



INDIAN *TINOSPORA* SPECIES: NATURAL IMMUNOMODULATORS AND THERAPEUTIC AGENTS

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ABSTRACT:

The substance which stimulates or suppresses the components of immune system is known as immunomodulator. Antibiotics have limited effective life span and its prolonged use is harmful. So, scientists are more relying on medicinal plants, which are natural immunomodulators and therapeutic agents. This review paper presents plant description, chemical properties, immunomodulatory and therapeutic properties of Indian *Tinospora* species. Indian *Tinospora* species are belonging from menispermaceae family. *Tinospora* species plants are climbing shrubs. They are mostly found in tropical and subtropical area of India. There are mainly three species: *Tinospora cordifolia, Tinospora malabarica and Tinospora crispa*. These three species are closely related with their morphology & chemical properties of stem, bark, leaves, flowers, *Tinospora cordifolia* and immunomodulatory activity so it is widely used in Ayurveda. *Tinospora malabarica* is giantdeciduous climber mainly found at Konkan, Karnataka, Tamilnadu, Bengal, and Orissa. It is mixed as adulterant or substitute with *T. cordifolia*. It is also an immunomodulator. *Tinopora crispa* is small herb which widely grows in temperate and tropical parts of India. It is on the contract of the properties and in diabetes therapy.

KEYWORDS:

Immunomodulators, Phytochemistry, T.cordifolia, T.crispa, T.malabarica/sinensis, Therapeutic agents, etc.

INTRODUCTION

The substance which stimulates or suppresses the components of immune system including both innate and adaptive immune responses is known as an immunomodulators[1]. Modulation of immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of immune system. There are generally two types of immunomodulators based on their effects: Immunomodulators and Immunosupressors. They have ability to mount an immune response or defend against pathogens or tumors [2]. Antibiotics have limited effective life span and its prolonged use is harmful, so scientists are investigated new alternate source of medicine forcombating and alleviating various disorders in humans. Medicinal plants have been used to cure human illness, which primarily show cellular rather than humoral immune response. It augments macrophages chemotaxis, phagocytosis & promotes interaction with other immune regulatory lymphoid cells[3].Menispermaceae family consists of about 70 genera and 450 species that are foundin tropical lowland regions. Tinospora is belonging from menispermaceae family. They are generally climbing or twining shrubs [4]. They are mostly found in tropical and subtropical area of India. There are mainly three species: *Tinospora cordifolia, Tinospora malabarica and Tinospora crispa*. These three species are closely related with their morphology & chemical properties of stem, bark, leaves, flowers, etc. The detail knowledge of Indian *Tinospora* species are given in this review one by one.

INDIAN TINOSPORA SPECIES

1.Tinospora cordifolia

- **1.1 Botanical name:** *Tinospora cordifolia* (willd.) Mier ex Hook. F & Thoms
- **1.2 Synonyms:** Cocculus cordifolius DC.; Menispermum cordifolium (willd); Tinospora glabra(N.Burm.) Merr.[5].
- 1.3 Taxonomy Kingdom: Plantae Division: Magnoliphyta Class: Magnoliopsida Order: Ranunculales Family: Menispermaceae Genus: *Tinospora* Species: *cordifolia*

1.4 classical names

Guduchi, Madhuparni, Amrita, Amritavallari, Chhinna, Chhinnaruha, Chhinnodbhava, Vatasadani,

Tantrika, Kundalini, Chakralakshanika, Somavalli, Dhira, Vishalya, Rasayani, Chandrahasa, Vayastha, Mandali, Devanirmita[6].

1.5 Plant description

Habit: large, deciduous, extensively spreading, climbing shrub with several elongated twinning branches[7].(**Fig.1**)

Distribution: Plant is distributed throughout the tropical region of India up to 800-1200 m above sea level, extending from Himalayas down to the southern part of peninsular India [8].

Stem: fibrous and the transverse section exhibits wedge shaped wood bundles, containing largea yellowish wood with radially arranged wedge shaped wood bundles, containing largevessels, separated by narrow medullary rays[9].(**Fig.2**)

Bark: creamy white to grey brown, warty, deeply left spirally, the space in between being spotted with large rosette like lenticels[10,11].

Root:succulent with long filiform fleshy aerial roots from the branches [10].(**Fig. 3**)

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[7].

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[7].(Fig. 4)

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 [7, 9].(**Fig. 5**)

Sepals: 6, free in two series of three each, the outer one are smaller than the inner [7].

Petals: 6, free smaller than sepals, obovate and membranous [7].

Fruits: aggregates of 1-3 ovoid smooth druplete on thick stalk with sub terminal style scars,

Scarlet or orange red color. Fruits grow during winter [7, 9].(Fig. 6)

Seeds: white, bean shaped, curved [6].(Fig.7).



Fig. 1 Tinosporacordifolia plant



Fig. 3 Tinosporacordifolia aerial roots



Fig 2. Tinosporacordifolia stem



Fig.4Tinosporacordifolia leaves

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Fig. 5 Tinosporacordifolia flowers



Fig. 6 Tinosporacordfolia fruits



Fig. 7 Tinosporacordifolia seeds

1.6 Phytochemistry (Active chemical constituents) A variety of constituents are isolated from *Tinospora cordifolia* Belonging to different classes such as alkaloids, glycosides, diterpenoid lactones, sesquiterpenoids, steroids, phenolics, aliphatic compounds and polysaccharides. Leaves are rich in protein (11.2%) and fairly rich in calcium and phosphorus [10, 12, 13]. **Table a.** Provides active chemical constituents of different parts of *T. cordifolia*[10].

Table a: Active chemical constituents of different parts of *Tinosporacordifolia* (S.S. singh et al, 2003).NoType of chemicalsActive chemical constituentPlant part

1	Alkaloids	Berberine, PalmatineTembetarine, Magnoflorine	Stem and root
		,Choline, Tinosporin, Isocolumbin, Palmatine,	
		Tetrahydropalmatine, Magnoflorine	
2	Glycosides	18-norclerodane glucoside	Stem
		Furanoidditerpeneglucoside	
		Tinocordiside, Tinocordifolioside.	
		Cordioside, Cordifolioside A, CordifoliosideB, Syringin,	
		Syringin-apiosylglycoside,	
		Palmatosides C, Palmatosides F,	
		Cordifoliside A, Cordiofoliside B,	
		Cordifoliside C, Cordifoliside D, Cordifoliside E	
3	Diterpenoid lactones	Furanolactone,	Whole plant
		Lactones Clerodane derivatives,	
		diepoxy-cleroda-13 (16), 14-dieno-17,12S:	
		18,1S-dilactone Jand Tinosporon,	
	~	Tinosporidesand Jateorine, Columbin	
4	Steroids	β -sitosterol, δ -sitosterol, 20 β - hydroxyecdysone,	Aerial parts and stem
		Ecdysterone, Makisterone A, Giloinsterol	
5	Sesquiterpenoid	Tinocordifolin	Stem
6	Aliphatic compouds	Octacosanol, Heptacosanol	Whole plant
		compound Nonacosan-15-one	
7	Micelleneous compounds	3,(<i>a</i> ,4-di hydroxy-3-methoxy-benzyl)-4-(4-	Whole plant and root
		Compounds hydroxy-3-methoxy-benzyl)-tetrahydrofuran.	
		Jatrorrhizine, Tinosporidine, Cordifol, Cordifelone, N-	
		trans-feruloyltyramine as diacetate, Giloin, Giloinin,	
		Tinosporic acid	

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1.7 Ayurvedic properties

Rasa- Tikta, Kashaya; Guna- Guru, Snigdha; Veerya- Ushna; Vipaka- Madhura; Doshaghnata-Tridoshashashamaka; Rogaghnata-Kushtha, Chhardi, vatarakta, Netraroga, Trishna, Daha, Aruchi, Agnimandya, shola, Yakrridvikara, Kamala, Amlapitta, Pravahika, Atisara, Raktatisara, Grahani, Krimi. Arsha. Hriddaurbalya, pleehavriddhi, Vastishotha, Raktavikara, Amavata, Pandu, Shwasa, Kasa, Shukradaurbalya, Prameha, Madhumeha, Mootrakrichchhra, Kushtha, Visarpa, Twagroga, Phiranga, Jwara, Vishamajwara, Jeernajwara; Karma- Vedanasthapana, Kusthaghna, Trishnanigrahana, Chhardinigrahana, Deepana, Pachana, Anulomana, Pittasaraka, Sangrahi, Krimighna, Hridya, Raktashodhaka, Raktavardhaka, Kaphaghna, Vrishya, Balya, Pramehahara, Mootrajanana, Jwaraghna, Dahaprashamana, Rasayana [6].

1.8 Uses

A) As an Immunomodulator

- *T.cordifolia* is commonly known as 'Guduchi'. Guduchi means to rejuvenate the dead cells. It improves the phagocytic & bactericidal activities in patients suffering from polymorphism in jaundice. It was also found that aqueous extract of *T.cordifolia* is capable of increasing leukocyte count in mice.
- Crude extract of *Tinospora cordifolia* contained a polyclonal B cellmitogen which enhanced immune response in mice. An arabinogalactanpolysaccharide, G1-4A from the stem of *T. cordifolia* examined tomodulate inducedimmunosuppression[2].
- Alcoholic extracts of *T. cordifolia* obtained from the dried ripe fruits possess good immunomodulatory activity. Enhancement in the bone marrow cellularity as well as α -esterase activity in the rats groups treated with alcoholic extracts of *T. cordifolia* which evidently show that these have immunomodulatory activity [14].
- T.cordifolia improves the phagocytic function without affecting the humoral & cell mediated immune systems. Active components syringing & cardiol inhibit the invitro immunohaemolysis of antibody coated sheep erythrocytes by guinea pig serum, which is due to inhibition of C3convertase of classical complement pathway. The compounds also give rise to significant increases in IgG antibodies in serum [7].
- Alcoholic extract of *Tinospora cordifolia* activated tumor associated macrophages and showed antitumor effect on the spontaneousT-cell lymphoma and may have some clinical implications [2].
- *T.cordifolia* has pronounced effect on inter abdominal sepsis to elucidate host defense

mechanism to counter infective stresses. The above results indicate that *T. cordifolia* has immunomodulating properties [7].

B) As a therapeutic agent

- *T.cordifolia* is useful in folk medicine& has also been claimed to be beneficial according to 'Ayurveda' for cure of jaundice, skin diseases, Diabetes, anemia, cancer, liver disorder, heart disease, Parkinson's disease & enaciations [1,7].
- Polyherbal formulation of T.cordifolia possesses favorable effect in patient with HIV infection [3].
- Oral administration of an aqueous root extract to analloxan diabetic rat caused a significant reduction in blood glucose & brain lipids. Ethanolic extract of root has protective action against stress induced ulceration [3].
- Parkinson's disease is neurological disease, which is treated with L-DOPA, which produces dopamine but it produces free radicles during its own oxidation, which show side effect. *Tinosporacordifoliais* co- administered with it to counteract toxicity of L-DOPA. Because *T. cordifolia* is a good antioxidant [3].
- Aqueous extract of *T.cordifolia* roots when administered 2.5-5.0g/kg body weight, for 6 weeks, resulted in serum & tissue cholesterol, phospholipids & free fatty acids in allaxon diabetic rats [7].
- North Gujarat people use powdered root and stem bark of *Tinospora cordifolia* with milk for the treatment of cancer; the decoction of root is useful in treatment of dysentery and diarrhoea and preparation of old stem useful in periodic fever [15].
- Powder of *Terminalia chebula* and *Tinospora cordifolia* and *Trachyspermum ammi* in equal quantity is administered orally in early morning daily with salt to treat cough [16].
- A decoction of the fresh root mixed with pepper and goat's milk is given for rheumatism, where the dose is half a pint every morning [17].

2. Tinospora malabarica/ sinensis

2.1 Botanical name: *Tinospora malabarica* (lam.) Miers.

2.2 Synonyms:

Tinospora tomentosa(colebr.) Miers; Menispermum malabaricum Cocculus malabaricus DC.; Tinospora sinensis (lour.) Merr.; Camphylus sinensis Lour.; Tinospora malabarica(lam.) Hook.f. &Thoms. [5].

2.3 Taxonomy Kingdom: Plantae Division: Magnoliphyta Class: Magnoliopsida Order: Ranunculales Family: Menispermaceae Genus:*Tinospora* Species: malabarica/ sinensis

2.4 Classical names

Malabar gulbel, Chinese tinspora, Hoguni-lota, Giloy, Gulancha, Gurch, Sudarsana balli, Pee-amerda, Kattu amrita, Gulval, Vhadlli-amrutvel, Guruj Vatsadani, Sudarsana, Amarta, Potchindil, Tippategu.

2.5 Plant description

Habit: A giant deciduous climber, young part clothed with whitish hairs [5, 18]. (**Fig.8**)

Distribution: Konkan, Karnataka, Tamilnadu, Bengal, Orissa [5].

Stem: half inch. In diameter, smooth, shining with light coloured, papery bark more or less worty [18].(**Fig.9**)

Leaves: membranous, 4-6 by 3.5-5 inch. In diameter, 7 nervaed, broadly ovate, cordate, acuminate, pubescent above, whitish tomentose beneath; petioles reaching 5 inch. Long, thickened & twisted at the base [18].(**Fig. 10**)

Flowers: green, in recemes 3-6 inch. Long; pedicles slender, clustered [18].

Sepals: 6, the outer small, ovate-oblong, obtuse, the inner larger, oblong or suborbicular, concave[18].

Petals: in male flowers obovate, cuneate rounded at the apex, not embracing the stamens[18].

Drupes: 1-3 (usually 2), ovoid, smooth, red on thick stalk; endocarp marked externally with many sharp pointed tubenecles, fruits in January [18].



Fig. 8 Tinosporamalabarica plant



Fig. 9 Tinosporamalabarica stem



Fig. 10 Tinosporamalabarica leaves

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Fig. 11 Tinosporacrispaplant





Fig. 13 Tinosporacrispa leaf

2.6 Phytochemistry (Active chemical constituents)

Root and stem contain starch, a bitter principle and a trace of berberin[5].

2.7 Ayurvedic properties

Tridosaghna, Vedanna sthapana, kasthaghna[5].

2.8 Uses

A) As an immunomodulator

• A process for the preparation of an immunomodulator from *T.cordifolia* and *T. malabarica* have been described here. A branched polysaccharide, arabinogalactan was selectively precipitated from the polar extracts in aqueous medium by methanol. The active polysaccharide was further purified by high-performance gel permeation chromatography. It is polyclonally mitogenic to β -cells, and augments antibody response as well as enhances T-cell responses to model antigens [2].

B) As a therapeutic agent

- Sudarsana is tonic, used almost in the same way as *T. cordifolia*. Leaf juice mixed with that of *Coleus amboinicus* and honey is employed in gonorrhea. Fresh leaves and stem are used in chronic rheumatism in china [5].
- Stems are used for treating piles, ulcerated wounds, liver complaints, chronic rheumatism and also a muscle relaxant [19].
- *T. malabarica* extracts produced antiulcerogenic effects possessing antisecretory, cytoprotective and H2 blocking/ proton pump inhibition mechanism[20].
- The Kavirajes of South Sahapur, Noakhali district used a mixture of *Santalum album*, *Tinospora sinensis*, and *Adenanthera pavonina* for treatment of tuberculosis, debility (weakness), as well as burning sensations during urination. In all three of the above cases, the same regimen for treatment was followed in that the mixture of the three plant

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parts were administered orally twice daily for 1-3 months [21].

- The fresh leaves & stem juice is used as a tonic & for body pain [22].
- Leaf juice of *Tinospora sinensis* is dropped in the ear for the treatment of ear pain by the local people of patiyala, Punjab [16].

3. Tinospora crispa

3.1 Botanical name: Tinospora crispa

3.2 Synonyms: Menispermum crispum Linn. Menispermum rimosum Blanco, Tinospora cordifolia F.-Vill., Cocculus cordifolius Walp., Cocculus villosus DC. Tinospora tuberculata, Tinospora rumphii, Cocculus crispum, Menispermum tuberculatum, Menispermum verrucosum Tinospora crispa (L.) Miers ex Hook. f. & Thoms.[23].

3.3Taxonomy

Kingdom: Plantae Division: Magnoliphyta Class: Magnoliopsida Order: Ranunculales Family: Menispermaceae Genus: Tinospora Species: crispa

3.4 Classical names

dier, faridbuti, faridbel; jamtike bet, dooara-tiga, huya [Drury], patalagarudi; vasanavalli; vanatiktika, patalagalori, dagadi. [Nadkarni], paliahan (Bisaya), kattukkodi, dagadi,vasanvel ,tana, faridbel; jamtike bel, bratawali, andawali, putrawali, daun gade, boraphet ,wan kab hoi yai.

3.5 Plant description

Habit: small herb which widely grows in temperate and tropical parts [24].(Fig. 11)

Habitat: Tropical and subtropical Philippines, Indonesia, Malaysia, Thailand, India, China & Vietnam [24].

Stem: Old stems fleshy, with very prominent blunt tubercles. Younger stems slightly fleshy, epidermis thin, membranous, brownish, glabrous. [25]. (**Fig.12**)

Leaf: lenticels large and prominentlyraised. Petiole 5– 15 cm, glabrous; leaf blade broadly ovate to orbicular, slightly fleshy, very thinly papery when dried, both surfaces glabrous, base deeply to shallowly cordate, lobes rounded, margin entire, apex acuminate, palmately 5–7 veined, abaxial basal vein axils with shallow glabrous pockets.[25]. (Fig.13)

Flower: flowers 2 or 3 fascicled. Male inflorescences is very slender, 5–10 cm or longer. Male flower has sepals 6 in 2 whorls, green, glabrous,outer 3 ovate, ca. 1 mm, inner 3 obovate, 2.5–3 mm; petals 3–6, yellow, obovate-spatulate, 1.6–2.5 mm; stamens 6, as long as petals. Female inflorescences 2–6 cm, flowers mostly 1 per node. Female flower has sepals and petals as in

male; staminodes 6 to 1 mm; carpels 3, ca. 2 mm, stigma lobes very short. Fruiting peduncle 15–20 mm; carpophores 2–3 mm [25].

Drupes: orange, subglobose, to 2 cm when fresh; endocarp semiovoid, with conspicuous ridge abaxially, surface finely rugulose to almost smooth, adaxial aperture elliptic, small [25].

3.6 Phytochemistry (Active chemical constituents)

The whole plant contains bitter principle, columbine, 2.22%, trace of in alkaloid and a glucoside. Amorphous bitter principle, picroretine & trace of barberine were isolated. Later from root bark a bitter principle glucoside and some alkaloid were isolated. Picrotine is trace of an alkaloid, & a substance similar to glycyrrhizin. There are two alkaloids tinosporine & tinosporidine also present. Three compounds, identified as N-cis-feruloyltyramine, N-transferuloyltyramine and secoisolariciresinol, exhibiting antioxidant and radical scavenging properties towards β-carotene and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, were isolated from the CH₂Cl₂ extract of stems of T. crispa. Tinospora crispa stem contains: flavone O-glycosides (apigenin), picroretoside, berberine, palmatine, picroretine, resin & five flavonoids [23].

3.7 Uses

A) As an immunomodulator

- Methanol, choloform, n- butanol extacts of *T. crispa* were demonstrated, which has lack of enhancing activity on immune system, still it is used as medicine for other immunological disorders such as autoimmune disease or cancers [26].
- *T. crispa* extract could induce cytokine which were likely to be involved in anti-imflammatory activity [27].
- It did not suggest that *T.crispa* could also inhibit other arms of the immune responses because, *T. cordifolia*, a closely- related plant compounds were shown to enhance both immunity. Wether, *T. crispa* compounds reveals a potent effect on the immune system should be further investigated [28].

B) As a therapeutic agent

- Antihyperglycaemic effect of *T. crispa* is physiological suggests that the extract contains compounds which could be purified for use in the treatment of type II diabetes [23].
- *Tinospora crispa* is as effect an appetite enhancer as compared against the reference drug megestrol acetate [23].
- The cycloeucalenol and cycloeucalenone present in the stems produced mild cardiotonic effects [23].
- It had been used as traditional medicine in rural society to treat fever, cholera, snake bites, rheumatism and fever due to malaria.*T. crispa* has shown to have an antihyperglycemia effect

by augmenting the release of insulin. Its antimalarial activity, antibacterial, antiinflammatory and anti-oxidant properties [23].

- *T. crispa* has a dose-dependent antiproliferative activity against many types of cancer cells where the lowest IC_{50} is found to be present in the methanol extract on breast cancer cells [29].
- *Tinospora crispa* can be used externally for its strong anti-oxidant and antiradical properties. Flavonoids (amongst them apigenin) are best known for their ability to act as powerful anti-oxidants, and also have anti-allergic and antiviral properties [23].
- Indonesians use an infusion of the stems to treat fevers and malaria. They can also be used to treat stomachache and jaundice. The infusion is also useful in fevers caused by smallpox and cholera. Another popular use of this infusion is in a mixture for treating indigestion [30].

CONCLUSION

India has rich diversity of flora and fauna. It has large amount of medicinal plants which belong from different families, which are traditionally used to treat many diseases. From that Tinospora species (Family-Menispermaceae) have great potential to treat different ailments like diabetes, jaundice, debility, tuberculosis, rheumatism, ulcer, fever, HIV, cancer, cardiovascular disease, parkinson's disease, etc. Indian Tinospora species provide an alternative to conventional chemotherapy for autoimmune disease because of their good immunomodulatory properties. T. cordifolia and T. malabarica have better immunomodulation action than T. crispa. Indian Tinospora species have ability to scavenge free radicals and to inhibit radical induced membrane damage. Indian Tinospora species have wide range of chemical constituents & have pharmaceutical approach towards various ailments. It is believed that T. cordifolia has effective properties against swine flu H₁N₁ virus, although researchers are trying to prove this scientifically. Due to therapeutic efficacy of Indian Tinospora species, they are novel candidates for bioprospection and drug development for treatment of ailments. Indian T. cordifolia, T.malabarica, T. crispa are magical plants, which could be good remedy for various ailments for animals and human beings.

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