**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, *Tinosporacordifolia*
Immunomodulatory activity of *Tinosporacordifolia*

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**Description and History**

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

of family menispermae is a perennial, wild climber, polyasaccharide, isolated from the dried stem of succulent, shrub often attaining a great height and. *T. cordifolia* showed polyclonal mitogenic activity sending down long thread like aerial roots. The bark is against beta cell [4]. It was reported that following oral creamy white and grey, leaves are membranous and treatment of mice with water and ethanol extracts of chordate. Flowers grow during the summer and fruits. *T. cordifolia* stems, there was a significant increase in during the winter. The viscous sap has a yellow colour, the total of count leucocytes. The aqueous extract ofrodu and nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various. The aqueous and ethanolic extract also induced an ailments throughout the centuries. Today the drug and increase in antibody 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 hepatitis, skin diseases and anemia. In compound 20% on placebo reported decrease in the incidence of formulation Guduchi is clinically used to treat jaundice, various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered. extracts inhibited cyclophosphamide-induced

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**Chemistry**

A variety of constituents have been isolated from *T. cordifolia* plant. They belong 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].

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**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. 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 of 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 *E. coli* infection were significant. Syringin, Cordiol, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticomplement and amrophy.
immunosuppression [7]. The polysaccharide-enriched T. cordifolia treatment, significantly caused the fraction from this plant is found to be very effective in reduction of cell count (p < 0.05) on day 15 of the reducing the metastatic potential of B16f-10 melanoma treatment period, however, reduction in total bacterial cells [8]. 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

enriched immunomodulatory fractions from Tinospora cordifolia cows treated with the T. cordifolia extract. The IL-8 cordifolia using the polymorphonuclear leukocyte function test. The results confirmed the 20B-ecdysone level in milk serum also increased significantly (p < 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].

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 T. cordifolia 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 immunomodulatory activity with an increase in

<table>
<thead>
<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Berberine, Palmatine, Magnoflorine, Tinosporine, Choline, Isocolumbin, Tetrabihydropalmitine, Magnoflorine</td>
<td>Stem, Root</td>
</tr>
<tr>
<td>Glycosides</td>
<td>Tinocordiside, Cordiside, Syringin, Cordifolioside A, B, C, D, E, Palmatoside C, Palmatoside P</td>
<td>Stem</td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol, gama-sitosterol, 20B-ecdysone, Ecdysone, Ecdysterone, Makisterone A, Giloinssterol</td>
<td>Aerial part, Stem</td>
</tr>
<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone, Celondane derivatives, Tinosporon, Tinosporides, Jateorine, Columbin</td>
<td>Whole plant</td>
</tr>
<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
</tr>
<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol, Heptacosanol</td>
<td>Whole plant</td>
</tr>
<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporidine, Cordifol, Cordifelone, Gilonin, Tinosporic acid</td>
<td>Root</td>
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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-formylmannotriol, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tinocordistine, 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 1-2.5 μg/ml [11].

Recently, the presence of an immunomodulatory protein (ImP) in guduchi has been investigated. Guduchi ImP showed ~3-fold mitogenic activity compared to untreated murine splenocytes in the 1-10 μg/mL concentration range; 5-7-fold increase in mitogenic 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; 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. Tinospora cordifolia had shown a significant level of macrophages activation and leads to increase in GMC-SF 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, lymphocyte, neutrophil count along with increased percentage phagocytosis was recorded in Guduchi supplemented cows in comparison to untreated cows, although plasma total antioxidant activity was similar between the two groups. Prepartum plasma progesterone concentration was significantly lowered in the treated group however there was no significant change in peripartum plasma total estrogens and PGFM levels due to Guduchi supplementation [16].

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-dihydroxyacetone (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 diabetes [30]. Intra-peritoneal administration of ALTC [35]. Intra-peritoneal administration of ALTC [35].

Diabetic retinopathy

T. cordifolia plays a role in prevention and management of diabetic retinopathy due to its ability to inhibit the tumor growth and increase the life span of tumor cells [35]. The results of the investigation also indicate that T. cordifolia has hypoglycemic, anti-angiogenic, anti-inflammatory, and anti-diabetic properties. It also prevents tumor formation by destabilizing the cell membrane integrity of tumor cells.

Progression of cataract and vascular changes, the aqueous extract of T. cordifolia was shown effective in several other important symptoms of diabetes. Although diabetic rats [60] treated with TC do not achieve the status of normal non-diabetic (EAC) in mice [36]. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a cell line compared to untreated diabetic rats. T. cordifolia thus acts as a potential therapeutic agent for prevention of diabetic retinopathy due to its anti-inflammatory properties.

Diabetic neuropathy

Tinospora cordifolia prevents the hyperalgesia in experimental diabetic neuropathy. It has an aldose reductase 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 outcomes with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing [32].

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 rats (2.5 and 5.0 mg/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. In another study in rats, the aqueous extracts also reduced levels of brain lipids [33].

Antineoplastic effects

Jagetia 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) and alloxan-induced diabetic rats. After 6 weeks, the level of spontaneous transplantable T-cell lymphoma, can be reduced by plasma barbituric acid reactive substances, activated by the aqueous liquid extract of T. cordifolia [35].

Cognitive effects

The memory impairment induced by cyclosporine was successfully overcome by both the alcoholic and aqueous extract of T. cordifolia. Even histopathologically, T. cordifolia has successfully reversed the hippocampal neuronal degeneration induced by cyclosporine revealed by the hippocampus histopathological investigation [40]. The alteration of immune function affected learning and memory process and T. cordifolia is a potent 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 behavioural 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 [41].

Adaptogenic 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 phagocytic function of peritoneal macrophages after exposure of rats to either carbon tetrachloride or serum, thus it satisfied the definition of adaptogen [42].

Antioxidant activity

The antioxidant properties of T. cordifolia roots were studied by administering the aqueous extract of macrophages (TAM) of Dalton's lymphoma (DL) and 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. In
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 was shown to inhibit the lipid peroxidation and reported to exert a significant anti-inflammatory effect [44]. Similarly, the reduced level of nitric oxide and superoxide and hydroxyl radical in vitro. Earlier studies [45] showed that dry stem crude extract (DSCE) contains 50850 mg/kg given orally) and formalin-induced arthritis in the polygonal beta cell mitogen; G1-4A, DSCE as well as 6A (1 mg/kg given orally) rat models. G1-4A also enhance immune response in mice [46]. In order to explore the possibility of using G1-4A/pp1 to modulate radiation-induced immune suppression, the hepatoprotective activity was found to be more effective than T. cordifolia in other models. The hepatoprotective action was reported in one of the studies [47]. A dose-dependent 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 benefitting the heart [54]. Administration of the extract of T. cordifolia roots (2.5 and 5.0 g/kg body weight) for 8 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids and free fatty acids in allophan-induced diabetic rats [55]. The extract of T. cordifolia that grow on neem-giloe [T. cordifolia] significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A 50% Rats treated with T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone formation was observed in a model of adjuvant-induced arthritis. It also significantly inhibited antibody osteocalcin and cross-laps levels were significantly increased. A mild analgesic effect of its own as well as potentiation of morphine analgesia has been reported [47]. In another study, antosteoporotic agent [56]. The aqueous extract of T. cordifolia showed a significant anti-inflammatory effect in the cotton pellet granuloma and formalin induced arthritis model, its effect was comparable with indomethacin and its mode of action appeared to resemble that of non-steroidal anti-inflammatory agent. 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 nasal discharge was reported in 69%; from nasal obstructions 61% and from nasal pruritis, in 71%. In...
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1. Introduction

Tinospora cordifolia was shown to impart protection to the human immune system and to make the body stronger and immune to disease. The aqueous extract of the stem evaluated on histamine-induced bronchospasm in guinea pigs, capillary permeability in mice, and mast cell disruption in rats showed that it significantly decreased bronchospasm. T. cordifolia protects against lead intoxication [68].

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, anti-neoplastic, antioxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunomodulatory activity [59]. In another experimental study, antipyretic effects have been reported in the hexane- and chloroform-soluble portions of T. cordifolia stems [60]. Various studies show remarkable antipyretic and antitussive activity of T. cordifolia. Pre-treatment with T. cordifolia was shown to impart protection against mortality induced by intraperitoneal sepsis following caecal ligation in rats and significantly reduced mortality from induced by E. coli–induced peritonitis in mice [61].

2. Antipyreric and anti-infective activity

The water-soluble fraction of 95% ethanolic extract of T. cordifolia plant has shown significant antipyretic activity [59]. In another experimental study, antipyreric effects have been reported in the hexane- and chloroform-soluble portions of T. cordifolia stems [60]. Various studies show remarkable anti-inflammatory and antitussive activity of T. cordifolia. Pre-treatment with T. cordifolia was shown to impart protection against mortality induced by intraperitoneal 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].

Guduchi is a natural aphrodisiac in females. Its immunomodulatory action helps to strengthen the immune system and to make the body stronger and hence make a woman more able and ready to enjoy the sex. It is a rejuvenator and a natural herbal aphrodisiac.

3. Other effects

In a clinical evaluation, a compound preparation of T. cordifolia was reported to significantly reduce the pain in patients suffering from rheumatoid arthritis. Either extract of the steam distillation of aerial part of T. cordifolia has inhibited the in vitro growth of Mycobacterium tuberculosis at 1:50,000 dilutions [63]. It is used for its anti-leptopirotic properties, along with wide use in other types of skin disorders and has been shown to exert antileptopirotic activity in a combination formulation. Ethanol extract of T. cordifolia has exhibited significant antipyretic activity in rats [64]. 'Septilin syrup' a compound preparation containing T. cordifolia was found to elicit good clinical response in children suffering from upper respiratory tract infection and chronic otitis media. In a scientific study on rats and human volunteers, T. cordifolia was found to have diuretic effects [65]. It was also found effective in modulation of morphology and some other...
Immunomodulatory activity of *Tinospora cordifolia*

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