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 immunomodulating activity and human studies.

**Keywords:** Immunomodulation, Immunomodulating agent, Tinosporacordifoliflora

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 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*  

**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.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, Cordiold, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticompliment and amruth.

**DESCRIPTION AND HISTORY**

*T. cordifolia* (Fig 1); common name guduchi, amrita. Immunomodulatory activities [6]. Anarabino galactan

95 as a powerful emetic and is used for bowel obstruction.
96 *T. cordifolia* is used as an antidote for snake bite and
97 used in malaria, environmental illness, asthma, upper
98 respiratory tract infection, UTI, general debility and
99 amelioration of symptoms from chemo or radiotherapy.

**CHEMISTRY**

A variety of constituents have been isolated from 100 *T. cordifolia* plant. They belong to different classes such 101 as alkaloids, diterpenoids, lactones, glycosides, steroids, 102 sesquiterpenoids, phenolic, aliphatic compounds and 103 polysaccharides (Table 1). Leaves of this plant are rich 104 in protein (11.2%), calcium and phosphorus [3]. 105 Anarabino galactan had been isolated from the dried 106 stem of *T. cordifolia* [4].

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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].

Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. Intramammary infusion of hydro-methanolic extract of T. cordifolia treatment, significantly caused the reduction in cell count (p < 0.05) on day 15 of the treatment period, however, reduction in total bacterial count was observed from day 3 onwards. The phagocytic activity and lysosomal enzyme content of 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 results suggest that the hydro-methanolic extract of T. cordifolia (stem) possesses antibacterial and immunomodulatory properties [10].

Sharma et al (2012) isolated and characterised the immunomodulatory active compounds of Tinospora cordifolia. It was found that ethyl acetate, water fractions and hot water extract exhibited significant 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].

Table 1. Chemical composition of T. cordifolia plant

<table>
<thead>
<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
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<tbody>
<tr>
<td>Alkaloids</td>
<td>Berberine</td>
<td>Stem</td>
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<td></td>
<td>Palmatine</td>
<td>Root</td>
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<td></td>
<td>Magnoflorine</td>
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<td>Tinosporine</td>
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<td>Choline</td>
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<td>Tetrahydropalmatine</td>
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<td>Magnoflorine</td>
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<td>Glycosides</td>
<td>Tinocordiside</td>
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<td></td>
<td>Syringin</td>
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<td>Cordifolioside A</td>
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<td>Cordifolioside B</td>
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<td>Cordifolioside E</td>
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<td></td>
<td>Palmatoside C</td>
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<td>Palmatoside P</td>
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<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
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<td>Gama-sitosterol</td>
<td>Stem</td>
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<td>20B-ecdysone</td>
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<td>Ecdysterone</td>
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<td>Makisterone A</td>
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<td>Giloinsterol</td>
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<td>Diterpenoid lactones</td>
<td>Furanolactone</td>
<td>Whole plant</td>
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<td>Celondane derivatives</td>
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<td>Tinosporon</td>
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<td>Tinosporides</td>
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<td>Jateorine</td>
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<td>Columhin</td>
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<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
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<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
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<td>Heptacosanol</td>
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<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporidine</td>
<td>Root</td>
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<td>Tinosporine</td>
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<td>Cordifol</td>
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<td>Cordifelone</td>
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<td></td>
<td>Gilonin</td>
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<td>Tinosporic acid</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-formylmannonan, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tinosoridine, 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 mitogenic activity compared to untreated murine splenocytes in the 1-10 μg/mL concentration range; 5-7-fold increase in mitogen 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 and 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 dendritic cells [13]. Tinospora cordifolia had shown a significant level of macrophages activation and leads to increase in GM-CSF which leads to leukocytosis and improved neutrophil function [14]. G1-4A, an immunomodulatory polysaccharide from Tinospora cordifolia, modulates macrophage responses and protects mice against lipo polysaccharide-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 lymphocyte, neutrophil lymphocyte ratio was recorded in Guduchi supplemented cows in comparison to untreated cows although plasma total antioxidant activity was similar between the two groups. Prepartum 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 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 insulinotrophic 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-dihydroxydihydrophine (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 Fox01 can improve hepatic metabolism during diabetes in DL-bearing mice not only augment the basic function of Fox01 but also the metabolic syndrome [30].

Diabetic retinopathy

*T. cordifolia* plays a role in prevention and management of diabetic retinopathy due to its antiangiogenic, anti-inflammatory, anti-oxidant, and hypoglycemic properties. It also prevents destablization of the membrane integrity of DL cells. The aqueous extract 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 (EAC) in mice [36]. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. *T. cordifolia* could be used as a potent therapeutic agent for prevention of macrophages-derived dendritic cells [38], is effective against various cancers, killing the cancer cells very effectively *in vitro*, inhibits skin carcinogenesis in mice [39], and inhibits experimental metastasis [8].

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 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* have 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 rat (2.5 and 5g/kg body weight for 6 weeks) an aqueous extract of *T. cordifolia* root was administered for treatment. 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 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 [41].

Antineoplastic effects

Jagetia et al. have found that the guduchi killed the HeLa cellsevery 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 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. Further investigation was undertaken to study whether the tumor associated macrophages (TAM) of Dalton's lymphoma (DL) alloxa 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
Immunomodulatory activity of Tinosporacordifolia

The aqueous extract of stem was shown to inhibit the lipid peroxidation reported to exert a significant anti-inflammatory effect and superoxide and hydroxyl radical in vitro. Earlier studies in both cotton pellet–induced granuloma (1, 250 and 500 mg/kg body weight) and dry stem crude extract (DSCE) contains a568500 mg/kg given orally) and formalin-induced arthritis showed strong free radical scavenging properties against reactive oxygen and nitrogen species as studied by electron paramagnetic resonance spectroscopy [45].

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 [46]. The water extract of the stem of neem-giloe [T. cordifolia] that grow on allophan-induced diabetic rats [55]. Aqueous extract of T. cordifolia showed a significant inflammatory effect in the cotton pellet granuloma and formalin induced arthritis model, its effect was comparable with indomethacin and its mode of action was similar to that of aspirin [56].

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placebo group, there was relief from sneezing only in the groups treated with 12.7% of T. cordifolia extract; nasal discharge, in 16.2%; from nasal pruritus, in 17%; and from nasal obstruction, in 17% [58]. The anti-allergic and bronchodilator properties of T. cordifolia were shown to impart protection against bronchospasm in guinea pigs, capillary permeability in mice and mast cell disruption in rats [58]. Results suggested that simultaneous supplementation of T. cordifolia and diazepam showed that it significantly decreased bronchospasm [58].

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, antinflammatory, anti-neoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunologic properties. There are limited human studies to support these use. T. cordifolia can also be used as an adjuvant drug in the treatment of hyper-reactive malarious splenomegaly [69]. Tinospora cordifolia appears to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome in patients with malignant obstructive jaundice [70].

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.

REFERENCES


Immunomodulatory activity of Tinospora cordifolia


