Original Article

A REVIEW ON *Tinospora cordifolia*: BIOLOGICAL AND MEDICINAL PROPERTIES

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Abstract

Tinospora cordifolia commonly known as giloy is used in traditional Ayurvedic medicine and the Indian system of medicine (ISM) since times immemorial. The plant is designated as Rasayana in ayurveda and is very well known for building up the immune system and body's defence against definite infecting micro-organisms. There are 40 species but 4 species are found in India. It is a herbaceous perennial vine that belongs to the family Menispermaceae. It is widely used as a unique ingredient of various natural medicine and traditionally use for numerous ailments like fever, vomiting, diabetes, jaundice, anaemia, polyuria and skin diseases etc. It has antimicrobial activity, anticancer activity, anti-diabetic activity, anti-inflammatory, antioxidant, and immunomodulatory properties. Giloy is also used in the treatment of coronaviruses because giloy built a strong immunity in the human body against covid-19. A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatic, and glycosides have been isolated from the different parts of the plant, like root, stem, leaves and whole plant. The current study explores and establishes the biological and medicinal properties and phytochemistry of *Tinospora cordifolia*.

Keywords: *Tinospora cordifolia*, Alkaloids, Immunomodulatory, Traditional medicine, Giloy.

Introduction

In India vast bio-diversity and huge knowledge of ancient traditional systems of medicine such as Ayurveda, Siddha, Unani which provide a strong base for the utilization of a large number of plants in general healthcare and common ailments of the people. According to WHO estimates, 81 % of people depend on traditional remedies such as medicinal plants for curing or prevention of ailments. Plants produce a diverse range of bioactive molecules, making them a rich source of different types of medicines. About 70–80% of people are still using herbal medicine for their primary health because of the fewer side effect and better compatibility with the human body. Herbal medicine has gained momentum and is more effective as compared to synthetic drugs. *Tinospora cordifolia* is a deciduous climbing, a large shrub which belongs to the family Menispermaceae (Rana et al., 2012). This plant is widely distributed in India, Burma, China, Myanmar and Sri Lanka, and is known by the common names Giloy and Heart-leaved moonseed. Other synonymous and common names are Guduchi, Amrita, Guduchika, Chinnobhava, Vatsadani, Kundalini, Gulancha (Bengali), Gurcha (Hindi), Gala (Gujarat), Amrutavalli (Kannada), Gilo (Punjab), Seendal, Seendil Kodi (Tamil) and Amarlata (Assamese) (Narayana, 2008). *Tinospora cordifolia* Is an important drug in Indian systems of medicine and used in medicines since time immemorial. The drug is well known Indian bitter and is prescribed for fevers, diabetes, dyspepsia, jaundice, urinary problems, skin diseases and chronic diarrhoea and dysentery. It has also been indicated as useful in treating heart disease, leprosy, and helminthiasis. The starch obtained from the stem is highly nutritive, digestive, and used in many diseases. Recently, the *Tinospora cordifolia* is of great interest to researchers across the globe because

of its reported medicinal properties like anti-periodic, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, hepatoprotective, immunomodulatory and anti-neoplasticism activities (Soham and Shyamasree, 2012). A variety of active compounds derived from plants like alkaloids, steroids, diterpenoid lactones, and glycosides have been isolated from different parts of the plant body which include the stem, root and whole plant (Upadhyay et al., 2010). Data were collected from all existing sources such as ancient and current indigenous textbooks, websites, proceedings, research and review articles and other related documents based on the prepared data entry form.

Table 1: Taxonomy.

Kingdom	Plantae - plant
Subkingdom	Tracheobionta - Vascular plant
Super division	Spermatophyta-Seed bearing plant
Division	Magnoliophyta - Flowering
Class	Magnoliopsida – Dicotyledons
Sub-class	Polypetalae – Petals are free
Series	Thalamiflorae – Many stamens and flower hypogynous
Order	Ranunculales
Family	Menispermaceae - The Moonseed family
tribe	Tinosporeae
Genus	Tinospora
Species	*T. cordifolia*

Growth requirement

The plant is very rigid and it can be grown in almost all climates but prefers warm climates. Planting is usually done during the rainy season (July to August). As it is a climber so it requires support for its growth. Fast-growing species such as Neem (*Azadirachta indica*), Jatropha (*Jatropha curcas*) and Moringa (*Moringa oleifera*) have been planted to provide support for its growth. *Tinospora cordifolia* growing with Neem (*Azadirachta indica*) is called Neem Giloy and has a chemical composition similar to neem as well as Giloy and show better therapeutic properties. *Tinospora cordifolia* prefers medium black or red soil for its cultivation. Giloy can also be successfully grown in a large variety of soils, ranging from sandy to clay loam. However, the soil should be well drained with sufficient moisture and rich with organic matter for its growth.

Botanical Description

Tinospora cordifolia is a large, fibrous, deciduous climbing shrub with a glabrous surface. A transverse cut of the yellowish wood of *Tinospora cordifolia* reveals radially-organized wedge-shaped wood bundles containing immense vessels divided by fine medullary rays. The stem has rosette-like lenticels, and the bark is creamy white to grey, spirally left. The leaves are cordate in form and membranous. Flowers are axillary and grow in a 2–9 cm long raceme on leaflet branches. They are unisexual, tiny, and yellow. Female flowers are normally solitary, while male flowers are grouped. The seeds have a curled shape. Fruits are fleshy and have only one seed. In the summer, flowers bloom, and in the winter, fruits ripen.

Nutrient composition of *T. cordifolia*

T. cordifolia is rich in nutrients, like carbohydrates, proteins, fiber, iron, calcium, vitamin C, and other essential nutritional elements (Sivakumar and Dhana, 2011). Traditionally, people consume the plant in crude form as a prophylactic measure and for remedial purposes in several ailments. All parts of *T. cordifolia*, like, leaves, stem, fruits, and roots are being used as a nutraceutical. The practice of using stem and leaves directly as a dietary supplement promotes health and additionally serves as both curative and preventive agents. The whole plant of *T. cordifolia* is a rich source of nutrients and essential macro- and micro-nutrients, and several phytochemicals. Being a rich source of nutrients and phytochemicals, it is used as a healthy dietary supplement for tuman beings as well as for animals. The nutraceutical agents present in the plant are responsible for its renowned immunomodulation, hepato-protection, anti-inflammatory, antipyretic, antispasmodic and memory-boosting properties (Nagarkatti et al.,1994; Singh et al., 2003; Chauhan et al., 2017; Jan et al., 2018).

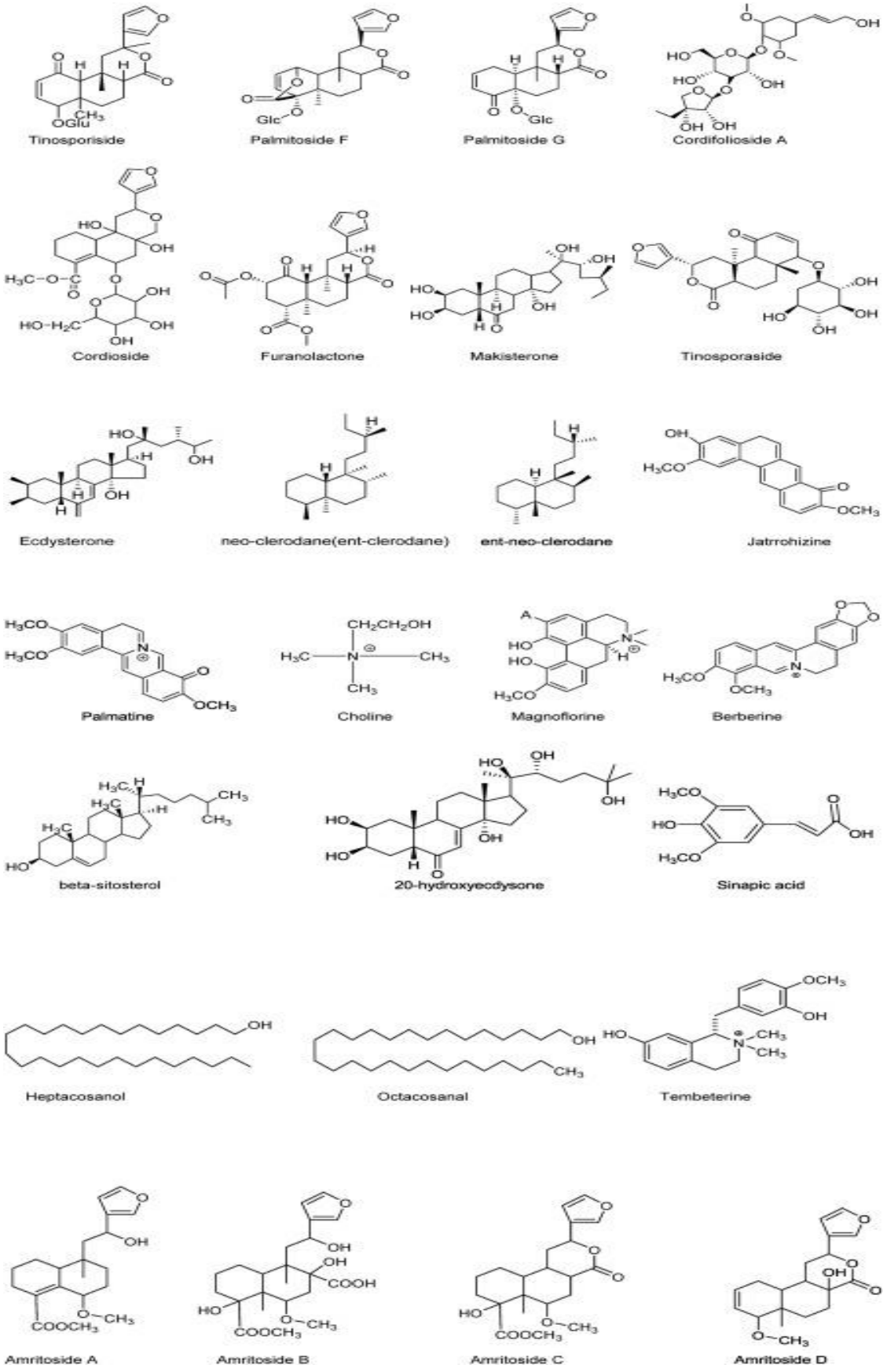
Phytochemical compound and their Biological Activities of *T. cordifolia*

Table 2: Major and sub-groups of natural products present in different parts of *Tinospora cordifolia* and their biological activities

Plant Part	**Active Component**	**Compound**	**Biological Activity (In Human beings)**
Stem, Root	Alkaloids	Berberine, Choline, Tembetarine, Magnoflorine, Tinosporin, Palmetine, Isocolumbin, Aporphine alkaloids, Jatrorrhizine, Tetrahydropalmatine,	Anti-viral infections, Anticancer, anti-diabetes, inflammation, Neurological, immunomodulatory, and psychiatric conditions
Whole Plant	Diterpenoid Lactones	Furanolactone, Clerodane derivatives [(5R,10R)-4R-8Rdihydroxy-2S-3R:15,16-diepoxy-cleroda-13 (16), 14-dieno-17,12S:18,1Sdilactone], Tinosporon, Tinosporides, Jateorine, Columbin	Vasorelaxant: relaxes norepinephrine-induced contractions, inhibits Ca++ influx, anti-inflammatory, anti-microbial, antihypertensive, and anti-viral. Induce apoptosis in leukaemia by activating caspase-3 and Bax, inhibits BCL-2.
Stem	Glycosides	18-norclerodane glucoside, Furanoid diterpene glucoside, Tinocordiside, Tinocordifolioside, Cordioside, Cordifolioside Syringin, Syringinapiosylglycoside, Pregnane glycoside, Palmatosides, Cordifolioside A, B, C, D and	Treats neurological disorders like ALS, Parkinson's, Dementia, motor and cognitive deficits and neuron loss in the spine and hypothalamus, Immunomodulation, Inhibits NF and acts as a nitric oxide scavenger to show anticancer activities
Shoot	Steroids	β–sitosterol, δ-sitosterol, 20 β-hydroxyecdysone,	IgA neuropathy, glucocorticoid-induced

		Ecdysterone, Makisterone A, Giloinsterol	osteoporosis in early inflammatory arthritis, induce cell cycle arrest in the G2/M phase and apoptosis through c-Myc suppression. Inhibits TNFα, IL-1 β, IL-6 and COX-2.
Stem	Sesquiterpenoid	Tinocordifolin	Antiseptic
Whole plant	Aliphatic compound	Octacosanol, Heptacosanol Nonacosan-15-one dichloromethane	nti-nociceptive and anti-inflammatory. Protection against 6- Hydroxyl dopamine induced parkinsonisms in rats. Down-regulate VEGF and inhibits TFN-α from binding to the DNA.
Root, Whole Plant	Others	3, (a 4-di hydroxy-3- methoxy-benzyl)-4-(4- compounds hydroxy-3- methoxy-benzyl)-tetrahydrofuran, Jatrorrhizine, Tinosporidine, Cordifol, Cordifelone, Giloinin, Giloin, N-transferuloyl tyramine as diacetate, Tinosporic acid.	Protease inhibitors for HIV and drug-resistant HIV

Fig. 1. Important phytochemicals from *T. cordifolia*



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Medicinal Properties

A myriad of biologically active compounds has been isolated from different parts of the plant body. These compounds have been reported to have different biological roles in disease conditions.

Antimicrobial Activity

Anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia, Proteus Vulgaris, Salmonella typhi, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene, and Serratia marcesenses (Gram-positive bacteria). Aqueous, ethanol, and acetone extracts of leaves and stem of *Tinospora cordifolia* Hook. F. Thoms showed maximum inhibitory activity against clinical isolates of urinary pathogens Klebsiella pneumonia and Pseudomonas aeruginosa. Silver nanoparticles synthesized from the stem of *Tinospora cordifolia* possess very good antibacterial activity against multidrug-resistant strains of Pseudomonas aeruginosa isolated from burn patients. The active compound [(5R, 10R)-4R, 8R-Dihydroxy-2S, 3R:15, 16-diepoxycleroda-13(16), 17, 12S, 18, 1S-dilactone] was isolated from ethanol extract of *Tinospora cordifolia* stem showed activity against bacteria and fungi.

Anticancer Activity

Tinospora cordifolia extracts are used in a radioprotective role to increase body weight, and tissue weight to inhibit the harmful effects of sublethal gamma radiations in male Swiss albino mice. *Tinospora cordifolia* extracts rise lipid peroxidation and decrease the level of cell viability, decreasing the level of GSH S-transferase activity (Rao SK et al., 2008). Lipid peroxidation is important and related to cell death and causes the impairment of membrane function through the increase the membrane permeability and membrane protein oxidation and cell death. Polysaccharide fractions from *Tinospora cordifolia* are effective in reducing the metastatic potential of melanoma cells. *Tinospora cordifolia* extracts increased the levels of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, granulocyte monocyte-colony stimulating factor and the vascular endothelial cell growth factor to increase the level of tissue inhibitor of metalloprotease-1 in the B 16- F10 extract (Leyon PV et al.,2004). The effect of *Tinospora cordifolia* extract is better than doxorubicin treatment (Jagetia GC. et al., 1998)

Antioxidant activity

In diabetic rats, there was a considerable increase in the concentration of thiobarbituric acid-reactive compounds (TBARS) in the brain, as well as a decrease in the heart. Treatment with *Tinospora cordifolia* reduced glutathione reductase (GSH) concentrations and activity of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) in diabetic rats' tissues. *T. cordifolia* root alcoholic extract (TCREt) given orally to diabetic rats at a dose of 100 mg/kg for 6 weeks restored the antioxidant state of the heart and brain. Although insulin (6 units/kg) returned all parameters to normal status, *T. cordifolia* root extract had a better effect than glibenclamide (600/kg) (Prince et al., 2004). The Fenton (FeSO4) reaction and radiation-mediated 2- deoxyribose degradation was both inhibited by an aqueous extract of *T. cordifolia* in a dose-dependent manner, with an IC50 value of 700/mL for both Fenton and radiation-mediated 2-DR degradation. Similarly, at 500/mL and higher, it displayed a moderate but dose-dependent suppression of chemically produced superoxide anion, with an IC50 value of 2000/mL (Goel et al., 2002). *T. cordifolia* has also been shown to increase GSH levels, gamma-glutamylcysteine ligase expression, and Cu-Zn SOD gene expression. Electron paramagnetic resonance spectroscopy revealed that the herb had high free radical-scavenging properties against reactive oxygen and nitrogen species (Rawal et al., 2004). *Tinospora cordifolia* also contains components that reduce HIV recurrent resistance to antiretroviral therapy (ART) and increase the medication's outcome. In the liver of Swiss albino mice, the effect of a hydroalcoholic (80 per cent ethanol: 20 per cent distilled water) extract of *Tinospora cordifolia* aerial roots on carcinogen/drug metabolising phase-I and phase-II enzymes, anti-oxidant enzymes, GSH content, LDH, and lipid peroxidation

was demonstrated. *Tinospora cordifolia* chemopreventive activity is suggested by increased GSH levels and enzyme activities involved in xenobiotic metabolism and cell anti-oxidant status (Singh et al., 2006).

Anti-toxic Activity

Aqueous extract of this plant has already been reported to show scavenge activity due to the presence of antioxidants against free radicals generated during aflatoxicosis. Further alkaloids such as choline, tinosporine, isocolumbin, palmetine, tetrahydropalmatine and magnoflorine from *T. cordifolia* showed protection against aflatoxin-induced nephrotoxicity. Furthermore, *T. cordifolia* shows a protective effect by lowering the concentration of a thiobarbituric acid reactive substance (TBARS) and enhancing the glutathione (GSH), ascorbic acid, protein and the activities of antioxidant enzymes viz., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, glutathione S-transferase (GST) and glutathione reductase (GR) in the kidney. However, leaf and stem extract of *T. cordifolia* has been reported to show a hepatoprotective effect in male albino mice against lead nitrate-induced toxicity. Similarly, oral doses of plant extract prohibited lead nitrate-induced liver damage.

Cardioprotective Activity

An alcoholic extract of *Tinospora cordifolia* (Giloy) is used in the cardioprotective activity. The effect of *Tinospora cordifolia* in cardioprotective is dose-dependent; as the dose increases the extract showed an increased effect as reflected by a progressive decrease in plasma calcium and sodium level and an increase in potassium level at a higher dose when compared to verapamil. Hence the *Tinospora cordifolia* is used for the treatment of atrial and ventricular fibrillation, flutters, and ventricular tachyarrhythmias. The main chemical constituents used in the cardioprotective and found in *Tinospora cordifolia* are furan lactone, tinosporin, tinosporide, jateorine, columbine and clerodane derivative

Anti-diabetic Activity

Tinospora cordifolia stems are commonly used in traditional Indian folk medicine to treat diabetes by controlling blood glucose levels. It has been suggested that it possesses anti-diabetic properties via reducing oxidative stress (OS), increasing insulin secretion, and decreasing gluconeogenesis and glycogenolysis, all of which help to regulate blood glucose levels. Tinospora cordifolia's principal phytoconstituents, including alkaloids, tannins, cardiac glycosides, flavonoids, saponins, and steroids, have been shown to have anti-diabetic properties (Sangeetha et al., 2011). Both in vitro and in vivo, the isoquinoline alkaloid-rich fraction from the stem, comprising palmatine, jatrorrhizine, and magnoflorine, has been shown to exhibit insulin-mimicking and insulin-releasing effects. Root extracts have been shown to lower blood glucose levels, increase insulin production, and inhibit OS indicators when taken orally. In vitro studies have shown the initiation and restoration of cellular defence anti-oxidant markers such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione (GSH), as well as the inhibition of glucose 6- phosphatase and fructose 1, 6-diphosphatase and the restoration of glycogen content in the liver (Patel and Mishra, 2011). In diabetic rats, the root extract was found to reduce glycosylated haemoglobin, plasma thiobarbituric acid reactive compounds, hydroperoxides, ceruloplasmin, and vitamin E levels. Oral administration of *Tinospora cordifolia* extract in the "Ilogen-Excel" formulation (Ayurvedic herbal formulation) containing eight medicinal plants, including Curcuma longa, Strychnos potatorum, Salacia oblonga, *Tinospora cordifolia*, Vetivelia zizanioides, Coscinium fenestratum, Andrographis paniculata, and Mimosa pudica, has been shown to reduce GSH and The heart and brain of diabetic rats have lower levels of GSH, GPx, and SOD, as well as lower catalase activity (Umamaheswari and Prince, 2007).

Anti-HIV Activity

T. cordifolia has been evaluated to find its importance in treating HIV-positive patients by decreasing the patient's resistance to the retroviral regimen. The anti-HIV activity of *T. cordifolia* uncovers its application in managing the disease by increasing the CD4 T-cells count and decreasing the eosinophil- (a type of WBC) count in HIV-positive patients. *T. cordifolia* extract showed significantly enhanced phagocytic and intracellular bactericidal activity. *T. cordifolia* also stimulated peritoneal macrophage. Furthermore, *T. cordifolia* increases phagocytosis and intracellular killing property. *T. cordifolia* significantly stimulates B-lymphocytes, polymorph nuclear leucocytes and macrophages.

Wound healing

Shanbhag T et al., The present study was aimed at evaluating the wound healing profile of the alcoholic extract of *T. cordifolia* and its effect on dexamethasone-suppressed healing. Incision, excision, and dead space of the wound models were employed to investigate the wound healing potential of the plant increased tensile strength extract of *T. cordifolia* may be attributed to the promotion of collagen synthesis. The extract of *T. cordifolia* did not reverse dexamethasone-suppressed wound healing.

Antipyretic activity

T. cordifolia is traditionally recognised for its jwarahara action (antipyretic activity). Antipyretic efficacy was found in the water-soluble fraction of a 95 per cent ethanolic extract of *T. cordifolia*. The hexane- and chloroform-soluble parts of *T. cordifolia* stems were found to exhibit antipyretic properties in another experiment. *T. cordifolia* has anti-infective and antipyretic effects, according to several research. In rats, pre-treatment with *T. cordifolia* protected them against mortality caused by intra-abdominal sepsis after coecal ligation, and dramatically reduced mortality caused by E. coli–induced peritonitis in mice (Jayachandran et al., 2003).

Immunomodulatory Activity

Aqueous extracts of *T. cordifolia* stems were shown to reduce mortality rates of chickens experimentally infected with very virulent infectious bursal disease virus (IBDV) through increased levels of IL-1, IL-2, IL-4, and IFN-γ in the peripheral blood mononuclear cells (PBMCs). In addition, *T. cordifolia* treatment also leads to the augmentation of vaccine response in terms of a greater antibody titer after administration of commercially existing IBDV vaccine. The methanolic fraction of *T. cordifolia* offers effective inhibition of lipoxygenase and cyclooxygenase enzymes with modest NO scavenging, indicating the free radical scavenging-independent mechanism of immunomodulation by *T. cordifolia*. Oral administration of alcoholic stem extract of *T. cordifolia* induced increased percentile adhesion of neutrophil to nylon fibres with increased antibody titre dose-dependently. In addition, the treatment potentiated a delayed-type hypersensitivity reaction induced by sheep red blood cells resulting in a conclusion that TCE increased humoral as well as cell-mediated immunity.

Against SARS-CoV-2 (COVID-19)

Six constituents (1a, 1e, 2a, 2b, 4a, 4g and 5a) present in *T. cordifolia* could effectively inhibit the binding of SARS-CoV-2 spike protein with the human receptor ACE2 protein in molecular docking and ADME/T studies, suggesting these 6 constituents as potential drug candidates for COVID-19. In silico studies using tools of network pharmacology, and molecular docking reveals that berberine from *T. cordifolia* can inhibit the main protease 3CLpro protein function, thereby preventing the SARS-CoV-2 virus replication. Phytoconstituents from *T. cordifolia* have high binding efficiency to the SARS-CoV-2 main protease enzyme and prevent COVID-19 virus replication. Compounds like Amritoside C, Amritoside B, Amritoside A, Tinocordifolin, Palmatoside G, Palmatoside F, and Maslinic acids from *T. cordifolia* have a docking score between −5.02 to −5.72 on in silico

molecular docking studies. Other molecular docking and molecular dynamic simulation studies reveal that the compound Tinocordiside present in *T. cordifolia* has a high affinity towards the SARS-CoV-2 main protease. Phytochemical compounds, namely tinosponone, xanosporic acid, cardiofolioside B, tembetarine and berberine of *T. cordifolia* strongly inhibit the main protease 3CLpro protein in molecular docking studies.

Home remedy preparation of Giloy juice used in the treatment of coronaviruses

Take the fresh stem of Giloy more than or equal to 1 foot.

♣ Cut into small pieces into 3 to 4 equal parts.

♣ Crush the pieces and add into the water approximately 1 litre.

♣ You may add Tulsi leaves, Ashwagandha etc.

♣ Boil the mixture on low flame till 250 ml water remains out of 1 litre.

♣ Let the mixture get cool (i.e., not to hot not to cool)

♣ Filter the mixture and drink in the morning empty stomach for better action.

♣ The juice can be drink 3 times a day.

Cultivation Practices

Giloy can be successfully grown in a large variety of soils, ranging from sandy to clay loam. However, the soil should be well drained with sufficient moisture and rich with organic matter for its growth. It grows under varying climatic conditions. The crop is grown under rain-fed conditions. The plant is very rigid and it can be grown in almost all climates but prefers warm climates. Stem cuttings are the best planting material for raising the commercial crop. Planting is usually done during the rainy season (July to August). The stem cuttings are sown directly in the field. Cuttings are obtained from older stems with nodes. Cuttings should be sown within 24 hours of their removal from the mother plant. Meanwhile, they should be half-dipped in water vertically. About 2500 cuttings are required for plantation in 1 hectare of land. The plant can also be raised using seeds. Seeds take almost more than double the time to mature and yield the same quantity of the drug. A basal dose of FYM (farmyard manure) @ 10 tonnes per hectare and half dose of nitrogen (75 kg) is applied at the time of land preparation. The stem cuttings with nodes are sown directly in the field. An optimum spacing of 3 m × 3 m is recommended for better yield. The plant requires support to grow, which can be provided by raising wooden stakes or a trellis. About two to three weedings and hoeings are required for good growth of twiner. No serious insect pest infestation or disease has been reported in this crop. The stem is harvested during autumn when it develops to a diameter of more than 2.5 cm. The basal part is left for further growth. The stem should be cut into small pieces and dried in shade. Stem bark peels off even by touch, thus stem should be cut very cautiously as the peeled stem decays very soon. The plant yields about (10-15 q /ha) 1500 kg of a fresh woody stem, reduced to 300 kg of dry weight per hectare in about two years.

Conclusion

Guduchi (*T. cordifolia*) is a well-known plant, especially in traditional medicine and the unique source of various types of compounds having diverse chemical structures. The present review spotlights the classical antidiabetic, anticancer, immunomodulatory, antioxidant, antimicrobial, and antitoxic claims of Tinospora cordifolia and their validation by contemporary researchers. For the last few years, there has been an increasing trend and awareness in medicinal plant research. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of Tinospora cordifolia. While Tinospora cordifolia has

been used successfully in Ayurvedic medicine for centuries, extensive research and development work should be undertaken on Tinospora cordifolia and its products for their better economic and therapeutic utilization. This review can be used for further research as well as clinical purpose.

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