

Tinospora Cordifoli: A literature Review on therapeutic use and pharmacological action

Comment [H1]: *Tinospora Cordifolia*

Comment [H2]: Therapeutic uses & Pharmacological Actions

Abstract

Tinospora cordifolia is a medicinal ayurvedic herb having vast benefit to human health. It is come under the climbing shrub, which belongs to family Menispermaceae and is inherent to India and some extent to China also, and some parts of Australia and Africa. Other names used for *Tinospora cordifolia* are Guduchi or Amrita or Giloy. Not a single part but whole plant has its own pharmacological effect for human well-being. *Tinospora cordifolia* has chemical constituents like terpenoids, alkaloids, steroids, lignans, flavonoids and glycosides. It has many pharmacological activities such as immunomodulation, anti-diabetic, antifungal, in hepatotoxicity (hepatic disorder), anti-cancer, anti-HIV potential, antitoxic effect, and in Parkinson disease. This review paper will discuss about the various properties/activities of the plant.

Comment [H3]: Italics through out manuscript

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Keywords: *Tinospora cordifolia*, pharmacological activity, Giloy, immunity, amrita, anti-diabetic, chemical constituents

Introduction

In today's world of globalisation and modernization, the increase in risk of a no. of diseases like infectious and non-infectious are because of the change in life style (stress, work pressure, change in climate) or food habits (unhealthy dietary habits) of human beings [1-3]. Beside from this, ailments like heart problem, cholesterol, stress, diabetes, rheumatoid arthritis, blood pressure have also increased. People losing interest in allopathy and seeking towards ayurvedic or natural drug sources because of increasing antimicrobial resistance from antibiotics, adverse effect and the cost of chemical drugs also decrease in their potency. In this situation researches have been going on for alternative to these medicines for betterment of human and animal health [4].

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Herbal preparation comprises of one or more herbs in given quantity for provide aesthetic, diagnostic, and mitigation benefits to humans and animals [1]. Botanical medicine, or phytomedicine, is another name for it.

Tinospora Cardifolia

Comment [H7]: Pictures with citation

Biological sources: A climbing shrub of Menispermaceae family found commonly in India, China and some parts of Australia.

It has many vernacular names as; in English: *Tinospora*; in Punjabi: Giloy; in Oriya: Guluchi; in Marathi: Gulvel; in Malayalam: Chittamrutu; in Kashmiri: Amrita, Giloy; in Haryana: Giloy; in Bengali: Gulancha; in Sanskrit: Chakralakshnika; in Hindi: Gurcha; in Gujrati: Garo, Galac.

Morphology

Comment [H8]: H7

It's a huge erratic, widely spreading climbing shrub with numerous coiled branches of various morphologies. The plant's stem is filamentous, ample, and climbs; the bark of this plant have color white to grey in [6]. Stem powder is creamish brown or light brown in shading, has a particular scent, and a harsh taste. It is utilized to

treat a few issues [7]. The "Guduchi-satva" stem is utilized for separating starch. It's a nutritious food that is likewise simple to process.

It is long-petioled, basic (around 15 cm) leaves with a roundabout, pulvinate, heart-formed shape that is curved outwards. The lamina is oval fit, 10–20 cm long, seven nerved, and exceptionally membranous [8].

Blossoms are unisexual, axillaries, and greenish-yellow in shading, with 2–9 cm long handout branches. Male and female blossoms have a qualification of accumulation and single respectively [9]. It has single-cultivated natural products that age in the colder time of year and blossom in the late spring [10]. The aeronautical roots have a tetra to penta curve fundamental design [11], are string like, elevated, squairshin, and now and then continually covers earth [12]. The seeds have a bended construction [13], and the endocarp is ornamented from numerous points of view, giving significant ordered attributes.

This plant is being consumed traditionally and each part of it have significant role in improvement of human health. It has been utilized as a constituent of a few people and Ayurvedic arrangements as juices, decoctions, glue, powders and pills to serve general weakness, fever, illnesses of skin, persistent the runs, jaundice, asthma and bone-crack, which were portrayed in old texts like Ras Ayana, Sangrahi, Balya, Agnideepana, Tridoshamaka, Dahnashaka, Mehnashaka, Kasa-swasahara, Pandunashaka, Kamla-Kushta-Vataraktanashaka, Jwarhara, Krimihara, Prameha, Arshnashaka, and Kricch-Hridroganashak [14]. Amrita used as a blood purifier, eliminating flawed and harmed red platelets from fringe blood flow. Due to its high alkaloidal substance, the Ayurvedic Pharmacopeia of India has recognized the stem of amrita as a medicine [15].

Comment [H9]: Can be included under Significance in Ayurveda

Leaves: Powder of leaves and their decoction, joined with cow's milk, have been utilized to fix gout, ulcers, jaundice, fever, and wounds, just as to oversee blood sugar [16].

Bark: for disease its underlying foundations and stem are utilized in North Gujrat (India) [17].

Stem extricate is utilized as mystical pill in jaundice fever, derma problems and fever while stem-starch (satva) is utilized as a tonic. As a remedy to wind chomp and scorpion sting, a mixture of root + stem is suggested [18].

Roots are recommended as an emetic in the treatment of visceral blockages, leprosy, diarrhoea, and dysentery [19, 20].

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Chemical constituents

T. Cordifolia contains various classes of mixtures: Di-terpenoid lactones, alkaloids, steroids, glycosides, polysaccharides, aliphatic synthetics, phenols, and sesquiterpenoids are a portion of the parts.

Comment [H11]: Uniformity in name

Table 1. List of chemical constituents

Class of Chemical	Constituent	Reference
Terpenoides	Tinosporide, Furanolactone diterpene, Furanolactone clerodane diterpene, furanoid diterpene, Tinosporaside, ecdysterone, makisterone and several glucosides isolated as poly acetate, phenylpropene disaccharides cordifolioside A, B and C, cordifolioside D and E, Tinocordioside, cordioside, palmatosides C and F, Sesquiterpene glucoside tinocordifolioside, Sesquiterpene tinocordifolin	[21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]
Alkaloid	Tinosporine, (S), Magnoflorine, (S), Berberine, (S), Choline, (S), Jatrorrhizine, (S), 1,2-Substituted pyrrolidine(S), Alkaloids, viz. jatrorrhizine, palmatine, beberine, tembeterine, choline.	[32, 33, 34, 35, 36]
Diterpenoid lactones	Diterpenoid (S), tinosporonolumbin (S), clerodane derivatives (W), tinosporon (W), tinosporisides (W), jateorine (W), columbin (W), tinosporal, tinosporide.	
Glycoside	18 Nonderodane glycoside (S), furanoid diterpene glycoside (S), tinocordioside (S), tinocordifolioside (S), cordioside (S), cordifolioside A, B, C, D (S), syringin (S), syringinapiosylglycoside (S), palmatosides	
Lignans	3 (a, 4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl), (S)	[37]
Steroids	Giloinsterol, (S), β -Sitosterol, (S), 20 α -Hydroxy ecdysone, (S)	[38, 39, 40, 41]
Others	Giloin, Tinosporan acetate, Tinosporal acetate, Tinosporidine, Heptacosanol, Octacosanol, sinapic acid, Tinosponone, two phytoecdysones, an	[42,43,44,45,46,]

	immunologically active arabinogalactan	
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PHARMACOLOGICAL EFFECT

Metabolism increasing properties

Greasy individual has a weight record (BMI) of more noteworthy than 25, and fat individuals have a BMI of more prominent than 30. To adjust the energy information and surge, great weight the executives is fundamental. Fat tissue secretes the chemicals adiponectin and leptin and assumes a part in controlling an assortment of physiological components. Low degrees of leptin advance food consumption, change the body's energy protection mode, and adjust neuroendocrine and immunological exercises. An ordinary leptin level brings down craving, but a stout individual's body with strangely high grouping of leptin, causing insulin obstruction like sort 2 diabetes. Adipocytes create and discharge adiponectin into the circulatory system. The counter diabetic, calming, against atherogenic, and cardioprotective properties of adiponectin are grounded [47]. Chatterji [49] has documented a patent application for a structure that brings down the leptin-toadiponectin proportion and advances weight reduction in individuals with corpulence/overweight issues. Gymnemic and boswellic acids are available in the recipe. Acetyl-keto- β -boswellic corrosive, a pentacyclic triterpenoid, advances lipolysis by upregulating lipolytic proteins, for example, adipocyte fatty oil lipase, just as bringing down perilipin articulation [50]. Gymnemic acids affect glucose assimilation in the gut [51]. Besides, they append to tongue receptors and forestall glucose retention [52]. In type 2 diabetes patients, it likewise initiates pancreatic β - cells to emit insulin and lessen glucose levels [53].

Comment [H12]: Abbreviations mentioned for first time should be elaborated and can be abbreviated from the next

Antioxidant activity

This present plant's cell reinforcement properties are inferable from a polysaccharide called arabinogalactan and a phenolic part called epicatechin [54, 55]. Its leaf extricate powder has preferred cancer prevention agent properties over its stem separate powder [56]. In light of the counter oxidant activity of its alkaloid parts, its root separate secures against aflatoxin-prompted nephrotoxicity[57].

Cell reinforcement pointers including GPx, SOD, and GSH can be reestablished by taking T. cordifolia root separates orally [59]. T. cordifolia separates have been accounted for to lessen malondialdehyde and receptive oxygen species (ROS) levels while expanding GSH levels in diabetic rodents in maternal livers [60].

Comment [H13]:

Anticancer effect

Berberine has shown anti-cancer properties in the mice Ascites carcinoma Ehrlich inhibits topoisomerase II at the dose 10 mg/kg body weight [61, 62, 63] Columbin, a furanolactone diterpenoid, on the other hand, has shown chemopreventive activity against human colon cancer [64]. Octacosanol, a long-chain aliphatic alcohol, inhibits cancer cells' production of vascular endothelial growth factor into ascites fluid, as well as the activity of matrix metalloproteinases (MMPs) and the translocation of transcription factor NF kappa B to the nucleus (in vivo) [65].

Palmitine, the plant alkaloid, can suppress tumours by recovering glutathione (GSH), superoxide dismutase (SOD), and catalase levels, together with reducing DNA impairment [66]. G1-4A can activate cytotoxic T lymphocytes capable of destroying cancer cells by stimulating bone marrow-derived dendritic cells [67, 68]. Its ethanolic extract can assist chemotherapy overcome such difficulties in cancer therapy by reducing the population which has cancer cells that are drug resistant (high in ATP-binding cassette transporters)[69]. Liver cells carcinoma induced by chemicals and MCF-7 breast cancer in human both can be prevented with ECD present in *Tinospora cordifolia* [70, 71]. ECD regulates the expression of Cdkn2A, p53, and the mdm2 gene in cancer cells, causing them to die [71]. This plant's octacosanol is an antiangiogenic drug that inhibits tumour growth and metastasis [72]. It exhibits therapeutic effect against neuroblastoma as it possess the ability that can lead to pro-apoptosis and senescence but blocks signals that reverse apoptosis [73]. The extraction of this plant can be used in combination with chemotherapy medications to provide an adjuvant effect due to its ability to inhibit CYP3A4, a key enzyme in their metabolism. This could help to reduce the dose in medicines like those used to treat cancer and causes reduction in the harmful effects that can arise on cells in normal conditions [74]. Its capacity to regulate pro-inflammatory cytokines and GSH like TNF- α also aids in the prevention of anti-cancer treatment toxicity [75].

T. cordifolia, which contains 17 to 23 percent *T. cordifolia*, has been patented as part of a herbal composition with eleven components for cancer treatment. When the conformation was as 450-480 mg of gelatinous capsule form TDS, a patient with pulmonary epidermoid carcinomas (which refused to take other treatments) experienced complete stoppage in haemoptysis and chest pain, as well as an improve the hunger and after one month of treatment. A patient suffering with third stage of pulmonary epidermoid carcinomas who had failed to respond to previous treatments, the same formulation was found to be successful as a tumoristatic medication [76].

Immunomodulator activity

It has immunomodulatory properties because it stimulates non-specific immune mechanisms [77]. The compound which shows immunomodulatory activity is caused by a polysaccharide containing monomer units of glucose, fructose, and arabinose [78]. Other than this, immune-modulatory active components discovered in *amrita* include 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, and syringin [79, 80]. Macrophage function is impaired in mice intoxicated with CCl₄ (lower the capacity to kill bacteria-, decreased phagocytosis, decreased NO generation, etc.) and is re-established by providing extract of *amrita* plant [81]. This plant produces G1-4A, a TLR4 agonist which is a non-microbial. The receptor is located at macrophages and B-lymphocytes in response to G1-4A stimulation, resulting in activation of macrophages and proliferation of B cells. It increases the cellularity of T-cells, B cells, and macrophages, which causes an enlargement of spleen size in mice. Cell survival is also improved by increased production of anti-apoptotic genes [82]. It is one of those ingredients in the "Bala compound," that is administered in babies and cause increased immunoglobulin production [83]. It's one of the ingredients in the "Bala compound," which helps babies produce more immunoglobulin [83]. This plant produced superior outcomes when used with antiretroviral medication for HIV infection. In this circumstance, drug resistance can be combated by integrating *guduchi* into the equation [84]. Furthermore, it was observed that after *guduchi* treatment, macrophages improved their phagocytosis activity against non-infectious micro-organisms (heat-

Comment [H14]:

killed-yeast) and *E. coli* (live-infective-bacteria) [85]. Rohatgi has been patented for an ayurvedic compound called LIVZON, which is used to prevent and treat diseases like hepatitis, liver sclerosis, AIDS, flu, and tuberculosis by increasing cellular and humoral immunity [86]. The lowered level of histamine is also reported by an antiallergic herbal combination containing guduchi, and Pushpangadan group has been granted the same patent [87].

Anti-ulcer and anti-diarrheal effect

This activity was tried in rodents, which showed a portion subordinate enemy of diarrheal impact just as a decrease in ulcer record. There was likewise a decline in stomach volume and an ascent in stomach pH [88]. PGE₂, mitigating cytokines (IL-4, IL-10) and proangiogenic factors (VEGF, EGF) are totally expanded by epoxy-clerodane-diterpene got from amrita [89]. Its concentrate gave defensive impacts in a 8-hour immobilization stress prompted ulceration mouse model, with results comparable to diazepam [90].

Hepatoprotective effect

Due to its capability to rummage free ROS, amrita has been shown to be a successful hepato-protective specialist, upgrading its liver recovery sway [91]. A few polyherbal plans for the therapy of different liver sicknesses are at present available, a few of which have *T. cordifolia*. The separated root of *T. cordifolia* have additionally been exhibited to shield the liver from rifampicin and pyrazinamide-incited liver damage[92]. *T. cordifolia* likewise showed against CCL4 impacts by bringing down the statement of liver catalysts AST, ALP and ALT. just like complete bilirubin forestalling stringy multiplication, and enacting tissue recovery [[93, 94].

In male Swiss pale skinned person mice, *T. cordifolia* leaf and stem watery concentrates have solid hepatoprotective properties against lead nitrate poisoning [95,95]. As per the investigations, lead nitrate harming incited a reduction in SOD and catalase levels while expanding ALT, AST, and ALP levels Simultaneous dosing of *T. cordifolia* stem and leaf watery concentrate improved these boundaries[96].

Antidiabetic effect

Anti-diabetic activities are attributed to alkaloids (Magnoflorine, Palmetine, and Jatrorrhizine), saponins, cardiac glycosides, tannins, saponins, and other substances[97].The alpha-glucosidase enzyme was studied in crude extracts of the stem in, dichloromethane (CDM), chloroform, ethyl acetate, and hexane. Giloy Prasant et al. identified anti-diabetic alkaloids, tannins, steroids, cardiac glycosides, saponins, flavonoids, and from Guduchi Prasant et al. Insulin-mediated effects were seen in alkaloids from this plant due to insulin hormone [98]. GSH levels and other reactive species can rise as a result of gestational diabetes, posing a risk to both the mother and the foetus. Giloy was added into the everyday diet of a pregnant rat with diabetes (model used: streptozocin-induced diabetes) and By lowering the oxidative load, it has a protective impact, limiting the relative occurrence of illnesses and any birth defect [99].

Guduchi root extract had an antihyperglycemic effect in an alloxan-induced diabetes animal, lowering extra glucose levels in urine along with in normal blood [100]. Certain herbal medicines, such as amrita like Ilogen-Excel, Hyponidd, and Dihar, were found showing anti-diabetic impact in diabetic rat models. Ilogen

Excel's actions lower blood glucose levels and improve insulin efficiency by boosting insulin levels in the systemic circulation.

Hyponidd was found to lower the glucose-mediated haemoglobin count while maintaining the oxidative burden via lowering reactive species. When 'Dihar' was tested in a streptozotocin-induced diabetic mouse for one and a half months, it lowered urea and creatinine levels in the blood while enhancing enzyme activity [101,102,103,104].

Comment [H15]: 101-104

Protective Effect on CVS

It's because this plant contains berberine (an alkaloid), which enhances vascular health by lowering endothelial inflammation [105]. This plant has also been discovered to influence lipid metabolism by blocking cholesterol and glucuronides in the case of impaired lipid metabolism caused to alcohol use [106]. It also protects against cadmium-induced cardiotoxicity via regulating antioxidants (superoxide dismutase, catalase, glutathione, glutathione peroxidase, and glutathione-S-transferase), glycoproteins, kinase, and lactate dehydrogenase levels (hexose, hexosamine, fucose, and sialic acid). Amrita can also help to normalise atrial and ventricular fibrillation, which is caused by calcium chloride [108]. Its anti-oxidant characteristics can defend the heart from infarction which is induced by ischemiareperfusion injury, which is most commonly caused by oxidative stress [109].

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Antistress effect

In comparison to the typical medicine diazepam (at dosage 2.5 mg per kg), Sarma et al. found that an EtOH-extract of amrita at a dose of 100 mg per kg has considerable anti-stress effect [110]. A modest degree of behaviour abnormalities and mental impairment reaction is produced by the plant extract. Patients' I. Q levels improved as a result of the clinical investigation. It functions as a MedhyaRasayana, or brain tonic, in Ayurveda, by improving mental abilities for example memory and recall [111].

Comment [H17]: Sarma et al.,

Analgesic, antipyretic, anti-inflammatory effect

its effects have been scientifically proven [112-114]. Both a peripheral and a centrally mediated mechanism has been shown to be responsible for analgesic effect [115]. Its anti-inflammatory properties have also been demonstrated the case of autoimmune arthritis, caused by a decrease in cytokines of pro-inflammation production. This plant is oftenly used to alleviate swelling, fever and pain and cytokines such, TNF- α , IL-1 and IL-17 [116]. Pushpangadan et al. developed and filed a patent for a synergistic antipyretic composition to treat fever [117].

Other beneficial effect

T. cordifolia have many more effects other then the effect shown above. it also has nephroprotective action, neuroprotective effect, osteoprotective effect, radioprotective ,thrombolytic effect, antianxiety effect, antiparasitic effect, and also shows anti Parkinson effect.

Comment [H18]: citation

Guduchi leaf powder improves the organoleptic, nutritional, and rheological properties of wheat flour by mixing it into it. Its addition boosts the amount of protein, fibre, beta-carotene, calcium, and iron in cookies, as well as increasing radical scavenging activity [118]. Drinking Amrita-based whey is a great keeping quality at

both ambient and refrigerated temperatures [119]. Besides, *T. cordifolia* has been shown to hasten wound healing and reduce the number of days required for Excision wound epithelization [120].

Its extract has been proven to be helpful in avoiding HIV infection, as it is indicated a decrease in eosinophil count (induced by B-lymphocytes, macrophages, and polymorphonuclear leucocytes) and an increase in haemoglobin percentage [121, 122].

Plant-based medicines are generally harmless, and Giloy is no exemption. Though, its water extract has been shown action that reduce blood pressure (temporarily), rise in ventricular contraction force, and cause bradycardia in dogs [123], therefore it ought to be used with care in cardiac patients. Minofil, a non-hormonal medication including Giloy and other plant extracts, showed minimal negative effects in women with postmenopausal syndrome [124] and could be used instead of hormone replacement treatment. This plant has been the subject of much research, but no adverse effects have been reported [125], and it is regarded safe at the dosages listed [126].

Another study found that leaf powder of Giloy has significant effects on growth parameters and possesses immune-stimulatory capacity in Amur carp [127]. It has been shown to have androgenic impact on prostate cancer cell line [128], hence it can affect prostate gland growth. Nanoparticles of *T. cordifolia* stem extract in prostate cancer cells have been shown to have no substantial apoptosis induction but do limit cancer cell proliferation [129].

Nanoparticles are gaining popularity in medical science for a variety of applications (imaging, medication administration, diagnostics, gene delivery, and so on). The physical or chemical manufacturing of nanoparticles consumes a lot of energy and produces harmful pollutants. The recently developed biomimetic technology is mainly depend upon the ability of microorganisms, algae, or plants to synthesis nanoparticles in an environmentally acceptable manner at ambient temperature and pressure. Because of the presence of alkaloids, Guduchi has been used as a bio-agent to synthesise gold(Au) nano-particles, which have been proven to be very steady [130].

Due to a variety of ongoing health-related threats, such as the increasing rate of drug failures, emerging anti-microbial resistance, and side-effects of chemical-based medicines, herbs like amrita got a huge attention in recent years as a safer and natural alternative to chemical-based medicines. Furthermore, new advancements in biotechnology, molecular tools, and nanotechnology are allowing herb and phytomedicine researchers to be more effective.

There have been several pre-clinical and clinical studies have looked at the cyto-protective, immune-modulatory, and immune-adjuvant potential of Ayurvedic drugs. The guduchi's unique, comprehensive, and systems approach advancements can serve as a potent search engine for novel, safer, and more affordable pharmaceuticals. This can even visualize the amrita's practical application for combating aforementioned health-related concerns.

Conclusion

The plant Amrita (*T. cordifolia*) is well-known, specifically in old-style remedy, and is one of the pharmaceutical industry's most commercially exploited species. Anti-oxidant, hepato-protective, anti-microbial,

Comment [H19]:

anti-hyperglycemic, anti-pyretic, antihyperlipidemic, cardiovascular-protective, anti-inflammatory, osteo-protective, neuro-protective, anti-anxiety, analgesic, anti-diarrheal, and anti-stress qualities are only a few of its benefits. It is a commercially low-cost and effective herbal supplemental medication due to its abundance in subtropical Asian countries. *T. cordifolia*'s biological studies and clinical trials indicate its safety or less side effect and significant healing value as a commercially important health supplement, along with a repository for forthcoming drug advancement in essential conditions where current therapies have slight therapeutic potential.

UNDER PEER REVIEW

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