**Review Article**

*Tinosporacordifolia*: 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. *Tinosporacordifolia* 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, *Tinosporacordilifolia*

Advances in molecular biology have revolutionized depending on the requirement of the situation. immunology and medicine. Initially the use of antibody 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 observed from the 19th century, that cancer investigated for their possible immunomodulatory sometimes regressed after acute bacterial infections, that properties, *Tinospora cordifolia*, an indispensable 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 *Tinosporacordifolia*. 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 epidemiologic 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*

**Description and History**

*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”.

**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]. Anarabinogalactan had been isolated from the dried stem of *T.cordifolia* [4].

**PHARMACOLOGICAL ACTIONS**

**Immunological effects**

*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. 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 treatment 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.aureaus* by peritoneal macrophages in rats. The phagocytic and intercellular killing capacity of polymorphs in rats, tested at 3.5 hours after *E. coli* infection were significant. Syringin, Cordiol, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticomplement and amelioration of symptoms from chemo or radiotherapy.

**Fig 1. Tinospora Cordifolia (Courtesy: KottakkalAryavaidyashala)**
immunosuppression [7]. The polysaccharide-enriched T. cordifolia treatment, significantly caused the fraction from this plant is found to be very effective in reduction in cell count (p < 0.05) on day 15 of the reducing the metastatic potential of B16f-10 melanoma [2] treatment period, however, reduction in total bacterial cells [8]. A total 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-rich milk polymorphonuclear cells enhanced in the diseased enriched immunomodulatory fractions from Tinospora cordifolia cows treated with the T. cordifolia extract. The IL-8 cordifolia using the polymorphonuclear leukocyte ROS level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The immunomodulatory activity of the polysaccharides of results suggest that the hydro-methanolic extract 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 evaluated the immunomodulatory active compounds of Tinospora biological activity of the Tinospora cordifolia extract at T. cordifolia. It was found that ethyl acetate, water standardized dose against bovine subclinical mastitis [8]. Fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of T. immunomodulatory activity with an increase in

<table>
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<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
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<td>Alkaloids</td>
<td>Berberine</td>
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<td>Palmitine</td>
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Table 1. Chemical composition of T. cordifolia plant
Immunomodulatory activity of Tinosporacordifolia

The stem of T.cordifolia has long been used in Indian Ayurvedic Medicine for the treatment of Diabetic 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 model, 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 glycosylation [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-dihydroxydihydrochlorothiazide (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of

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insulin signaling with mitochondrial function. Inhibition of FoxO1 can improve hepatic metabolism during diabetes in DL-bearing mice not only augment the basic function of macrophages such as phagocytosis as well as their antigen-presenting ability and secretion of IL-1 and TNF. The results of the investigation also indicate that T. cordifolia plays role in prevention and management of diabetic retinopathy due to its antiangiogenic, anti-inflammatory properties. It also prevents destabilizing the membrane integrity of DL cells. Antihyperglycemic properties of T. cordifolia was shown effective in several other important symptoms of DR. Although diabetic rats treated with TC do not achieve the status of normal non-diabetic controls (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a milder way than doxorubicin treatment. T. cordifolia thus acts as a potential therapeutic agent for prevention of the vascular complications of diabetes.

Diabetic neuropathy

Tinospora cordifolia prevents the hyperalgesia in experimental diabetic neuropathy. It has an adolsecent inhibitory activity in vitro which may contribute to the beneficial effects [31].

Diabetic foot ulcer

Diabetic patients with foot ulcers on T. cordifolia as an adjuvant therapy showed significantly better final outcome with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing [32].

Hypolipidemic effects

Diabetics are 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 5 g/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 [33].

Antineoplastic effects

Jaegia 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 [34]. When HeLa cells were exposed to various doses of the extract, a dose-dependent increase in cell killing was observed as compared with non-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. Further investigation was undertaken to study whether the tumor associated macrophages (TAM) of Dalton’s lymphoma (DL) was activated by the aqueous liquid extract of T. cordifolia. In vitro antitumor activity was observed when the extract was activated by the aqueous liquid extract of T. cordifolia and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. Furthermore, it was found that T. cordifolia was a potential immunomodulator and cognitive enhancer. The dual property of T. cordifolia may bear a potential use in neurodegenerative disease affecting cerebral neurons and immunosuppression induced memory changes. Significant response has been found in children with moderate degree of behaviour disorders and mental deficit, along with improvement in IQ levels. The root of T. cordifolia is known to be used traditionally for its anti-stress activity. The pure aqueous extract of the root was found to enhance verbal learning and logical memory. Both the alcoholic and aqueous extracts of T. cordifolia produced a decrease in learning scores in Hebb William maze and retention memory, indicating enhancement of learning and memory [35].

Adaptogetic effects

The aqueous extract not only reversed the effect of cisplatin on gastric emptying, but also normalized cisplatin-induced hypermotility. The plant was also found to normalize the phosphatase function of peritoneal macrophages after exposure of rats to either carbon tetrachloride or serum, thus it satisfied the definition of adaptogen [42].

Antioxidant activity

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addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was the most effective one [43]. In another study, guduchi has shown significant clinical and hematobiological effects of its own as well as potentiation of morphine induced analgesic action [22]. Interestingly, is also exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species. The herb has been found to exert anti-inflammatory effect in both acute and subacute models of inflammation. The alcoholic extract was shown to inhibit the lipid peroxidation and nitric oxide production in rat liver homogenates [44]. A mild analgesic effect of the root extract at a dose of 5 g/kg was the most effective one [44]. It is traditionally used in compound formulations 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. It also significantly inhibited antibody formation by typhoid "H" antigen. A mild analgesic effect was observed with guduchi in another study. Its water extract was effective at a dose of 500 mg/kg given orally [45]. The stem extract of this plant was effective at a dose of 500 mg/kg given orally in a study conducted in Albino Wistar rats against CCL-induced reperfusion–induced myocardial infarction in rats [53]. The extract has also been reported to elevate GSH levels, expression of the gamma-glutamylcysteine ligase and Cu-Zn SOD genes. The herb also exhibited strong free radical-scavenging properties against reactive oxygen and nitrogen species as studied by electron paramagnetic resonance spectroscopy [45].

**Hepatoprotective effects**

It is traditionally used in compound formulations 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. It also significantly inhibited antibody formation by typhoid "H" antigen. A mild analgesic effect was observed with guduchi in another study. Its water extract was effective at a dose of 500 mg/kg given orally in a study conducted in Albino Wistar rats against CCL-induced reperfusion–induced myocardial infarction in rats [53]. The extract has also been reported to elevate GSH levels, expression of the gamma-glutamylcysteine ligase and Cu-Zn SOD genes. 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-arthritic and anti-osteoarthritis activities**

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placebo group, there was relief from sneezing only in 73 patients. From nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritis, in 85% Miers and C. asiatica Linn were observed to induce a 12% reduction in respiratory symptoms of allergic rhinitis and was well tolerated. The activity being comparable to [58]. The anti-allergic and bronchodilator properties of T. cordifolia were observed to induce a significant decrease in respiratory symptoms of allergic rhinitis and was well tolerated. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-induced of T. cordifolia stem and leaves extract prevented the induced bronchospasm in guinea pigs, capillary permeability in mice and mast cell disruption in rats. Results suggested that simultaneous supplementation of T. cordifolia with other drugs showed that it significantly decreased bronchospasm. T. cordifolia protects against lead intoxication [68].

Reduced mortality from induced by intra-abdominal sepsis following caecal ligation in rats and significantly reduced mortality from induced by E. coli-induced peritonitis in mice [61].

**Antifertility & aphrodisiac activity**

Oral administration of 70% methanolic extract of T. cordifolia stem to male rats at a dose level of 100 mg/kg for 60 days did not cause body weight loss but decreased the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner [62].

**Conclusion**

The pharmacological actions attributed to T. cordifolia in ayurvedic texts and folk medicine have been validated by a remarkable body of modern evidence suggesting that this drug has immense potential in modern pharmacotherapeutics.

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