**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*
Immunomodulatory activity of *Tinosporacordifolia*

**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, amrta131, immunomodulatory activities [6]. Anarabinogalactan of family *menispermaeae* is a perennial, wild climber,132 polysaccharide, isolated from the dried stem of succulent, shrub often attaining a great height and133 *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 oral134 against beta cell [4]. It was reported that following oral creamy white and grey, leaves are membranous and135 treatment of mice with water and ethanol extracts of chordeate. Flowers grow during the summer and fruits136 *T. cordifolia* stems, there was a significant increase in during the winter. The viscous sap has a yellow colour,137 the total of count leucocytes. The aqueous extract of edourand nauseating bitter [2]. It has been used in138 *T. cordifolia* was found to increase phagocytosis in *in vitro*. ayurvedic preparations for the treatment of various139 The aqueous and ethanolic extract also induced an ailments throughout the centuries. Today the drug and140 increase in antibody production. *T. cordifolia*141 extracts treatment cause significant reduction in fever, dyspepsia, dysentery, gonorrhea, secondary142 eosinophil count and improved hemoglobin in HIV syphilis, urinary diseases, impotency, gout, viral143 patients [5]. Sixty percent patients receiving TCE and hepatitis, skin diseases and anemia. In compound14420% on placebo reported decrease in the incidence of formulation Guduchi is clinically used to treat jaundice,145 various symptoms associated with the disease. All146 rheumatoid arthritis and diabetes. The root is considered147 extracts inhibited cyclophosphamide-induced

**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**

*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 sepsis 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 *E. coli* infection were significant. Syringin, Cordiol, Cordiside, Cordifosides/A&B were identified as the active principle responsible for the anticompliment and diotherapy.
The polysaccharide-enriched fraction from this plant is found to be very effective in reducing the metastatic potential of B16f-10 melanoma cells. 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. Mukherjee et al. evaluated the biological activity of the Tinospora cordifolia extract against bovine subclinical mastitis. Intramammary infusion of hydro-methanolic extract of T. cordifolia (stem) possesses antibacterial and immunomodulatory properties. 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 with an increase in the phagocytic activity and lysosomal enzyme content of milk polymorphonuclear cells. The IL-8 level in milk serum also increased significantly in diseased cows treated with the extract.

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>
</tr>
</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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<td></td>
<td>Choline</td>
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<td>Isocolumbin</td>
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<td></td>
<td>Tetrabutyldipalmatine Magnoflorine</td>
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<tr>
<td>Glycosides</td>
<td>Tinos_docside Cordiside Syringin Cordifolioside A Cordifolioside B Cordifolioside C Cordifolioside D Cordifolioside E Palmatoside C Palmatoside P</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol gama-sitosterol 20β-ecdysone Ecdysone Ecdysterone Makisterone A Giloisteryl</td>
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<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone Celondane derivatives Tinosporon Tinosporides Jateorine Columbin</td>
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<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
</tr>
<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
</tr>
<tr>
<td></td>
<td>Heptacosanol</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporidine Cordifol Cordifelone Cordifelone Gilonin Tinosporic acid</td>
<td>Root</td>
</tr>
</tbody>
</table>

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 treatment period, however, reduction in total bacterial cells [8]. A 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 Tinospora70 cows treated with the T. cordifolia extract. The IL-8 cordifolia using the polymorphonuclear leukocyte level in milk serum also increased significantly (p < function test. The results confirmed the 0.05) in diseased cows treated with the extract. The immunomodulatory activity of the polysaccharides of3 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]. Sharma et al. (2012) isolated and characterised the highest activity and with highest sugar content showed Sharma 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. Fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of immunomodulatory activity with an increase in
percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylmannotriose, 11-hydroxystachyosine, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tincoside and syringin by nuclear magnetic resonance and mass spectrometry. Cordifoliside 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 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 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 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 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 C-reactive protein 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 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 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 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 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 disaccharidases 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-dihydroxystilbene (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 C-reactive protein levels due to Guduchi supplementation [16].
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during fasting 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

**Diabetic retinopathy**

T. cordifolia plays role in prevention and in the intra-peritoneal administration of ALTC slow down management of diabetic retinopathy due to its the tumor growth and increase the life span of tumor antihyperglycemic, anti-angiogenic, anti-inflammatory, and anti-oxidant properties. It also prevents the progression of cataract and vascular changes, the T. cordifolia was shown effective in several other important symptoms of DR. Although diabetic rats tumour models including Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-cancerous (EAC) in mice. It induces proliferation and myeloid diabetic rats, but they achieve significant levels as differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host, activates tumor-associated act 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 [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 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 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-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 a anti-neoplastic agent. Further investigation were undertaken to study whether the tumor associated macrophages (TAM)of Daltons lymphoma (DL) alloxa-induced diabetic rats. After 6 weeks, the level spontaneous transplatable T-cell lymphoma, can be ceruloplasmin and alpha tocopherol were reduced. In

**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**

Aqueous extracts of T. cordifolia roots (20% v/v) showed significant antioxidant activity against various free radicals like superoxide dismutase, catalase, and glutathione peroxidase. The results also indicated that the plant has the potential to act as an antioxidant and can be used in the treatment of oxidative stress-related disorders. The aqueous extract was found to have a significant effect on the reduction of the lipid peroxidation level, as measured by the production of thiobarbituric acid reactive substances, ceruloplasmin, and alpha tocopherol. In

**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 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 behaviour disorders and mental deficit, along with improvement in IQ levels. The root of T. cordifolius 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].

Published online: January 31, 2013
In addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was showe......

469. It is traditionally used for the treatment of......

500. Rats treated with...acetylsalicylic acid in acute inflammation, although in......

510. *T. cordifolia* is traditionally used for the treatment of......

515. In another study, guduchi (Phyllanthus emblica) [48]. The aqueous extract of stem was......

518. *T. cordifolia* also exhibited strong free radical......

520. Extract of *T. cordifolia* has also exhibited *in vitro*......

523. The hepatoprotective action was reported in one of......

526. A dose-dependent reduction in infarct size and in......

527. The hepatoprotective action was reported in one of......

530. Extract of *T. cordifolia* has also exhibited......

533. The stem extract can normalize the alterations in lipid......

535. Oral administration of......

538. In another study, guduchi (Phyllanthus emblica) [48]. The aqueous extract of stem was......

541. The hepatoprotective action was reported in one of......

542. Extract of *T. cordifolia* has also exhibited......

545. Extract of *T. cordifolia* has also exhibited......

548. Anti-inflammatory, anti-arthritis and anti-osteoporotic activities

554. Aqueous extract of *T. cordifolia* showed a significant......

562. T. cordifolia showed a significant......

565. T. cordifolia was found to be more effective than......

568. In a clinical study, 100% relief......

571. The dried stem of *T. cordifolia* was reported from sneezing in 83% of the patients on......

574. Formalin-induced arthritis model, its effect was......

577. *T. cordifolia* is traditionally used for the treatment of......

580. Anti-allergic activity

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586. T. cordifolia also exhibited a significant......

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601. Osteoprotective activity

604. Anti-allergic activity

607. Immunomodulatory activity of *Tinospora cordifolia*

610. The aqueous extract of *T. cordifolia* showed a significant......

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616. T. cordifolia was found to be more effective than......
The ethanol extracts of the roots of *T. cordifolia* possess immunologically active principles. A review. Phytother Research 2009; 23:910-4. Miers and C. *asiatica* Linn were observed to induce a 12% decrease in symptoms of allergic rhinitis and was well tolerated. The activity being comparable to that of diazepam [67]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-test induced ulceration, the activity being comparable to [58]. The anti-allergic and bronchodilator properties of *T. cordifolia* were shown to be significant at 1:50,000 dilutions [67, 68]. T. *cordifolia* protects against lead intoxication [69].

**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, antimarial, antistress, antipyretic and immunomodulatory properties. There are limited human studies to support these uses. *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].

**Toxicology**

The ayurvedic literature reports that *T. cordifolia* can cause constipation, if taken regularly in high doses. It has no side effect and toxicity. When *T. cordifolia* extract was administered to rabbit up to the highest oral doses of 1.6 g/kg, there were no predictable adverse drug effects.

**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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