**Immunomodulation: A Potential Plant with Immunomodulatory Activity**

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**ABSTRACT**

Immunomodulation is a procedure, which can alter the immune system of an organism by interfering its function. Modulation of immune system may result in suppression or stimulation of immunological reactivity. Recently the effect of immunomodulators in the treatment of various diseases is significant. *Tinospora cordifolia* is a widely used shrub in ayurvedic system of medicine. It is reported to benefit the immune system in a variety of ways. The medicinal properties incorporated with this plant are anti-diabetic, hypolipidemic, anti-neoplastic, anti-oxidant, anti-inflammatory, immunomodulatory, cognitive, adaptogenic, aphrodisiac, cardioprotective and hepatoprotective effect. Many compounds belonging to different classes such as alkaloids, diterpenoids, phenol, aliphatic compounds and polysaccharides have been isolated from this plant. But it is not well known that which of these compounds are responsible for various activities. Therefore, it needs further exploration of its components, pharmacological action and mechanism of action. This review presents a detail survey of literature on immunomodulatory properties of *T. cordifolia*. The main aim of the survey is to reinforce scientific reconfirmation of its immunological activities and human studies.

**Keywords:** Immunomodulation, Immunomodulating agent, *Tinospora cordifolia*

Advances in molecular biology have revolutionized depending on the requirement of the situation. Immunology and medicine. Initially the use of antibody Alternative medicine is now recognized as an invaluable as therapeutic agents was limited by their purity and resource even by the most intransigent clinicians of heterogeneity. Immunotherapy derives from the advanced countries. Plant extracts have been widely observation from the 19th century, that cancer investigated for their possible immunomodulatory sometimes regressed after acute bacterial infections, that is, there may be no specific immunostimulant effect. medicinal plant, has been used for the treatment of The rapidly expanding discipline of immunology various diseases and has been recommended for contributes to diagnosis, therapy and prevention of improving the immune system. There is great interest in human diseases in many ways. The role of development of new drugs from traditionally used immunocompetents in prevention of malignancy is medicinal plants like *Tinospora cordifolia*. Ayurveda currently of great interest in experimental science as refers to *Tinospora cordifolia* as 'Amruth' or the 'Nectar well as clinical medicine. Interest in the immune of Immortality'. The term 'Amruth' is attributed to this response has been stimulated by the alarming increase drug in recognition of its ability to impart youthfulness, in a novel epidemic form of immune deficiency, vitality and longevity. Immunomodulation can be "Acquired ImmunoDeficiency Syndrome" (AIDS). determined by the capacity of the compounds to Immunomodulation relates to potentiation or influence the cytokine production, mitogenicity, suppression of the immune responses of the host, stimulation and activation of immune effector cells.
Immunomodulatory activity of *Tinospora cordifolia*

**Fig 1. Tinospora Cordifolia (Courtesy: KottakkalAryavaidyashala)**

Panchabhai et al done a study “Validation of therapeutic claims of *Tinospora cordifolia*: a review” on 2008 [1]. As *Tinospora cordifolia* is a plant of high pharmacological potential, day by day new studies are conducted and novel therapeutic activities are revealed. Recently, isolation and characterisation of phytoconstituents responsible for the activities are done. So, there is a scope for a new study. *Tinospora cordifolia* is a plant of high pharmacological potential, day by day new studies are conducted and novel therapeutic activities are revealed. Recently, isolation and characterisation of phytoconstituents responsible for the activities are done. So there is a scope for a new study. The current survey is aimed to include the updated informations available with special emphasis on immunomodulatory activity, as its name suggests “amruth”.

**DESCRIPTION AND HISTORY**

*T.cordifolia* (Fig 1); common name guduchi, amrutha

T. *cordifolia* is a perennial, wild climber, succulent shrub often attaining a great height and sending down long thread like aerial roots. The bark is creamy white and grey, leaves are membranous and deciduate. Flowers grow during the summer and fruits during the winter. The viscus sap has a yellow colour, the total of count leucocytes. The aqueous extract of *T.cordifolia* was found to increase phagocytosis *in vitro*. Ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and in antibiotic production *in vivo. T.cordifolia* tincture are used for the treatment of general weakness, extracts treatment cause significant reduction in fever, dyspepsia, dysentery, gonorrhea, secondary eosinophil count and improved hemoglobin in HIV syphilis, urinary diseases, impotency, gout, viral patients [5]. Sixty percent patients receiving TCE and 20% on placebo reported decrease in the infection. Those activities were not due to its antibacterial activity as shown by the negative *in vitro* antibacterial activity of the plant extract. It was reported that in rats had resulted in significant leucocytosis and predominant neutropenia. It has been also observed that it stimulated the macrophages as evidenced by an increase in the number and percentage phagocytosis of *S.aureus* by peritoneal macrophages in rats. The phagocytic and intercellular killing capacity of polymorphs in rats, tested at 3.5 hours after infection were significant. Syringin, Cordiol, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticompartment and immunomodulatoryactivities [6]. Anarabinogalactan as a powerful emetic and is used for bowel obstruction. *T.cordifolia* is used as an antidote for snake bite and used in malaria, environmental illness, asthma, upper respiratory tract infection, UTI, general debility and amelioration of symptoms from chemo or radiotherapy.

**CHEMISTRY**

A variety of constituents have been isolated from *T.cordifolia* plant. They belongs to different classes such as alkaloids, diterpenoids, lactones, glycosides, steroids, sesquiterpenoids, phenolic, aliphatic compounds and polysaccharides (Table 1). Leaves of this plant are rich in protein (11.2%), calcium and phosphorus [3]. Arabinogalactan had been isolated from the dried stem of *T.cordifolia* [4].

**PHARMACOLOGICAL ACTIONS**

*T. cordifolia* benefits the immune system in variety of ways. The alcoholic and aqueous extract of this plant have been tested successfully for immunomodulatory activity [5]. Pretreatment with *T.cordifolia* lead to protection against mortality induced by intra-abdominal sepsis following caecal ligation in rats. It also significantly reduced mortality from *E. coli* induced peritonitis in mice [6]. In a clinical study, it was afforded protection in cholestatic patients against *E. coli* infection. So, there is a scope for a new study.
immunosuppression [7]. The polysaccharide-enriched T.cordifolia treatment, significantly caused the fraction from this plant is found to be very effective in reducing the metastatic potential of B16f-10 melanoma cells [8].

Sharma et al. (2012) evaluated the immunomodulatory activity of three polysaccharide-enriched immunomodulatory fractions from Tinospora cordifolia using the polymorphonuclear leukocyte function test. The results confirmed the count was observed from day 3 onwards. The Sharma et al. (2012) evaluated the phagocytic activity and lysosomal enzyme content of immunomodulatory activity of three polysaccharide-enriched milk polymorphonuclear cells enhanced in the diseased cows treated with the T.cordifolia extract. The IL-8 level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The immunomodulatory activity of the polysaccharides of T.cordifolia, and also it was conclude that the T.cordifolia (stem) possesses antibacterial and polysaccharide with lowest sugar content showed immunomodulatory properties [10]. The highest activity and with highest sugar content showed Sharma et al. (2012) isolated and characterised the lowest activity [9]. Mukherjee et al evaluate the immunomodulatory active compounds of Tinospora biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. Fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of Tinospora cordifolia (stem) possesses antibacterial and immunomodulatory properties [10].

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percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylmannosan, 11-hydroxymustakone, 32-N-methyl-2-pyrrolidone, tinocordisolide A, magnoflorine, tinocordiside, syringin by nuclear magnetic resonance and mass spectrometry. Cordifolioside A and syringin have been reported to possess immunomodulatory activity. Other five compounds showed significant enhancement in phagocytic activity and increase in nitric oxide and reactive oxygen species generation at concentration 0.1-2.5 μg/ml [11].

Recently, the presence of an immunomodulatory protein (ImP) in guduchi has been investigated. Guduchi ImP showed ~3-fold mitogenetic activity compared to untreated murine splenocytes in the 1-10 μg/mL concentration range; 5-7-fold increase in mitogenetic activity was seen in the case of murine thymocytes vs control. The purified protein also induced nitric oxide production from macrophages present in isolated murine peritoneal exudates cells. Guduchi ImP displays enhanced phagocytosis of yeast cells by macrophages.

Guduchi ImP does not possess haemagglutination activity indicating that the immunomodulatory protein is not a lectin. The confirmation of an immunomodulatory protein in guduchi stem showing lymphoproliferative and macrophage-activating properties reinforces the rationale of the use of guduchi preparations for immunomodulation [12].

Cordifolide A, a novel unprecedented sulfur-containing clerodane diterpene glycoside, together with other two new diterpene glycosides, cordifolides B and C, and four known analogues, were isolated from a methanol-soluble extract of the stems of Tinospora cordifolia. The structures of the new compounds were determined on the basis of spectroscopic data. The interpretation, with that of cordifolide A confirmed by a single-crystal X-ray crystallographic analysis. All isolates were evaluated for their in vitro immunomodulatory activity using mouse bone marrow-derived denticritic cells [13]. Tinospora cordifolia had shown a significant level of macrophages activation that leads to increase in GM-CSF which leads to leucocytosis and improved neutrophil function [14]. G1-4A, an immunomodulatory polysaccharide from Tinospora cordifolia, modulates macrophage responses and protects mice against lipopolysaccharide induced endotoxic shock and G1-4A appeared to induce tolerance against endotoxic shock by modulation of cytokines and nitric oxide [15].

T. C. was evaluated for the possibility of enhancing the reproductive performance of crossbred cows by its peripartum supplementation, as the crossbred periparturient cow is highly susceptible to various diseases that effectively reduce its reproductive performance postpartum. A higher total leukocyte, neutrophil count along with increased progesterone concentration was recorded in Guduchi treated group however there was no significant change in peripartum plasma total estrogens and PGFM levels due to Guduchi supplementation [16].

**Antidiabetic effects**

The stem of T. cordifolia has long been used in Indian Ayurvedic Medicine for the treatment of Diabetes mellitus. Oral administration of aqueous T. cordifolia root extract to alloxan-induced diabetic rats caused a significant reduction in blood glucose level and brain lipids [17]. Though the aqueous extract at a dose of 400 mg/kg could elicit significant hypoglycemic effect in different animal models, its effect was equivalent to only one unit /kg of insulin [18]. It was reported that the daily administration of either aqueous or alcoholic extract of T. cordifolia decreases the blood glucose level and increases glucose tolerance in rodents [19, 20]. Berberine, an alkaloid obtained from the stem of T. cordifolia has been tested and used successfully in experimental and human diabetes mellitus. Berberine has been shown to lower elevated blood glucose as effectively as metformin [21]. The mechanisms of action include inhibition of aldose reductase [22], inducing glycolysis [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcomes insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells [26]. Berberine might exert its insulinotropic effect in isolated rat islets by up-regulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge [27]. Berberine also seems to inhibit human dipeptidyl peptidase-4 (DPP IV), as well as the pro-diabetic target human protein tyrosine phosphatase 1B (h-PTP 1B), which explain at least some of its anti-hyperglycemic activities. Berberine suppresses intestinal disaccharides with beneficial metabolic effects in diabetic states [28]. A recent comprehensive metabolomics method, applied to type 2 diabetes, suggested administration of berberine down-regulates the high level of free fatty acids which are known to be toxic to the pancreas and cause insulin resistance. These results suggest berberine might play a pivotal role in the treatment of type 2 diabetes [29]. Berberine has been shown to boost the effects of metformin and 2,4-dihydroxydiphenyl (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter. Berberine inhibits Foxo1, which integrates...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during diabetic retinopathy due to its role in regulating glucose metabolism. The tumor growth and increase in life span of tumor cells were studied by administering the aqueous extract of T. cordifolia to diabetic rats. T. cordifolia thus act as a potential therapeutic agent for prevention of diabetic retinopathy.

Diabetic neuropathy

T. cordifolia plays a role in prevention and management of diabetic neuropathy due to its antioxidant properties. It also prevents destabilizing the membrane integrity of DL cells. The tumor growth and increase in life span of tumor cells were studied by administering the aqueous extract of T. cordifolia to diabetic rats. T. cordifolia thus act as a potential therapeutic agent for prevention of diabetic neuropathy.

Diabetic foot ulcer

T. cordifolia was shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity. An aqueous extract of T. cordifolia root was administered to alloxan induced diabetic rat (2.5 and 5g/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. In another study in diabetic rats, the aqueous extracts also reduced levels of brain lipids.

Hypolipidemic effects

Diabetes is often associated with hyperlipidemia and as T. cordifolia has been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity. An aqueous extract of T. cordifolia root was administered to alloxan induced diabetic rat (2.5 and 5g/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. In another study in diabetic rats, the aqueous extracts also reduced levels of brain lipids.

Antineoplastic effects

Jagota et al. have found that the guduchi killed the HeLa cells very effectively in vitro. In this study, the stem extracts were evaluated in vitro for their cell killing effects. When HeLa cells were exposed to various doses of the extract, a dose-dependent increase in cell killing was observed as compared with non drug treated controls. The methylene chloride extract was the most potent. The effect of guduchi extract was comparable or better than doxorubicin treatment and thus it indicates that the plant warrants a future study as an anti-neoplastic agent.

Adaptogenic effects

The aqueous extract not only reversed the effect of cisplatin on gastric emptying, but also normalized the inflammatory and hypermotility. The plant was also found to normalize the phagocytic function of peritoneal macrophages after exposure of rats to either carbon tetrachloride or serum, thus it satisfied the definition of adaptogen.

Antioxidant activity

The antioxidant properties of T. cordifolia roots were undertaken to study whether the tumor associated macrophages (TAM) of Daltons lymphoma (DL) alloxan-induced diabetic rats. After 6 weeks, the level of plasma barbituric acid reactive substances, activated by the aqueous liquid extract of T. cordifolia ceruloplasmin and alpha tocopherol were reduced.
addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was found to inhibit peroxidation and the drug was inferior to the most effective one [43]. In another study, guduchi showed a significant reduction in serum and heart lipid peroxide levels was observed with prior treatment with *T. cordifolia* in ischemia-reperfusion-induced myocardial infarction in rats [53]. The stem extract can normalize the alterations in lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats, indirectly benefiting the heart [54]. Administration of the extract of *T. cordifolia*roots (2.5 and 5.0 g/kg body weight) for 6 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids and free fatty acids in alloxa-induced diabetic rats [55].

Osteoprotective activity

It is traditionally used for the treatment of rheumatoid arthritis. The alcoholic extract of *T. cordifolia* has been found to exert anti-inflammatory actions in models of acute and subacute inflammation [46]. The water extract of the stem of neem-giloe [ *T. cordifolia*] that grow on alkalin-induced arthritis was reported in one of the experiment in which goats treated with phenylbutazone [48] showed an osteoprotective effect, as the bone loss in tibia was slower than that in controls. Serum osteocalcin and cross-laps levels were significantly reduced. This study demonstrates that extract of *T. cordifolia* has the potential for being used as an osteoantagonist [48].

**Antioxidant effects**

Reduced glutathione (GSH) and vitamin C are the most important, constitutive and non-enzymatic antioxidants in vivo. A number of studies have demonstrated the protective effects of *T. cordifolia* and its extracts against oxidative damage [49]. Earlier studies showed that dry stem crude extract (DSCE) contains a high amount of active compounds [49]. The extract of *T. cordifolia* exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species. The extract of *T. cordifolia* also showed a significant clinical and hematobiological effect of its own as well as potentiation of morphine against reactive oxygen species. The herb also exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species as studied by electron paramagnetic resonance spectroscopy [45].

*Anti-inflammatory, anti-arthritis and anti-osteoarthritic activities*

It is traditionally used for the treatment of rheumatoid arthritis. The alcoholic extract of *T. cordifolia* has been found to exert anti-inflammatory actions in models of acute and subacute inflammation [46]. The water extract of the stem of neem-giloe [ *T. cordifolia*] that grow on alkalin-induced arthritis was reported in one of the experiment in which goats treated with phenylbutazone [48] showed an osteoprotective effect, as the bone loss in tibia was slower than that in controls. Serum osteocalcin and cross-laps levels were significantly reduced. This study demonstrates that extract of *T. cordifolia* has the potential for being used as an osteoantagonist [48].

**Anti-allergic activity**

Formalin induced arthritis model, its effect was comparable with indomethacin and its mode of action appeared to resemble that of non-steroidal anti-inflammatory agents. The dried stem of *T. cordifolia* was reported from sneezing in 83% of the patients on treatment with *T. cordifolia*. Similarly, the relief from acute and subacute models of inflammation. *T. cordifolia* was found to be more effective than nasal obstructions 61% and from nasal pruritis, in 71%. In order to explore the possibility of using *G1-4A/pp1* to modulate radiation-induced immune suppression, the herb was found to be more effective than *G1-4A/pp1* to modulate radiation-induced immune suppression, the herb was found to be more effective than acetylsalicylic acid in acute inflammation, although in subacute inflammation, the drug was inferior to the most effective one [43]. In another study, guduchi showed a significant reduction in serum and heart lipid peroxide levels was observed with prior treatment with *T. cordifolia* in ischemia-reperfusion-induced myocardial infarction in rats [53]. The stem extract can normalize the alterations in lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats, indirectly benefiting the heart [54]. Administration of the extract of *T. cordifolia*roots (2.5 and 5.0 g/kg body weight) for 6 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids and free fatty acids in alloxa-induced diabetic rats [55].

Hepatoprotective effects

The hepatoprotective action was reported in one of the studies. The selectivity of ROS-like agents was examined [47]. The experiment in which goats treated with *T. cordifolia* showed a significant reduction in infarct size and in serum and heart lipid peroxide levels was observed with prior treatment with *T. cordifolia* in ischemia-reperfusion-induced myocardial infarction in rats [53]. The stem extract can normalize the alterations in lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats, indirectly benefiting the heart [54]. Administration of the extract of *T. cordifolia*roots (2.5 and 5.0 g/kg body weight) for 6 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids and free fatty acids in alloxa-induced diabetic rats [55].

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placebo group, there was relief from sneezing only in 73% of patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritis, in 5% [67]. The ethanol extracts of the roots of *T. cordifolia* was observed to decrease nasal pruritis by 12.8% and nasal obstruction by 17% in nasal pruritis in 75% Miers and *C. asiatica* Linn were observed to induce a 12% reduction of allergic rhinitis and was well tolerated [58]. The anti-allergic and bronchodilator properties of *T. cordifolia* are comparable to that of diazepam [67]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-induced bronchospasm in guinea pigs, capillaries and to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome in 60 patients with malignant obstructive jaundice [70].

**Clinical uses**

*T. cordifolia* is used clinically in the Indian system of medicine for the treatment of jaundice, diabetes and rheumatoid arthritis. It has also been found to possess adaptogenic, anti-inflammatory, antineoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipruritic and immunomodulatory action helps to strengthen the immune system and to make the body stronger and hence make a woman more a rejuvenator and a natural herbal aphrodisiac.

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Immunomodulatory activity of Tinospora cordifolia


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