**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, Tinosporacordilifolia

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 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 Tinosporacordifolia

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

**CHEMISTRY**

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

**PHARMACOLOGICAL ACTIONS**

109 *T.cordifolia*benefits the immune system in variety 
110 of ways. The alcoholic and aqueous extract of this plant 
111 have been tested successfully for immunomodulatory 
112 activity [5]. Pretreatment with *T.cordifolia* lead to 
113 protection against mortality induced by intra-abdominal 
114 sepsis following caecal ligation in rats. It also 
115 significantly reduced mortality from *E. coli* induced 
116 peritonitis in mice [6]. In a clinical study, it was 
117 afforded protection in cholestatic patients against *E. coli* 
118 infection. Those activities were not due to its 
119 antibacterial activity as shown by the negative *in vitro* 
120 antibacterial activity of the plant extract. It was reported 
121 that treatment in rats had resulted in significant 
122 leucocytosis and predominant neutropenia. It has been 
123 also observed that it stimulated the macrophages as 
124 evidenced by an increase in the number and percentage 
125 phagocytosis of *S.aureus* by peritoneal macrophages in 
126 rats. The phagocytic and intercellular killing capacity of 
127 polymorphs in rats, tested at 3.5 hours after 
128 infection were significant. Syringin, Cordiol, 
129 Cordioside, Cordifolsiosides A&B were identified as the 
130 active principle responsible for the anticomplement and 
131 immunomodulatoryactivities [6]. Anarabinogalactan 
132 of family menispermaceae is a perennial, wild climber, 
133 poly saccharide, isolated from the dried stem of 
134 succulent, shrub often attaining a great height and 
135 *T.cordifolia* showed polyclonal mitogenic activity 
136 sending down long thread like aerial roots. The bark is 
137 against beta cell [4]. It was reported that following oral 
138 creamy white and grey, leaves are membranous and 
139 stems, there was a significant increase in 
140 during the winter. The viscous sap has a yellow colour, 
141 the total of count leucocytes. The aqueous extract of 
142 odour and nauseating bitter [2]. It has been used in 
143 *T.cordifolia* was found to increase phagocytosis *in vitro*. 
144 ayurvedic preparations for the treatment of various 
145 The aqueous and ethanolic extract also induced an 
146 alterations throughout the centuries. Today the drug and 
147 tincture are used for the treatment of general weakness, 
148 extracts treatment cause significant reduction in 
149 fever, dyspepsia, dysentery, gonorrhea, secondary 
150 eosinophil count and improved hemoglobin in HIV 
151 syphilis, urinary diseases, impotency, gout, viral 
152 patients [5]. Sixty percent patients receiving TCE and 
153 hepatitis, skin diseases and anemia. In compound 
154 20% on placebo reported decrease in the incidence of 
155 formulation Guduchi is clinically used to treat jaundice, various 
156 symptoms associated with the disease. All 
157 rheumatoid arthritis and diabetes. The root is considered 
158 extracts inhibited cyclophosphamide-induced
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 immunomodulatory activity of the polysaccharides of T.cordifolia, and also it was conclude that the polysaccharide with lowest sugar content showed highest activity and with highest sugar content showed lowest activity [9]. Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. It was found that ethyl acetate, water fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of Tinospora 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 and highest sugar content showed highest activity and with highest sugar content showed highest activity [9]. Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. It was found that ethyl acetate, water fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of Tinospora cordifolia (stem) possesses antibacterial and 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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</thead>
<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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<tr>
<td></td>
<td>Magnoflorine</td>
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<td></td>
<td>Tinosporine</td>
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<tr>
<td></td>
<td>Choline</td>
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<td></td>
<td>Isocolumbin</td>
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<tr>
<td></td>
<td>Tetrabruptalamin</td>
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<tr>
<td></td>
<td>Magnoflorine</td>
<td></td>
</tr>
<tr>
<td>Glycosides</td>
<td>Tinocordiside</td>
<td>Stem</td>
</tr>
<tr>
<td></td>
<td>Cordiside</td>
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<tr>
<td></td>
<td>Syringin</td>
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<tr>
<td></td>
<td>Cordisidiol A</td>
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<td></td>
<td>Cordisidiol B</td>
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<tr>
<td></td>
<td>Cordisidiol C</td>
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<tr>
<td></td>
<td>Cordisidiol D</td>
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<tr>
<td></td>
<td>Cordisidiol E</td>
<td></td>
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<tr>
<td></td>
<td>Palmatiside C</td>
<td></td>
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<tr>
<td></td>
<td>Palmatiside P</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
</tr>
<tr>
<td></td>
<td>gama-sitosterol</td>
<td>Stem</td>
</tr>
<tr>
<td></td>
<td>20B-ecdysone</td>
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<tr>
<td></td>
<td>Ecdysone</td>
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<tr>
<td></td>
<td>Ecdysterone</td>
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<tr>
<td></td>
<td>Makisterone A</td>
<td></td>
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<tr>
<td></td>
<td>Giloinsterol</td>
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<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone</td>
<td>Whole plant</td>
</tr>
<tr>
<td></td>
<td>Celondane derivatives</td>
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<td></td>
<td>Tinosporon</td>
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<tr>
<td></td>
<td>Tinosporides</td>
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<tr>
<td></td>
<td>Jateorine</td>
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<td></td>
<td>Columbin</td>
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<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
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<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
</tr>
<tr>
<td></td>
<td>Heptacosanol</td>
<td></td>
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<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporidine</td>
<td>Root</td>
</tr>
<tr>
<td></td>
<td>Cordifol</td>
<td></td>
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<tr>
<td></td>
<td>Cordifolene</td>
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<tr>
<td></td>
<td>Cordifolene</td>
<td></td>
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<tr>
<td></td>
<td>Gilonin</td>
<td></td>
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<tr>
<td></td>
<td>Tinosporic acid</td>
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</table>
Immunomodulatory activity of Tinosporacordifolia

T. cordifolia, modulates macrophages. 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, a 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 overcome 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-4), 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 diabetics, 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 -dihydroxyphenylalanine (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of lymphocyte, neutrophil count along with increased the latter. Berberine inhibits Foxo1, which integrates...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during diabetes, decreasing the tumor growth and increasing the life span of tumor-bearing hosts through anti-hyperglycemic, anti-angiogenic, anti-inflammatory, and anti-oxidant properties. It also prevents stabilizing the membrane integrity of DL cells. Progression of claudicant and vascular changes, the T. cordifolia was shown effective in several other important symptoms of DR. Although diabetic rats are tumor models including Ehrlich ascites carcinoma treated with T. cordifolia do not achieve the status of normal non-diabetic (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a tumor-bearing host, thus acting as a potential therapeutic agent for prevention of macrophages-derived dendritic cells, is effective against various cancers, killing the cancer cells very effectively in vitro, inhibits skin carcinogenesis in mice and induces experimental metastasis.

Diabetic retinopathy

T. cordifolia plays a role in prevention and management of diabetic retinopathy due to its antihyperglycemic effect. The tumor was also managed by T. cordifolia for their cell impairment induced by cyclosporine.

Diabetic foot ulcer

Diabetic patients with foot ulcers on T. cordifolia showed significantly better healing compared with non-drug treated controls. The aqueous extract not only reversed the effect of alloxan in DL-bearing mice but also augmented the biding ability and secretion of IL-1 and TNF. The results of the investigation also indicate that T. cordifolia activates tumor-bearing host, thus acting as a potential therapeutic agent for prevention of diabetes.

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.

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 outcome with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing.

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.

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. 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 indicates that the plant warrants a future study as an anti-neoplastic agent. Further investigation were undertaken to study whether the tumor associated macrophages (TAM) of Daltons lymphoma (DL) were 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 more effective in acute inflammation, although in most cases the drug was inferior to the most effective one [43]. In another study, guduchi exhibited anti-inflammatory and antioxidant effects in vitro. Earlier studies reported that dry stem crude extract (DSCE) contains ascorbic acid and formalin-induced arthritis in the cotton pellet granuloma (1, 250 and 500 mg/kg given orally) and formalin-induced arthritis in polyglucosan beta cell mitogen; G1-4A, DSCE as well as 169 (1 mg/kg given orally) rat models. G1-4A also enhanced immune response in mice [44].

To explore the possibility of using G1-4A/pp1 to modulate radiation-induced immune suppression, a study was conducted. The hepatoprotective action was reported in one of the antioxidant effect PPI from the plant was examined in the experiment in which goats treated with T.cordifolia showed a significant clinical and hematobiological effect of its own as well as potentiation of morphine analgesia has been reported [45].

Antioxidant activity: The dried stem of T.cordifolia produces significant inhibition of formation of TBARS thus decreased. The root extract at a dose of 5 g/kg was the most effective one [46]. In another study, guduchi and Bicillin (neem) also exhibited type 2 photosensitization mechanism. T. cordifolia 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 [47].

Anti-inflammatory, anti-arthritis and anti-osteoporotic activities: It is traditionally used in 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 [48].

Osteoprotection: T. cordifolia significantly inhibited acute inflammatory responses and prevented bony damage in a dose of 50 mg/100 g given orally and intraperitoneally. A study showed that T. cordifolia (10 mg/kg body weight) significantly inhibited osteoprotection, as the bone tissue cholesterol, phospholipids and free fatty acids in neem-giloe [T. cordifolia] that grow on alloxaan-induced diabetic rats [55].

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 agent. The dried stem of T. cordifolia was reported to be more effective than 256 obscurations 61% and from nasal cornifolia was found to be more effective from nasal pruritis, in 71%. In
placebo group, there was relief from sneezing only in 21% patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritis, in 12%. Thus, T. cordifolia significantly decreased all symptoms of allergic rhinitis and was well tolerated [58]. The anti-allergic and bronchodilator properties of T. cordifolia have been validated by a remarkable body of modern pharmacological evidence suggesting that this drug has immense potential in modern pharma-
Immunomodulatory activity of *Tinospora cordifolia*


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