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THERAPEUTIC SCOPE OF *TINOSPORA CORDIFOLIA* IN MODERN ERA: A REVIEW

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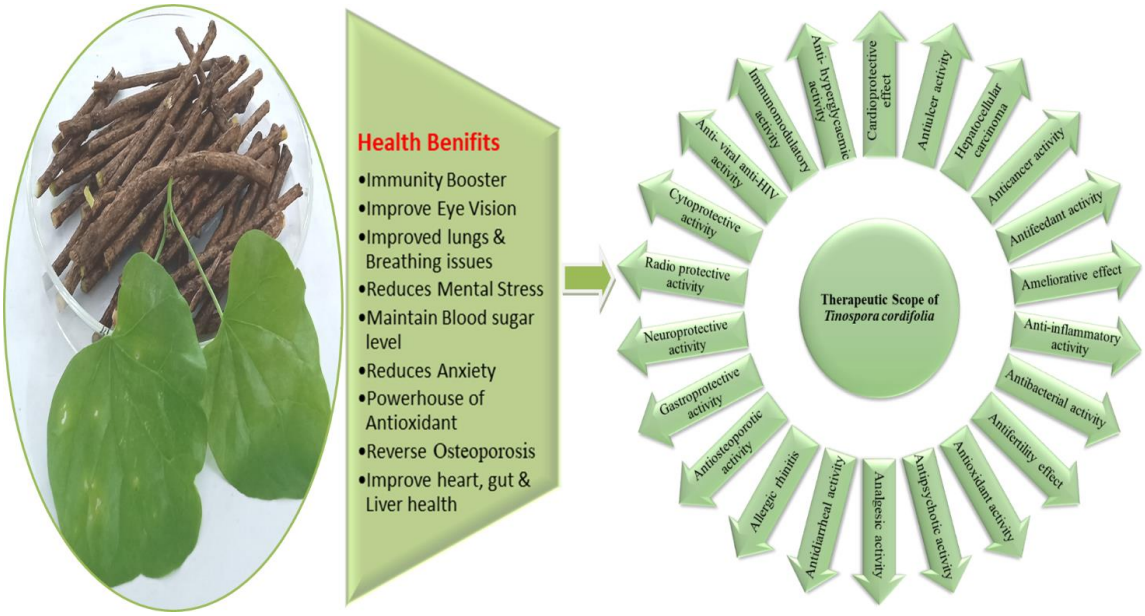
ABSTRACT

Several medicinal plants have been claimed to have the activity of immunomodulation and Tinospora species constitute a significant class of therapeutic herbs with various pharmacological uses. *Tinospora cordifolia* is one, that has potential to modulate the immune system. This review article describes the prominence and information regarding the morphological, phytochemical and pharmacology aspects of *T. cordifolia.* It is generally acknowledged as an important herb to cure a variety of conditions, including diabetes, cancer, skin illnesses, helminthiasis, leprosy, fever, jaundice, etc. Phytochemicals have been isolated from different parts of *T. cordifolia* such as glycosides, phenolics, diterpenoid lactones, steroids, alkaloids, sesquiterpenoid, aliphatic compounds, essential oils, and a mixture of fatty acids. *T. cordifolia* possesses various notable therapeutic properties like anti-hyperglycemic, anti-microbial, anti-oxidant, anti-inflammatory, anticancer immunomodulatory, etc. The immunomodulatory properties of *T. cordifolia* along with its role as a traditional Indian herb have contributed to its use in Ayurveda and alternative medicine for treating COVID-19. The potential involvement in managing Coronavirus disease has been investigated primarily through molecular docking (in-silico research), retrospective investigations, animal experimentation, and randomized controlled

trials. This review article explores the therapeutic scope of *T. cordifolia*, examining its uses in traditional Ayurvedic medicine as well as its relevance in modern healthcare.

KEYWORDS: Medicinal Plants, Plant Extract, Natural Products, Immunomodulatory, *Tinospora cordifolia.*

Graphical abstract



1. INTRODUCTION

Herbal medicines have been commonly utilized worldwide since ancient times. Traditional medical systems, like the Ayurvedic system (AYUSH), have been practiced extensively.[1] Factors such as population growth, high treatment costs, limited drug availability, side effects of many allopathic medications, and the development of resistance to current drugs have increased the focus on using plant-based materials as sources of medicine.[2] A significant class of therapeutic herbs with a range of pharmacological uses is the Tinospora species. *T. cordifolia* is a plant of significant medicinal importance in the indigenous system of medicine and is designated as Rasayana.[3] It is used as an important drug in Ayurvedic medicine and is recommended to enhance Immunity (General body resistance).[4] Immunomodulation hints primarily at the non-antigen dependent function and efficiency of macrophages, granulocytes, and white blood cells and comprises also a therapeutic concept.[5] *T. cordifolia* is a dioecious plant belonging to the Menispermaceae family.[6] *T. cordifolia* is a large spreading, and deciduous, twiner with a succulent climber stem. It is a climbing shrub found all over India, especially in tropical regions. It is known as heart-leaved moonseed plant in English, Giloy in

Hindi, and Guduchi in Sanskrit. In Indian traditional Ayurveda for its anti-inflammatory, immunomodulatory, anti-diabetic, antioxidant, anti-allergic, antiviral activities, and various other medicinal properties. Almost all parts of this herb have been used in different aspects.[7,8]

1.1 Habitat

T. cordifolia is one of 34 species of genus of Tinospora[9] and is widely distributed in most of the entire country from the Himalayas to the Southern part of India and Southeast Asian countries such as Malaysia, Philippines, Indonesia, Borneo, Thailand, Vietnam, and China, as well as in North, West and South Africa. Apart from India it is also distributed in Sri Lanka, Bangladesh and Myanmar. In India it has been found in Andhra Pradesh, Assam, Kerala, Bihar, Maharashtra, Odisha, Madhya Pradesh, Uttar Pradesh, Rajasthan and Himayalan foothills, tropical countries. Considering the distribution of plant expected because of extensive variation in genetic as well as phytochemical constituents.[10]

1.2 Taxonomical description

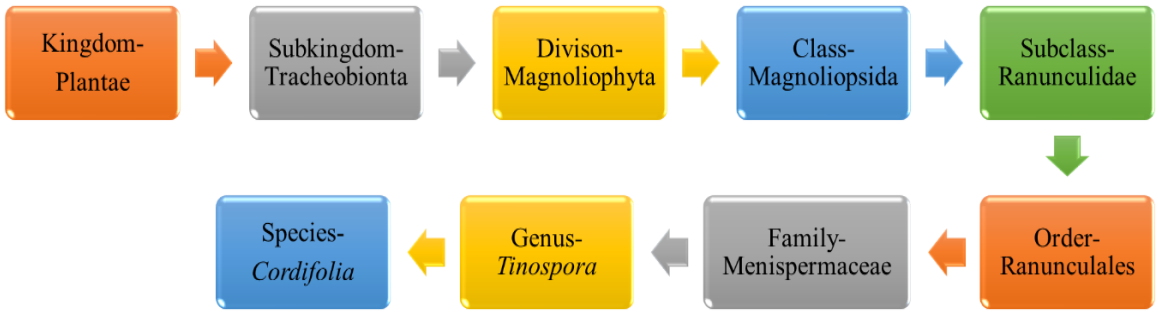


Fig. 1: Taxonomical Position of *T. cordifolia.*

The genus Tinospora includes 34 species (Fig.2) and the taxonomical position of *T. cordifolia* is shown in Fig.1 however, phytochemical investigations, pharmacological experiments, and clinical applications have mainly focused on four species of Tinospora, viz. *T. cordifolia*, *T. sagittata*, *T. capillipes*, and *T. crispa*.

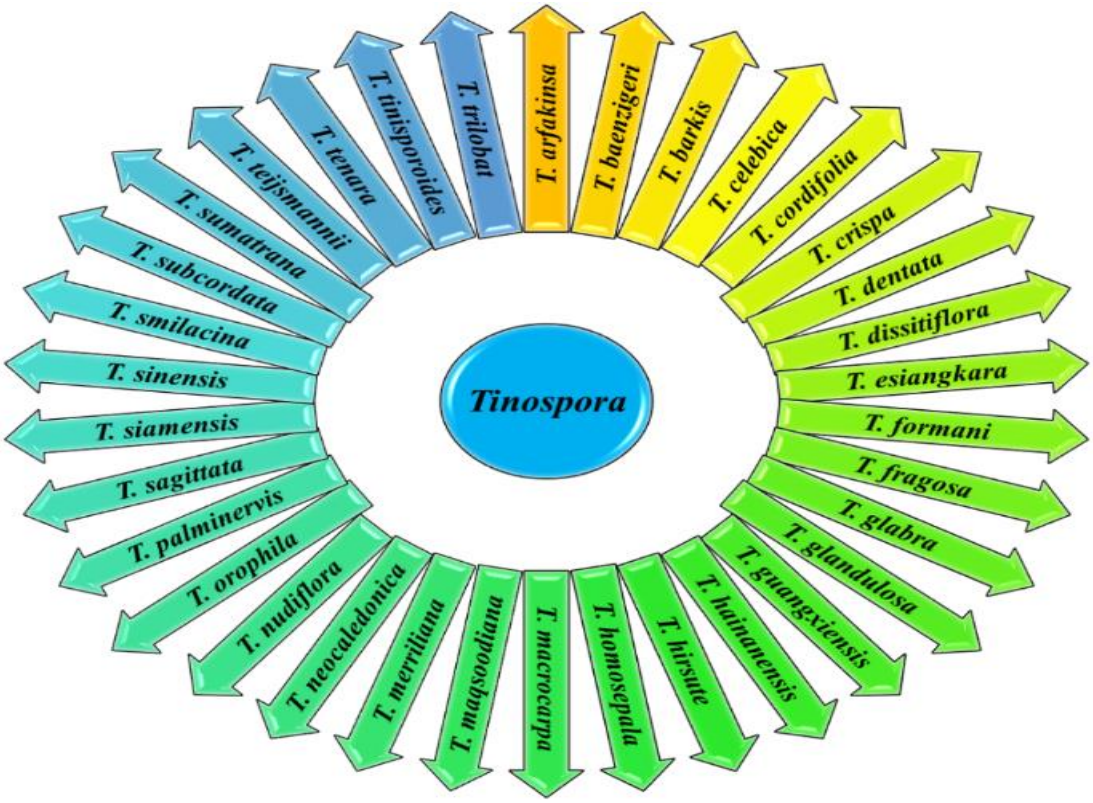


Fig. 2: Various Species of *T. cordifolia.*

1.3 Morphological description

T. cordifolia is a rigid plant that can grow in mostly warm and every climate during July to August.[11] It is a deciduous plant that grows to 1 m tall (3.3 feet) and 0.5 meters (1.65 feet) wide and prefers different types of soils ranging from acidic to alkaline and requires partial to full sun with moderate moisture.[12] The plant is a climber shrub hence it requires another supporting plant for growth e.g. Neem (Azadirecta indica), Moringa (Moringa oleifera), and Jatropha (Jatpha curcas). Neem Giloy which shows better therapeutic characteristics because of the transfer of some bioactive components from Neem. Different parts of Tinospora have following type of morphology.[13]

1.3.1 Stem

The Stem of *T. cordifolia* is succulent with long, fleshy, filiform having branches like Arial roots. Bark is thin, greyish, or creamy white in colour and deeply left spirally.[14] When a stem is sectioned transversely shows a wheel-like structure. The stem powder is bitter in taste with a characteristic odour and colour brown to dark brown.[10]

1.3.2 Arial root

New growing arial roots are filiform, threadlike, mature arial roots are fleshy and dried arial roots are 2-3 in diameter. Arial root cortex has region external thick walled and internal parenchymatous zone containing mucilage cell with tannin cell.[15]

1.3.3 Leaves

Leaves of this plant are simple, broadly alternate, ovate to roundish shape, heart shape, having a smooth surface. Leaves are present in bulk, and green in colour but mature leaves are yellowish green to yellow. They are rich in proteins, calcium, and phosphorus. Leaves have a different odour and are bitter in taste, around 10-20 cm long and 8-15 cm broad.[10]

1.3.4 Flowers

T. cordifolia has greenish-yellow unisexual flowers and appears leafless in summer. Small, green, or yellowish male flowers occur in clusters while female flowers arrange in solitary inflorescence. Sepals and petals are 6 in number. Flowering mainly occurs in March to June.[11]

1.3.5 Seed

Seeds of *T. cordifolia* are curve-shaped and pea-sized. Hence this family is called as moonseed family. As seeds and embryo also turns into curve shaped automatically. This is ornamented endocarp is important characters of taxonomy.[15]

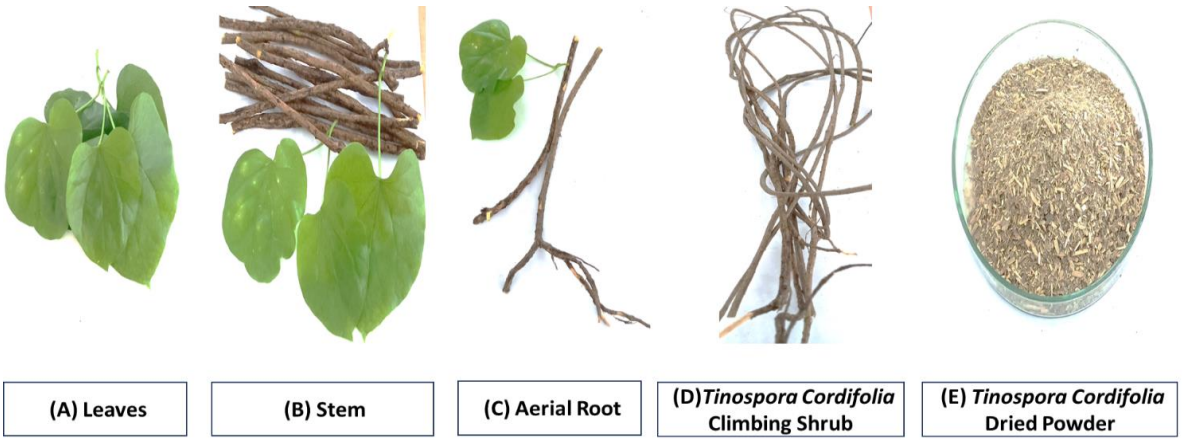


Fig. 3: Morphology of different parts of *T. cordifolia*.

2. Chemical Constituents and Bioactive components

Alkaloids, diterpenoid lactones, sesquiterpenoids, glycosides, steroids, alipathic compounds, phenolics and polysaccharides are different classes bioactive components are reported.[7] A

maximum of compounds which are responsible for immunonomodulation are N- methyl-2-pyrrolidone, N- formylannonain, cordifolioside-A, Syringin, Magnoflorine, Tinocordioside and 11-Hydroxymustakone. Cordifolioside-A and syringin both bioactive components have been reported activity of immunomodulation and other components involve in enhancement of phagocytic activity and generation of ROS.[16] The immunomodulatory effects of *T. cordifolia*, particularly through its stem compounds cordifolioside-A and syringin, occur through several mechanisms: increasing the phagocytic activity of macrophages, enhancing nitric oxide production by activating splenocytes, and boosting the production of ROS in human neutrophil cells.[17] The chemical structures of medicinally potent chemical compounds reported in literature are shown in Fig.4 and the biological activity of bioctive compound are summarized in Table.1

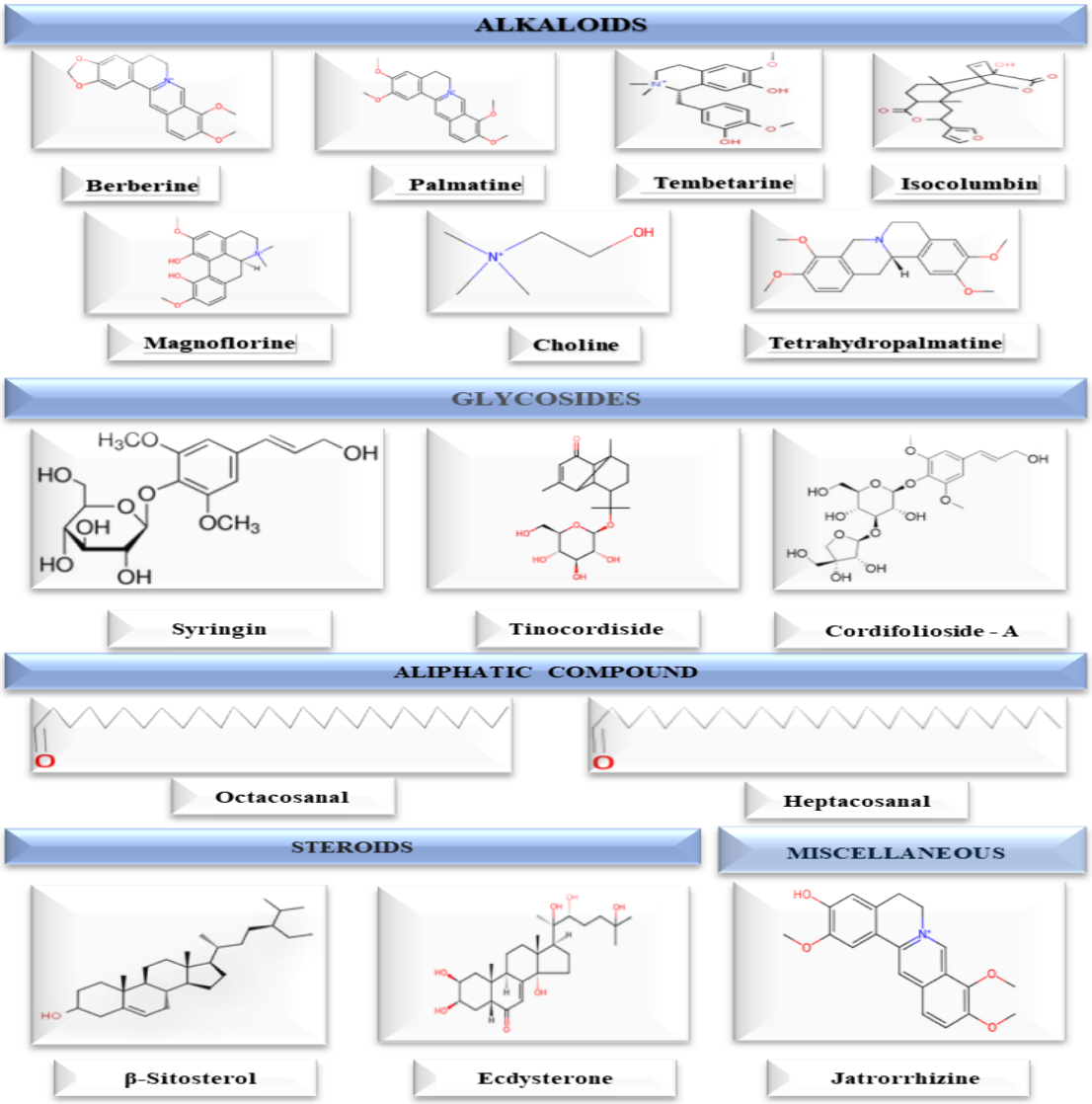


Fig. 4: Chemical structures of medicinally potent Bioactive compound of *T. cordifolia.*

Table 1: Bioactive components present in *T. cordifolia* and their biological activities.

Phytochemicals	Bioactive compounds	Part of plant	Biological activity	References
Steroids	Giloinsterol δ- sitosterol β–sitosterol, Ecdysterone, 20 β-hydroxyecdysone, Makisterone A.	Root	Inhibits TNFα, IL-1 β, IL-6 and COX-2, glucocorticoid induced osteoporosis in early inflammatory arthritis, IgA neuropathy, induce cell cycle arrest in G2/M phase and apoptosis through c-Myc suppression	[18]
Alkaloids	Magnoflorine, Berberine, Jatrorrhizine, Palmetine, Tembetarine, Tinosporin, Choline, Isocolumbin, Tetrahydropalmatine, Aporphine alkaloids.	Stem and Root	Anti-diabetic, Anti-viral, Anticancer, Anti-inflammatory, immunomodulatory, Neurological.	[19]
Glycosides	Tinocordiside, Syringin Tinocordifolioside, Furanoid diterpene glucoside, Cordifolioside A, Cordioside, Cordifolioside.	Stem	Neurological disorders like Parkinsons, ALS, Dementia and loss of neuron in hypothalamus and spine, anticancer activities, Immunomodulation,	[20]
Diterpenoid Lactones	Jateorine, Tinosporon, Furanolactone, Columbin Tinosporides,	Whole plant	Anti-inflammatory, anti-viral, antihypertensive, anti-microbial, induce apoptosis in and inhibits bcl-2, Inhibits Ca++ influx.	[21]
Aliphatic compounds	Dichloromethane, Heptacosanol, Octacosanol.	Whole plant	Protection against 6-hydroxydopamine induced parkinson in rat modle, Anti-inflammatory	[22]
Sesquiterpenoid	Tinocordifolin	Stem	Antiseptic	[23]
Others	Jatrorrhizine, Tinosporidine, Tetrahydrofuran, Cordifol, Cordifelone, Giloin, Tinosporic acid, Giloinin.	Root, Whole plant	Inhibits protease for HIV.	[24]

3. Pharmacological aspects

T. cordifolia is one of the important medicinal plants used in the Ayurvedic system of medicine and its therapeutic activity is shown in fig.-5 and Table-2 for the treatment of various diseases like anti-hyperglycaemic, anti-microbial, anti-oxidant, anticancer, anti-inflammatory, immunomodulatory etc and so this plant has golden gift for humankind.[9] Improve the phagocytic activity of macrophages it shows immunomodulatory activity. *T. cordifolia* has been the interest of phytochemical and bioactive investigations because of its importance in traditional folk and Ayurvedic system of medicine.[25]

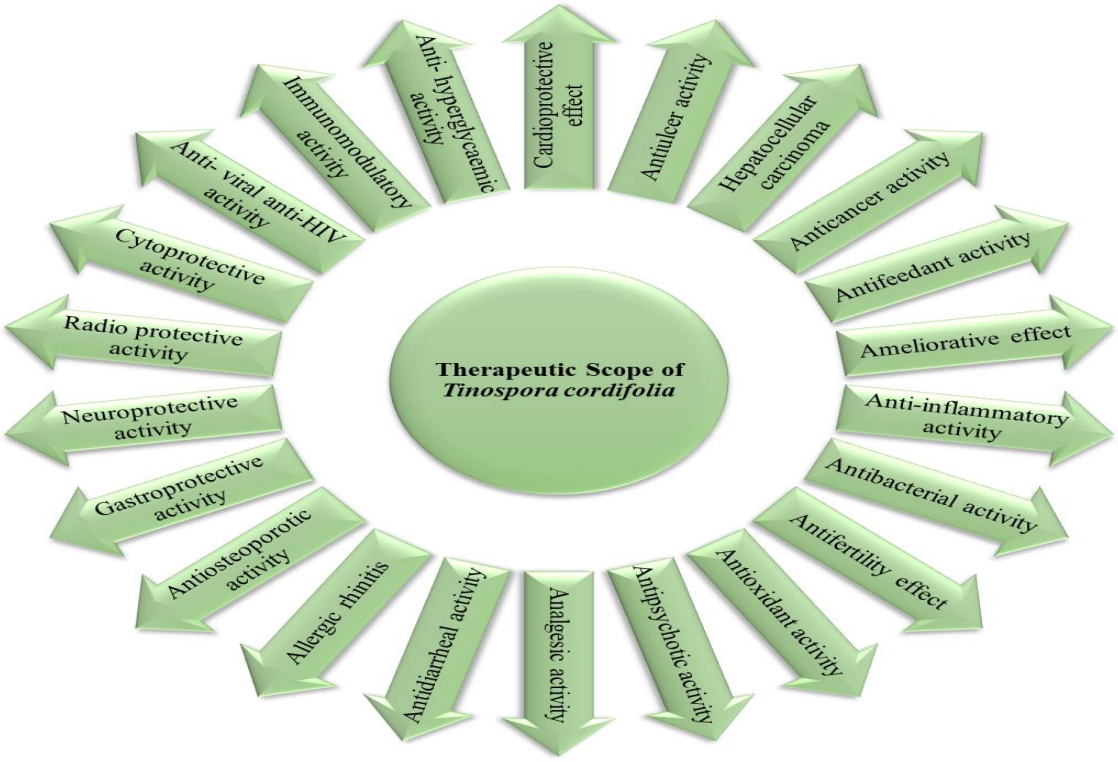


Fig. 5: Various Therapeutic Activities of *T. cordifolia.*

Table 2: Therapeutic Activities of *T. cordifolia.*

S. No.	Therapeutic Activities	Extract/ Formulation /Medicine	Significant	Model used	References
1	Anti-sickle cell anemia Activity	500 mg of each drug Guduchi Ghanvati and Kiratatikta Ghanvati were given. after meal with suitable fluid twice a day for a period of two months	Trial drugs are very effective in the sickle cell anemia management.	Human	[31]

2	Anti-COVID-19 Activity	*T. cordifolia* (Guduchi) and Piper longum (Pippali) formulation	Reduction in the time of recovery and hospital stay.	Human	[32]
		2 g of Swasari Ras,1 g of Giloy Ghanvati, Tulsi Ghanvati,0.5 g each of Ashwagandha	Reduced inflammation in asymptomatic COVID-19	Human	[33]
3	Anti-plaque and gingivitis and antimicrobial Activity	*T. cordifolia* was administered as a mouthwash prepared from a decoction. Specifically, 50 grams of coarse, Its powder was boiled with 45 mint leaves in 1800 ml of water until 200 ml of decoction was obtained.	*T. cordifolia* decoction as a mouthwash led to a significant reduction in gingivitis by 30.28%. The decoction was effective against Streptococcus mutans, which is a key bacterium associated with dental caries.	Human	[34]
4	Anti-inflammatory activity	Stem Aqueous extract	It has significantly inhibited acute inflammatory response evoked by carrageenan and histamine when administered orally and intraperitoneally (carrageenan is a phlogistic agent).	Albino rats	[35]
		Leaves aqueous and methanolic extract	Lipoxygenase enzyme activity inhibited by the extract with an IC50 value of 389.3 µg/ml. hence inhibition of LOX indicated anti-inflammatory activity	In Vitro Models	[36]

		Stem aqueous extract	Reduction in edema was observed in Group A (Guduchi Ghana prepared from Kwatha 50 mg/kg) and Group B (Guduchi extract market sample 50 mg/kg) at 3 h interval by 33.06% and 11.71% respectively.	Rats	[37]
5	Anti-viral anti HSV-1(oral herpes cause sores or lesions in gums or near the mouth).	Stem methanolic and ethyl acetate (80:20) extract.	Viral titration was carried out followed by virucidal assay and concluded that *T. cordifolia* inhibits the growth of HSV by 61.43%.	Invitro Mono layer cell culture in 96 well microtitre plates	[38]
		Root extract	Root extract decrease the regular resistance against HIV. This anti-HIV effect was exposed by stimulation of B-lymphocytes, reduction in eosinophil count, macrophages, level of haemoglobin and polymorphonuclear leucocytes.	Human	[39]
6	Anti-thrombocytopenia activity	*T. cordifolia* and Carica papaya leaf extract	Effectively increase platelet count	Human	[40]
7	Anti-alcoholism	*T. cordifolia* (TCJ) used in the study was 100 ml of the standardized water extract, which corresponds to 3.0 grams of solid extract, administered 14 days empty stomach in morning	*T. cordifolia* reduces in these elevated levels and indicating a potential modulatory effect.	Human	[41]

8	Anticancer activity	Whole plant aqueous and ethanolic extract	TCE (300 µg/ml) mediated differentiation of IMR-32 cells suggest that TCE or the phytochemicals derived from this plant may be used as safe pharmacological agents along with conventional chemotherapies/radiotherapies for the treatment of malignant neuroblastomas.	cell lines	[42]
9	Antioxidant activity	Whole plant ethanolic extract	The administration of ethanolic extract of *T. cordifolia* reverted the lipid peroxidation levels, antioxidants to near normal of cancer bearing animals	Rats	[43]
10	Anti-hyperglycemia & Anti - hyperlipidemia	*T. cordifolia* in the paper was 10% of the poly-herbal formulation G-400	The poly-herbal formulation improved diabetes-linked biochemical parameters like blood glucose levels, HbA1c, and lipid profiles after 8 weeks of treatment	Human	[44]
11	Analgesic activity	Whole plant Ethanolic extract	Extract showed Analgesic activity probably involves peripheral as well as central in both hot plate and abdominal writhing method.	Albino rats	[45]
12	Antidiarrheal activity	Whole plant Aqueous extract	Extract reduced number of total stools in both the models of diarrhea.	Albino rats	[46]
13	Gastroprotective activity	Whole plant aqueous extract	Traditionally as an anti-ulcer drug. Based on our results we believed that the compound Epoxy	Rats	[47]

			clerodane diterpene (ECD) may be responsible for gastroprotective activity.		
14	Neuroprotective effect activity	Whole plant ethanolic extract	Results showing the neuroprotective activity of TCEE in experimental PD. The mitochondrial activity retained by TCEE showed a promising way for the treatment of clinical PD.	Rats	[48]
15	Radio protective and Cytoprotective activity	Stem aqueous extract	Cordifolioside-A compound of extract induce this activity.	mice	[49]
16	Antifeedant activity	Whole plant Chloroform extract	P. xylostella, S. litura and E. vitelli were tested by Diterpenoids isolate of extract as insect antifeedants.	Microorganism	[50]
17	Antiulcer activity	Whole plant aqueous and ethanolic extract	In pylorus ligated rats, *T. cordifolia* extract reduced the gastric volume, total acidity & ulcer index as compared to control.	Albino rats	[51]
18	Anti-osteoarthritis Activity	*T. cordifolia* two capsules three times a day 3. Each SGCG capsule contained 400 mg	The Ayurvedic drugs, especially SGCG, reduced knee pain and improved function, comparable to the established treatments.	Human	[52]
		Polyherbal formulation "TLPL/AY/03/2008" two capsules taken twice daily	Synergistic effect of the herbs in the formulation contributes to its overall anti-inflammatory and analgesic activities, which may be partly attributed to the	Human	[53]

			immunomodulatory properties of *T. cordifolia*		
19	Immunomodulatory activity	Stem aqueous and ethyl acetate extract	Enhancement of macrophages phagocytic activity and nitric acid production by stimulation of splenocyte, ROS reactive oxygen species in human neutrophil cells.	Human	[16]
		Stem ethanolic extract	Immunomodulatory effects through enhancement of WBC counts and Bone marrow cells showed stimulatory effect on haemopoietic system also enhanced α-esterase activity in rats.	Wistar rats	[54]
	Enhaced Reproductive Function	Guduchi supplementation Prepartum: 60 grams per day for 45 days. Postpartum: 120 grams per day for 45 days	Guduchi supplementation was found to enhance reproductive performance in cows by improving their immunity and reducing prepartum plasma progesterone concentrations.	Cow	[55]
20	Cardioprotective effect	Whole plant ethanolic extract	Extract increases the potassium level with decrease in calcium level for cardioprotective or antiarrhythmic activity	Rats	[56]
21	Ameliorative effect	Root ethanolic extract	Extract showed protection against aflatoxin-induced nephrotoxicity due to having alkaloids compounds.	Mice	[57]

22	Antipsychotic activity	Whole plant aqueous and ethanolic extract	Amphetamine induced hyperactivity of mice have no antipsychotic activity.	Mice	[58]
23	Hepatocellular carcinoma	Aerial part ether extract	Epoxy clerodane diterpene can be important chemo preventive drug for hepatocellular carcinoma.	Rats	[59]
24	Anti-osteoporotic activity	Stem ethanolic extract	Extract showed estrogen like effects in bone thus used as anti- osteoporotic agent	Rats	[60]
25	Activity of drug safety Profiling of *T. cordifolia*	Aqueous extract or placebo	*T. cordifolia* is safe at dose of 500mg per day for a period 21 days in healthy volunteers for the parameter	Human	[61]
26	Immunostimulatory activity	Ethanolic and petroleum ether leaves extract	*T. cordifolia* leaf extracts use as immunoprophylactic to prevent diseases in fin fish aquaculture	Fish	[62]
26	Anti-tuberculosis (TB) activity	Patients were randomly given either *T. cordifolia* or a placebo for a duration of 8 weeks	The study demonstrated that *T. cordifolia* significantly alleviated symptoms of allergic rhinitis, including: Sneezing: 83% of patients reported complete relief. Nasal Discharge: 69% experienced improvement. Nasal Obstruction: 61% reported relief. Nasal Pruritus (itching): 71% experienced improvement	Human	[63]
27	Allergic rhinitis	Stem aqueous extract	Extract decreased all symptoms of	Human	[64]

			allergic rhinitis		
28	Efficacy of *T. cordifolia* on Learning and Memory in Healthy Volunteers	One tablet of aqueous extract *T. cordifolia* 500mg, or placebo was taken once daily foe 21 days.	Enhanced the cognition by increasing the synthesis of IL-1 and acetylcholine (an important neurotransmitter in learning and memory)	Human	[65]
29	Antibacterial activity	Stem aqueous and ethanolic extract	Aqueous and solvents extracts did not effectively inhibit the growth of the bacteria.	Microor ganisms	[66]
30	Antifertility effect	Stem methanolic extract	Oral administration of crude methanolic extract of *T. cordifolia* stem can lead to an infertile state in male rats due to interference in the testicular androgen levels altering the process of spermatogenesis.	Rats	[67]

4. *T. cordifolia* in immunomodulation

There distinct mechanism by which *T. cordifolia* exhibits modulatory effect on immune system in the human body are;

A. Activation and Elevation of white blood cell count:- Giloy enhance the activation of specialized cells responsible for the secretion of cytokines that mediate inflammatory responses known as macrophage. Methanolic extract from the stem of *T. cordifolia* also increases the total white cells count studied in mice model.[26]

B. Enhancement of phagocytic activity:- The promotion in the secretion of pro-inflammatory cytokines (IL-6, TNF-α) helps in recruiting and activating phagocytic cells and *T. cordifolia* simulate the phagocytic cell neutrophile by phytochemical constituent present in the plant.[27]

C. Improvement of bone marrow cellularity: Introduction of extract obtained from plant led to enhances the bone marrow cellularity and α-esterase positive cell population which serves as an indication of increase stem cell maturation.[28]

D. Implication of T cell proliferation: Secondary metabolites of *T. cordifolia* exhibit binding affinity to protein and receptors which plays a important role in T cell proliferation.[29]

Various bioactive compound of *T. cordifolia* including 11-hydoxymustakone, N-methyl-2-pyyrolidone, N-formylannonain and syringing have shown immune regulation and cytoxic activity.[30]

5. *T. cordifolia's* usage as alternative medicine to treat COVID-19

T. cordifolia's immunomodulatory properties, combined with its status as an Indian traditional herb, have led to its usage in Ayurveda and alternative medicine to treat COVID-19. The potential involvement of *T. cordifolia* in managing Coronavirus disease has been investigated primarily through molecular docking, retrospective investigations, animal experimentation, and randomized controlled trials.[68] In silico molecular docking studies have examined the role of several *T. cordifolia* phytoconstituents.[69] The chemicals were investigated for their ability to prevent viral binding to host cells.[70-72] Berberine and tinosponone have been shown to inhibit viral replication while also targeting the virus's primary protease. Similar results have been seen when testing another bioactive, Cordifolioside. Tinocordiside, on the other hand, inhibits the electrostatic contacts between the viral spike protein and the human ACE2 receptor protein.[73-75] These in-silico research serves as the foundation for subsequent in-vitro and in-vivo investigations. As a result, the findings of in-silico research cannot be considered a complete therapeutic cure for COVID-19. *T. cordifolia* has immunomodulatory effects, which are validated by extensive study in human and animal models involving rats infected with E. coli in the intraperitoneal region and subsequently provided plant extract, enhanced phagocytic activity and neutrophil action were observed.[76-79] A large range of giloy compounds have immune-modulating activity, which has been explored in literature. Ayurvedic treatments such as Amritadi Kwath, Guduchi Ghan Vati, and Gudichyadi Kwatham have also been investigated for their potential benefits in COVID-19 management.[79-81] However, a number of research in this approach are retrospective, necessitating controlled trials to ensure the efficacy of these preparations in the recovery of patients with SARS-CoV-2 infection. COVID-19 triggers a "cytokine storm" because to elevated amounts of pro-inflammatory cytokines and chemokines in plasma. This cytokine storm is primarily responsible for the severity of the disease and its effect on other organs, which leads to additional consequences. COVID-19 is characterized by immune

response changes and disruptions in immunological homeostasis, both of which can be alleviated by *T. cordifolia* treatment.[82]

6. CONCLUSION

This review concluded that *T. cordifolia* is rich in various phytoconstituents with significant therapeutic potential. However, limited scientific studies have been conducted on the biological activities and possible applications of these phytochemicals. There is required scientific effort to application of compounds to improve patient compliance and reduce for repeated dosing. It can be achieved by formulating novel drug delivery standards for herbal components, enhancing their therapeutic value by increasing bioavailability and reducing toxicity. A deep investigation is necessary to fully explore their potential in disease treatment. This review can lead future research and clinical applications. Given that immunosuppressive viruses like HIV, and RNA-based viruses such as SARS, MERS, and COVID-19, compromise the immune system in unique ways, developing direct antiviral medications remains challenging. Therefore, the phytoconstituents of *T. cordifolia* deserve focused attention in medicine, particularly for their impressive immunomodulatory effects, such as immunostimulant and macrophage activation against viral infections. *T. cordifolia* should be utilized in modern drug development and therapeutic strategies.

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Conflicts of interest disclosure

There is no conflict of interest to disclose.

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