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Tinospora cordifolia; A Pharmacological Update

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Abstract
The present review gives information regarding the morphological, phytochemical and pharmacology aspects of *Tinospora cordifolia* (Guduchi). It is a plant of significant medicinal importance in the indigenous systems of medicine and designated as *Rasayana* and it forms an important drug of the Ayurvedic Medicine. All the parts of this plant are reported for various ethnobotanical and therapeutic uses. It is prescribed for many diseases such as general debility, fever, diabetes, dyspepsia, urinary infections, jaundice and skin diseases**.** Vegetative aerial parts, viz. leaves, stem and aerial root were collected in various seasons and studied for macroscopical, anatomical, physicochemical and phytochemical studies. Microscopically leaf of *T. cordifolia* showed presence of anomocytic stomata, unicellular trichomes. Stem showed wheel shaped appearance at the transverse cut surface, a peculiar characteristic feature of the family Menispermaceae. Stem and aerial root exhibit abundant mucilage canals, dense ceratenchyma and characteristics wedge shaped medullary rays. Phytochemically, the various extracts showed the presence of diverse phytochemicals such as alkaloids, glycosides, polyphenols, steroids, tannins, etc. Leaf of *T. cordifolia* showed the maximum concentration of sugar, starch, flavonoids, phenolic, and tannin content as compare to aerial roots and stem. Tinosporaside and berberine were evaluated as biomarkers for the plant *T. cordifolia* using TLC fingerprinting.

Keywords: Berberine, Microscopy, Pharmacognosy, Tinosporaside, *Tinospora cordifolia*

1. Introduction
Tinospora cordifolia (Willd.) Miers, (*Guduchi*) is one of the important dioecious plants belongs to the family Menispermaceae. In Hindi, the plant is commonly known as *Giloe* which is a Hindu mythological term that refers to the heavenly elixir that has saved celestial beings from old age and kept them eternally young. In Ayurveda, it is designated as *Rasayana* drug recommended to enhance general body resistance, promote longevity and as antistress and adaptogen. This significant plant is also mentioned in important pharmacopoeias. Phytochemistry of *T. cordifolia* belongs to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. *T. cordifolia* is widely used in folkloric veterinary medicine and traditional Ayurvedic medicine in India for its, anti-inflammatory, immuno-modulatory, anti-pyretic activity, antioxidant, anti-diabetic, anti-allergic and anti-arthritic activities and various other medicinal properties. Almost all the parts of the plant are documented to be useful in ethnobotanical surveys conducted by ethnobotanists. Details of various important aspects such vernacular names of *T. cordifolia* and its important ethnobotanical, Ayurvedic properties, pharmacological and phytochemistry have already been published. In the present communication the vegetative parts, viz. leaf, stem and aerial roots of this plant were investigated pharmacognostically by using macro-microscopical characters, physico-chemical analysis and phytochemical evaluation along with TLC fingerprinting.

Description
Tinospora cordifolia is a deciduous plant that grows to 1.0 meters tall (3.3 feet) high by 0.5 meters (1.65 feet) wide and prefers many types of soil ranging from acid to alkaline and partial to full sun with moderate moisture. Stems of *Tinospora cordifolia* are succulent and having long filiform fleshy aerial roots, which arise from the branches. Bark is thin, greyish or creamy white in colour, when peeled fleshy stem is exposed. It often attains a great height and mostly climbs up the trunks of large neem trees. Leaves of *Tinospora cordifolia* are heart shaped, membranous, juicy and cordate. The leaf blade is broadly ovate to roundish, cordate, 5 to 12 cm in diameter with smooth surfaces. Wood of this plant is porous soft and white in colour. *Tinospora cordifolia* has greenish flowers which are unisexual and bloom in summer. Male flowers are small, yellow or green coloured occur in clusters whereas female flower occur singly. Fruits are pea shaped, fleshy, shiny turn red when boiled and occur in winter. Seeds of *Tinospora cordifolia* are curved and pea sized.

Synonyms
Tinospora crispa, Tinospora malabarica

Selected vernacular names
English: heartleaf moonseed
Bengali: giloe, gulancha
Hindi: giloya

Chemical constitution of *Tinospora cordifolia*
A variety of constituents have been isolated from *Tinospora cordifolia* such as alkaloids, diterpenoid, lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. *Tinospora cordifolia* contains about 11.2 percent of protein and rich in Ca and Phosphorous (Zhao *et al*.1991; Khosa *et al*. 1971).
Other compounds that have been isolated from *Tinospora cordifolia* are tinosporone, tinosporic acid, cordifolisides A to E, syringen, berberine, giloin, gilenin, crude giloininand, arabinogalactan polysaccharide, picrotene, bergenin, gilosterol, tinosporol, tinosporidine, sitosterol, cordifol, heptacosanol, octacosonal, tinosporide, columbin, chasmanthin, palmarin, palmatosides C and F, amritosides, cordioside, tinosponone, ecdysterone, makisterone A, hydroxyecdysone, magnoflorine, tembetarine, syringine, glucan polysaccharide, syringine apiosylglycoside, isocolumbin, palmatine, tetrahydropalmaitine, jatrorrhizine respectively

Medicinal uses
It is used in the treatment of jaundice because it reduces body heat. Plant stem is used in general debility, dyspepsia, fever and urinary diseases. *Tinospora cordifolia* helps in increasing the scavenging and de-sloughing action of PMN cells and macrophages. These phagocytic cells contributes in pro-healing processes like growth factor activation, angiogenesis and granulation tissue formation which are otherwise inhibited and suppressed in chronic wounds. The exact function of these immunomodulated cells is not proven in this study and the results are only based on the observation of better wound healing in the drug group. The powder of root and stem is used along with milk for the treatment of cancer. It has been observed that polyherbal formulation of *T.cordifolia* possesses favourable effect in patient with HIV infection. Oral administration of the juice of stem with honey can also be used for treatment of asthma. Since *T. cordifolia* is a good antioxidant, it is given with L-DOPA during Parkinson's disease. L-DOPA produces free radicals during the formation of dopamine. Thus *T. cordifolia* neutralizes the side effect of drug. In Urinary disorder, the juice of the roots is very much effective. Diabetes mellitus is a worldwide chronic disease of humans related with the elevated blood sugar level due to insulin deficiency. . Diabetes is broadly classified in to Type-1 and Type-2 Diabetes. *Tinospora cardifolia* has shown signification reduction in blood sugar level in both normal and Allaxon induced Diabetic mice. The extract of plant parts decreases the blood sugar level. Guduchi is also used for soothing inflamed and injured mucous membranes in the digestive tract. It protects the stomach and duodenum by increasing the production of mucin. It is regarded as one of the best psychotropic drugs in India. It also works as immunomodulators in diseases like obstructive jaundice, hepatic fibrosis, peritonitis and sepsis. Bacterial infection triggers host defence mechanism which is initiated by macrophage activation and differentiation. These activated macrophages have perfect surface morphology. Intensive rough surface or spherical macrophage (abnormal) count is increased to several folds in the presence of carbon tetrachloride. Studies have shown that *Tinospora cordifolia* extract helps in the protection from CCl4 toxication, probably by the production of monocyte colony stimulating factor or granulocytemonocyte stimulating factor (M-CSF/GM-CSF).
This plant has great potential for developing useful drugs. The leaves extract have shown anti-HIV 1 activity. Thus it can be said that biological extract from this plant will certainly be helpful in protecting and treating various viral diseases in humans Giloy (*Tinospora cordofolia*) is widely used against monkey malaria. Studies have shown that giloy juice which is a mixture of Giloy herb and Tulsi leaves increases body resistance upto 3 times and serves as a powerful counter of Plasmodium virus attacks. Crude extract of *Tinospora cordifolia* contains a polyclonal B cellmitogen which increases immune response in mice. An arabinogalactan polysaccharide, G1-4A from the stem of *T. cordifolia* has been examined to affect induced immunosuppression. Studies have shown that *T.cordifolia* improves the phagocytic function without affecting the humoral & cell mediated immune systems. Active components syringing & cardiol inhibit the *in vitro* 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. Role of *Tinospora cordifolia* can be seen in tumor suppression also. Studies have shown that the polysaccharide fraction of *T. cordifolia* when injected intraperitoneally in mice resulted in the inhibition of lung metastatic colonies. *Tinospora cordifolia* extract is a plant derived immunostimulant. It has been observed that it significantly affects the symptoms of HIV as validated by clinical evaluation. *Tinospora cordifolia* can be used as an adjunct to HIV/AIDS management.

Activity studies
Anti-Diabetic Activity
Pharmacological studies have proven *in vivo* antidiabetic potential of various extracts of T. cordifolia. It has been reported to mediate its antidiabetic potential through myriad of biologically active phytoconstituents isolated from different parts of plant, including alkaloids, tannins, cardiac glycosides, flavanoids, saponins and steroids. These compounds have been reported to encompass different target activities in diabetic conditions, thus enabling the potential application in experimental and clinical research. Kannadhasan R and Venkataraman S study reported that 30 days treatment of Sedimental extract of *Tinospora cordifolia* (SETc) (1000mg/kg/p.o) on diabetic subjects was proven for its efficacy and clearly establishes the antidiabetic activity with antiobese body built. The Ethanolic extract of *Tinospora cordifolia* leaves in different dosages (200 and 400 mg/kg b.w.) administered orally for 10 days and 30 days in streptozotocin diabetic albino rats. It is clearly showed that TC has significant antidiabetic activity in diabetic animals and has an efficacy of 50% to 70% compared to insulin. Borapetoside C isolated from Tinospora crispa (5 mg/kg, i.p.) attenuated the elevated plasma glucose in diabetic mice, increased glucose utilization, delayed the development of insulin resistance and then enhanced insulin sensitivity. The activation of insulininduced IR-Akt-GLUT2 expression in liver and the enhancement of insulin sensitivity may have contributed to the hypoglycemic action of borapetoside C. The isoquinoline alkaloid rich fraction from stem, including, palmatine, jatrorrhizine, and magnoflorine have been reported for insulin-mimicking and insulinreleasing

effect both *in vitro* and *in vivo*. In Ehrlich ascites tumor cells model, water, ethanol and methanol extracts of the herb showed glucose uptake-stimulatory activity. The protective effects of *Tinospora cordifolia* root extract were reported in presence of higher levels of anti-oxidant molecules and enzymes. *Tinospora cordifolia* root extract has been shown to significantly counterbalance the diabetes-associated oxidative stress in the maternal liver by lowering the levels of malondialdehyde and reactive oxygen species and the increased levels of glutathione and total thiols. Oral treatment of *Tinospora cordifolia* (100 and 200 mg/kg body weight) for 14 days mediates its antidiabetic potential through mitigating oxidative stress, promoting insulin secretion and also by inhibiting gluconeogenesis and glycogenolysis.

Anti-Cancer Activity

Tinospora cordifolia shows anti-cancer activity, this activity is mostly shown in animal models. The extraction of alkaloid palmatine from *Tinospora cordifolia* by using response surface methodology (RSM) clearly indicate the anticancer potential in 7,12- dimethylbenz (a)anthracene DMBA induced skin cancer model in mice. A single application of *Tinospora cordifolia* extract at a dose of 200, 400 and 600 mg/kg dry weight, 24 hrs prior the i.p. administration of cyclophosphamide (at the 50 mg/kg), significantly prevented the micronucleus formation in bone marrow of mice, in a dose dependent manner. C57 Bl mice when received 50% methanolic extract of *Tinospora cordifolia* at a dose 750 mg/kg body weight for 30 days showed increase in life span and tumour size was significantly reduced as compared to control. Mishra R *et al* study investigated the anti-brain cancer potential of 50% ethanolic extract of *Tinospora cordifolia* (TCE) using C6 glioma cells. TCE significantly reduced cell proliferation in dosedependent manner and induced differentiation in C6 glioma cells. Manju Bala *et al* study evaluated eight secondary metabolites from *Tinospora cordifolia* against four different human cancer cell lines, KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT-29 (human colon cancer) and SiHa (human cervical cancer) and murine primary cells respectively. All extracts and fractions were active against KB and CHOK-1 cells whereas among the pure molecules palmatine was found to be active against KB and HT-29; tinocordiside against KB and CHOK-1; yangambin against KB cells. Two molecules from hexane and methanol fractions (T1 and T2) from the plant *Tinospora cordifolia* show that in MCF-7 cells, T1 treatment significantly suppressed the proliferation, migration and invasion of MCF-7cells when compared to that of T2. Epithelial–mesenchymal transition related genes, Twist and Snail, were downregulated by T1 with increased transcription of E-cadherin.

Anti-oxidant activity

The *Tinospora cordifolia* has potential application in food systems as an antioxidant and probably in biological systems as a nutraceutical. Methanolic, ethanolic and water extracts of *Tinospora cordifolia* showed significant antioxidant potential compared to other solvents and also possess metal chelation and reducing power activity. V Sivakumar *et al* study Results suggest that *Tinospora cordifolia* stem methanol extracts administered orally increased the erythrocytes membrane lipid peroxide and catalase activity. It also decreased the activities of superoxide dismutase, glutathione peroxidase in alloxan-induced diabetic rats. *Tinospora cordifolia* has the ability to scavenge free radicals generated during aflatoxicosis. *Tinospora cordifolia* showed protection against aflatoxin-induced nephrotoxicity due to the presence of alkaloids such as a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine. Neha Upadhyay *et al* study results suggest that *Tinospora cordifolia* bark ethanol extracts showed the highest free radical scavenging activity compared to the methanol extracts and also ethanol extracts had the highest phenolic content. The administration of ethanolic extract of *Tinospora cordifolia* (EETC) in N-nitrosodiethylamine (DEN) induced liver cancer in male Wister albino rats reverted the lipid peroxidation (LPO) levels, enzymic and nonenzymic antioxidants to near normal. Essential oil isolated from leaf of *Tinospora cordifolia* (Willd.) was shown strong 2,2- diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (IC50= 25±0.3 µg/mL). It also showed dose dependent reducing power activity. The leaves of *Tinospora cordifolia* was extracted with methanol and partitioned in water with ethyl acetate and butanol At 250 mg/ml concentration, the antioxidant activity of the free radical scavenging activities of the extracts assayed through DPPH, reducing power, phosphomolybdenum and metal chelating activity were found to be highest with methanol, followed by ethyl acetate, butanol and water extract. The antioxidant activity of BHT was higher than the extracts at each concentration points.

Immunomodulatory Activity

Tinospora cordifolia is well known for its immunomodulatory response. Active compounds 11- hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringin has been reported to have potential immunomodulatory and cytotoxic effects. Vaibhav Aher *et al* study confirms the immunomodulatory activity of *Tinospora cordifolia* ethanolic extract (100 mg/Kg/p.o.) stem through altering the concentration of antioxidant enzymes, increasing T and B cells and antibody which play an important role in immunity, enhancing the concentration of melatonin in pineal gland and increasing the level of cytokines like IL-2, IL-10 and TNF-α which plays an important role in immunity.

Anti-Microbial Activity

The anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, 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 on clinical isolates of urinary pathogens Klebsiella pneumoniae and Pseudomonas aeruginosa. Silver nanoparticles synthesized from stem of *Tinospora cordifolia* possess very good antibacterial activity against multidrugresistant 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. The lowest MIC values were observed against Enterococcus faecalis (125 µg/ml) and Bacillus subtilis (200 µg/ml). The compound also showed activity against fungi; the lowest minimum inhibitory concentration values were seen against Trichophyton simii (31.25 µg/ml), Trichophyton rubrum 57 (62.5 µg/ml), Trichophyton rubrum 296 (62.5 µg/ml). Francesca Bonvicinia *et al* study results indicate that constituents from *Tinospora*

cordifolia exhibited a higher inhibitory activity against reference microbial strains and clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA) and carbapenemase-producing Klebsiella pneumoniae. Constituents from *Tinospora cordifolia* may be a potential source of new therapeutic strategies for infectious diseases.

Anti-Toxic Activity

The gold standard drug for the treatment of Parkinson's disease is L-DOPA, but various studies have proved that the treatment with L-DOPA leads to the death of surviving dopaminergic neurons in the CNS. The coadministration of *Tinospora cordifolia* crude powder protected the dopaminergic neurons when compared with Sham operated control group. The treatment with *Tinospora cordifolia* crude powder could reduce the toxicities of L-DOPA therapy for Parkinson's disease [37]. *Tinospora cordifolia* alkaloids such as choline, tinosporine, isocolumbin, palmetine, tetrahydropalmatine and magnoflorine showed protection against aflatoxin induced nephrotoxicity. *Tinospora cordifolia* extracts have beenreported to scavenge free radicals generated during aflatoxicosis. It exhibited protective effects by lowering thiobarbituric acid reactive substances (TBARS) levels and enhancing the GSH, ascorbic acid, protein, and the activities of anti-oxidant enzymes viz., SOD, CAT, GPx, Glutathione S-transferase (GST) and glutathione reductase (GR) in kidney [38]. Cyclophosphamide an anti-cancer drug has been reported to reduce the glutathione content in both bladder and liver and lowered levels of cytokines Inerferon-γ and IL-2 an increased levels of pro-inflammatory cytokine TNF-α. This effect could be reversed on *Tinospora cordifolia* treatment indicating the role of *Tinospora cordifolia* in overcoming Cyclophosphamide induced toxicities in cancer treatment [39]. Leaf and stem extract of T. cordifolia has been reported to show hepatoprotective effect in male albino mice against lead nitrate induced toxicity. Similarly, oral dose of plant extract prohibited the lead nitrate induced liver damage

Conclusion

Tinospora cordifolia, the versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. Very little work has been done on the biological activity and plausible medicinal applications of these compounds and hence extensive investigation is needed to exploit their therapeutic utility to combat diseases. A drug development programme should be undertaken to develop modern drugs with the compounds isolated from *Tinospora cordifolia*. Present review spotlights the classical antidiabetic, anticancer, immunomodulatory, antioxidant, antimicrobial, antitoxic claims of *Tinospora cordifolia* and their validation by contemporary researches. For the last few years, there has been an increasing trend and awareness in medicinal plants 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, an 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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