emerged as potential molecular targets associated with Alzheimer's disease-related neuroprotection.[43] These results provide a mechanistic basis for further investigation but should presently be regarded as hypothesis-generating rather than evidence of clinical efficacy.

Anticancer Activity

Experimental studies have reported antiproliferative and cytotoxic effects of *T. cordifolia* extracts and selected constituents against different cancer cell models. Proposed mechanisms include modulation of apoptosis, oxidative stress, inflammatory signalling and cell-cycle-associated pathways. Recent network-pharmacology and molecular-docking studies have attempted to identify compound-target relationships underlying the anticancer effects of *T. cordifolia*.[47] However, most available evidence remains based on cell culture, animal or computational studies. Consequently, *T. cordifolia* should not presently be considered an established anticancer therapy, and clinical studies using chemically characterized preparations are required.

Antimicrobial and Antiviral Activity

T. cordifolia has demonstrated antimicrobial and antiviral potential in experimental models, with activity attributed to multiple classes of secondary metabolites and their effects on microbial growth, inflammatory signalling and host immune responses.[39,40] During the COVID-19 pandemic, its immunomodulatory and antiviral potential attracted considerable interest; however, evidence generated from experimental or computational studies should not be interpreted as proof of clinical efficacy against COVID-19 or other viral diseases. The major requirement for future research is to distinguish direct antiviral activity from indirect effects mediated through host immune modulation.

Integrated Interpretation of Pharmacological Evidence

Overall, the pharmacological profile of *T. cordifolia* is supported by a large body of preclinical research, but the strength of evidence varies considerably among indications. Immunomodulatory, antioxidant, hepatoprotective and antidiabetic activities have substantial experimental support, whereas molecular mechanisms, clinical efficacy and dose-response relationships remain incompletely established. Recent systems-level approaches are beginning to connect phytochemical composition with molecular targets and signalling pathways; however, rigorous validation using standardized extracts, authenticated plant material, pharmacokinetic studies and well-designed clinical trials is required before definitive therapeutic claims can be made.[43,46]

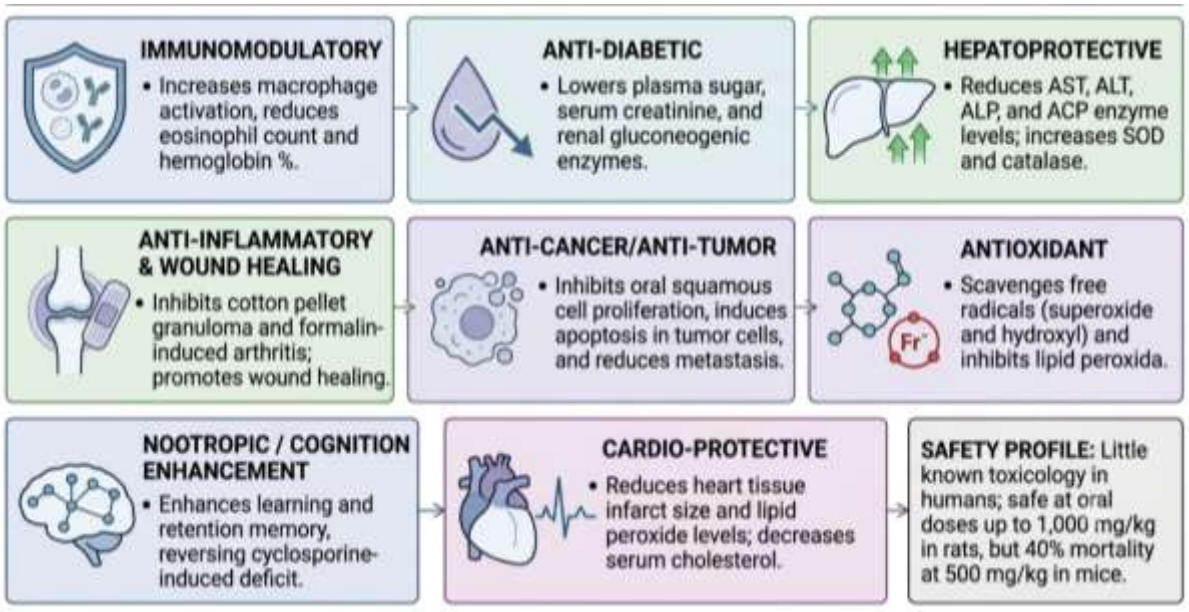

Figure 2: Schematic overview of the major pharmacological activities and therapeutic properties of *Tinospora cordifolia* (*Guduchi*).

CLINICAL EVIDENCE AND HUMAN STUDIES

Although *T. cordifolia* has a long history of traditional use, human clinical evidence remains considerably smaller than the preclinical literature. Several clinical investigations have nevertheless provided preliminary evidence of biological activity. An early randomized double-blind placebo-controlled trial involving 75 patients with allergic rhinitis reported improvement in symptoms such as sneezing, nasal discharge, nasal obstruction and nasal pruritus following administration of *T. cordifolia* extract for eight weeks.[48] Another randomized clinical investigation evaluated *T. cordifolia* as an add-on therapy in patients with type 2 diabetes mellitus and reported improvements in fasting blood glucose, postprandial glucose and HbA1c over six months.[49]

Clinical investigations have also explored its immunomodulatory and anti-inflammatory effects. A randomized double-blind placebo-controlled study involving 68 HIV-positive patients evaluated *T. cordifolia* extract for six months and reported changes in selected clinical and hematological parameters, although adverse symptoms including anorexia, nausea, vomiting and weakness were also reported.[50]In patients with rheumatoid arthritis, studies using *T. cordifolia* preparations as add-on therapy have reported improvements in disease activity and patient-reported outcomes, although these investigations have limitations related to study design, sample size and the use of combination or adjunctive therapy.[51]

More recently, a pilot clinical study investigated *T. cordifolia* aqueous extract in 24 patients with severe hypertriglyceridemia. A 14-day intervention was associated with reductions in triglyceride and VLDL concentrations and an increase in HDL concentration. Importantly, the study incorporated metabolomic and proteomic profiling, demonstrating the potential of integrating clinical outcomes with systems-biology approaches.[52] Nevertheless, the small sample size and short duration substantially limit the generalizability of these findings.

Therefore, available human evidence suggests biological activity of *T. cordifolia* in selected conditions, but it remains insufficient to establish the plant as an evidence-based therapeutic agent for any major disease indication. Future clinical research should use authenticated and chemically standardized preparations, clearly defined doses, validated biomarkers, adequate sample sizes, appropriate placebo or active controls, longer follow-up and systematic adverse-event monitoring. Such studies would be essential for translating traditional use and preclinical mechanistic evidence into clinically meaningful therapeutic applications.

Safety, Hepatotoxicity and Pharmacovigilance

The safety profile of *T. cordifolia* requires careful and balanced consideration because the literature contains both supportive toxicological data and reports of clinically apparent liver injury. Experimental studies have generally reported a relatively

broad safety margin for aqueous or crude extracts at certain doses, while some human studies have reported acceptable short-term tolerability.[40] However, the occurrence of herb-induced liver injury (HILI) associated with products reported to contain *T. cordifolia* has raised important concerns regarding botanical authentication, preparation quality, dosage, duration of use and patient-specific susceptibility.

During the COVID-19 pandemic, several cases of autoimmune-like hepatitis were reported following consumption of products described as Guduchi or Giloy.[53] Subsequent investigations emphasized an important confounding issue: *T. cordifolia* can be morphologically confused with related species such as *Tinospora crispa*, and species identity was not always established in reported cases.[54]Analytical investigations using HPTLC and DNA barcoding have therefore highlighted the importance of confirming the botanical identity of the material involved in suspected hepatotoxicity.[55] At the same time, other clinical reports have described probable liver injury temporally associated with products containing *T. cordifolia*, indicating that the possibility of genuine idiosyncratic hepatotoxicity should not be dismissed.[56]

The current evidence therefore does not justify either extreme conclusion that *T. cordifolia* is universally hepatotoxic or that it is completely free from hepatotoxic risk. Instead, hepatotoxicity should be considered in the context of species authentication, contamination/adulteration, extract composition, dose, duration, concomitant medicines, pre-existing liver disease and individual susceptibility. Recent hepatology literature also emphasizes the importance of systematic causality assessment in suspected herbal-induced liver injury. [53,57] Pharmacovigilance of *T. cordifolia* should consequently include batch traceability, botanical authentication, chemical fingerprinting, documentation of concomitant medications, liver-function monitoring in susceptible populations and standardized reporting of adverse events. This safety-oriented framework is particularly important because the traditional perception of an herb as "natural" does not by itself establish clinical safety.

Quality Control, Standardization and Adulteration

The therapeutic reproducibility of *T. cordifolia* depends strongly on botanical authentication, chemical standardization and control of raw-material variability. Closely related species including *T. crispa* and *T. sinensis* may occur in overlapping geographical regions and can be confused with *T. cordifolia* because of morphological similarities. [54,55] Such substitution is of particular concern because differences in phytochemical composition may result in differences in pharmacological activity and toxicity.

Conventional quality-control approaches include organoleptic evaluation, microscopy, physicochemical parameters, extractive values, ash values and chromatographic fingerprinting. HPTLC has historically been used for standardization using marker compounds such as tinosporaside, while more recent analytical methods have employed HPLC, HPTLC-MS/MS and multi-component chromatographic approaches to simultaneously quantify several bioactive constituents including tinosporide, 8-hydroxytinosporide, tinosporaside, cordifolioside A, 20-β-hydroxyecdysone, columbin and selected alkaloids. [58,59]

Recent work has also demonstrated the utility of UHPLC-PDA and HPTLC for evaluating temporal variation in phytochemical composition, including compounds such as magnoflorine, cordifolioside A and β-ecdysone.[60] These findings indicate that harvesting season, geographical origin and processing conditions can influence the chemical profile of the plant. Accordingly, future standardization should move beyond single-marker analysis towards multi-marker chromatographic fingerprints combined with orthogonal analytical techniques such as LC-MS/MS, DNA-based authentication and, where appropriate, elemental or contaminant profiling.

Adulteration and substitution should therefore be considered major quality and safety issues rather than merely pharmacognostic concerns. A robust quality-control strategy for *T. cordifolia* should integrate macroscopic and microscopic authentication, DNA barcoding, chromatographic fingerprinting, quantitative marker analysis, contaminant testing and batch-to-batch chemical consistency. Such an integrated approach would improve reproducibility of pharmacological studies and enhance the reliability of commercial and pharmaceutical preparations.

Emerging Approaches: Metabolomics, Network Pharmacology and Computational Pharmacology

The chemically complex and multi-component nature of *T. cordifolia* makes conventional single-target pharmacological investigation insufficient to fully explain its biological activity. Consequently, metabolomics, network pharmacology, molecular docking and other computational approaches are increasingly being incorporated into *T. cordifolia* research. These approaches enable simultaneous investigation of multiple metabolites, proteins, pathways and biological processes and may help establish mechanistic relationships between traditional use and modern pharmacology.

A notable recent study combined untargeted LC-MS/MS metabolomics with network pharmacology and molecular docking and identified 1186 metabolites in *T. cordifolia*. The study predicted interactions with 591 human proteins and identified enrichment of cAMP, mTOR, MAPK and PI3K/Akt pathways, together with neurotransmitter-related signalling pathways. BACE1 and MAO-B were highlighted as potential targets associated with neuroprotective activity.[43] Similarly, network-pharmacology investigations have been used to identify potential inflammatory targets and compound-target relationships associated with the immunomodulatory properties of *T. cordifolia*.[61]

Computational pharmacology has also been applied to explore the antidiabetic potential of *T. cordifolia* constituents against targets such as PPAR-γ, PPAR-α, SGLT2 and RAGE.[45] Such approaches can prioritize compounds for experimental validation and reduce the number of candidate molecules requiring laboratory screening. However, molecular docking or target-prediction results represent hypotheses rather than proof of pharmacological activity. Future research should therefore integrate computational predictions with biochemical assays, cellular experiments, animal models, pharmacokinetic studies and clinical biomarkers.

The future direction of *T. cordifolia* research should consequently shift from isolated compound screening towards an integrated systems-pharmacology framework combining metabolomics, proteomics, transcriptomics, network pharmacology and experimental validation. Such approaches may also help identify pharmacological biomarkers and establish relationships between chemical fingerprints and therapeutic or adverse outcomes.

Formulation and Translational Drug-Development Potential

The broad pharmacological profile of *T. cordifolia*, together with its long history of traditional use, provides a rationale for investigating its potential as a source of standardized phytopharmaceutical products. Traditional preparations such as Guduchi Sattva, aqueous extracts, decoctions and powdered stem material have been used in Ayurvedic practice, while modern pharmaceutical approaches have explored tablets, capsules, extracts and other dosage forms. Standardized manufacturing procedures for Guduchi Sattva and its tablet formulations have demonstrated the feasibility of applying physicochemical, pharmaceutical and chromatographic quality-control parameters to traditional preparations.[62]

From a drug-development perspective, the major challenge is not simply to formulate *T. cordifolia* but to establish a reproducible relationship between botanical identity, chemical composition, pharmacological activity, pharmacokinetics and clinical outcome. Modern formulation development should therefore employ authenticated raw material and chemically standardized extracts, followed by optimization of extraction conditions, marker-compound content, stability, dissolution/release characteristics and dosage-form performance. Where appropriate, advanced delivery systems may also be explored to improve the bioavailability of poorly soluble or unstable phytoconstituents.

A translational development pathway for *T. cordifolia* should progress through four interconnected stages: (i) authenticated and standardized botanical material; (ii) chemical fingerprinting and identification of pharmacologically relevant markers; (iii) mechanistic and pharmacokinetic validation using appropriate experimental models; and (iv) well-designed clinical trials evaluating efficacy, safety and dose-response relationships. This approach could facilitate the transition of *T. cordifolia* from a traditionally used medicinal plant towards evidence-based phytopharmaceutical development while minimizing problems associated with batch variability, adulteration and uncertain safety.

Importantly, future formulations should not be evaluated solely on the basis of traditional claims or in-vitro activity. Demonstration of chemical consistency, biological reproducibility, stability, bioavailability and clinically relevant therapeutic outcomes should form the basis of translational development. The integration of modern analytical science with Ayurvedic knowledge may therefore provide a rational framework for developing standardized *T. cordifolia*-based pharmaceutical or nutraceutical products.

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