**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. *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*

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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 *Tinospora cordifolia*. 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*  

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 intended 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, amritha*. 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, alphatic compounds and polysaccharides (Table 1). Leaves of this plant are rich in protein (11.2%), calcium and phosphorus [3]. Anarabinoagalactan had been isolated from the dried stem of *T.cordifolia* [4].

**CHEMISTRY**

**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 peritonitis following caecal ligation in rats. It also significantly reduced mortality from *E. coli* induced peritonitis in mice [6]. In a clinical study, it was afforded protection in cholestatic patients against *E. coli* infection. Those activities were not due to its antibacterial activity as shown by the negative *in vitro* antibacterial activity of the plant extract. It was reported that treatment in rats had resulted in significant leucocytosis and predominant neutropenia. It has been also observed that it stimulated the macrophages as evidenced by an increase in the number and percentage phagocytosis of *S.aureaus* by peritoneal macrophages in rats. The phagocytic and intercellular killing capacity of polymorphs in rats, tested at 3.5 hours after infection were significant. Siringin, Cordiol, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticompliment and amelioration of symptoms from chemo or radiotherapy.

*T.cordifolia* is used as an antidote for snake bite and as a powerful emetic and is used for bowel obstruction. *T.cordifolia* is used as an antidote for snake bite and used in malaria, environmental illness, asthma, upper respiratory tract infection, UTI, general debility and various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered...
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]. 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 results confirmed 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 [9].

<table>
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<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
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<td>Alkaloids</td>
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<td>Aliphatic Compounds</td>
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<td>Heptacosanol</td>
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<td>Miscellaneous Compounds</td>
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<td>Tinosporic acid</td>
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Sharma et al. (2012) evaluated the immunomodulatory activity of three polysaccharide-enriched milk polymorphonuclear cells enhanced in the diseased fraction from Tinospora 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, and also it was conclude that the T.cordifolia (stem) possesses antibacterial and immunomodulatory properties [9].

Sharma et al (2012) isolated and characterised the lowest activity [9], Mukherjee et al evaluate the immunomodulatory active compounds of Tinospora 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 Tinospora cordifolia extract at the biological activity of the Tinospora cordifolia extract at.

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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-formylmonanion, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifolisid A, magnoflorine, tinocordisid, syringin by nuclear magnetic resonance and mass spectrometry. Cordifolisid 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 spleen cells 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 macrophage 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 lymphocyte, neutrophil and monocyte count, along with increase in GM and MNC was observed. Guduchi supplementation of peripartum supplementation, as the crossbred periparturient cow is highly susceptible to various diseases that effectively reduce its reproductive performance postpartum. A higher total number of leukocyte, neutrophil and monocyte count, along with increase in GM and MNC was observed.

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-dihydroxydizedione (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 periods of fasting, thus amplifying the basic function of insulin resistance and the metabolic syndrome [30].

**Diabetic retinopathy**

*T. cordifolia* plays a role in retinal degeneration, due to its ability to slow down progression of diabetes by regulating the levels of cytokines, such as TNF, which is known to cause retinal damage in diabetic patients. The aqueous extract not only reversed the effect of TNF on retinal cells but also protected against the hyperglycemic condition.

**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 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 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 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 Dalton's lymphoma (DL) were stimulated by the aqueous extract of *T. cordifolia* roots. After 6 weeks, the levels of plasma barbituric acid reactive substances, ceruloplasmin and alpha tocopherol were reduced. In vitro studies have revealed that *T. cordifolia* has antiangiogenic, anti-inflammatory, anti-oxidative properties, and it also prevents the hyperalgesia in diabetic rats [37].

**Adaptogenic effects**

The aqueous extract not only reversed the effect of cisplatin on gastric emptying, but also normalized its 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 *T. cordifolia* root to rats bearing peritoneal administration of ALTC slow down 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].
In addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was effective in acute inflammation, although in subacute inflammation, the drug was inferior to most effective one [43]. In another study, guduchi [45]. The aqueous extract of stem was shown to inhibit the lipid peroxidation in DBS [46] and reported to exert a significant anti-inflammatory effect. The superoxide and hydroxyl radical in vitro. Earlier studies in both cotton pellet–induced granuloma (1, 250 and 500 mg/kg given orally) and formalin-induced arthritis showed that dry stem crude extract (DSCE) contains 68500 mg/kg given orally) [47]. In another study, guduchi (1 mg/kg given orally) rat models. G1-4A also enhances immune response in mice [44]. In order to explore the possibility of using G1-4A/pp1 to modulate radiation-induced immune suppression, the Hepatoprotective effects of the gamma-glutamylcysteine ligase and Cu-Zn SOD genes. The herb also exhibited strong free radical-scavenging properties against reactive oxygen and nitrogen species as studied by electron paramagnetic resonance spectroscopy [45].

Cardioprotective activity

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-inflamatory actions in models of acute and subacute inflammation [46]. The water extract of the stem of T. cordifolia that grow on neem-giloe has significantly inhibited acute inflammatory response evoked by carrageenan in a dose of 50 mg/100 g given orally and intraperitoneally. A premature loss of tibia was slower than that in controls. Serum induced arthritis. It also significantly inhibited antibody against chronic arthropods and cross-laps levels were significantly reduced. This study demonstrates that extract of T. cordofila has the potential for being used as an osteoanalgic agent [47]. In another study, antosteoporotic agent [56].

Osteoprotective activity

Anti-allergic activity

The hepatoprotective action was reported in one of the most important studies [48]. The aqueous extract of stem was shown to have significant clinical and hematobiological effects. Selective inhibitors of ROS-like ROX Swiss Albino mice [51]. T. cordifolia exhibited time–mammotol, super oxide dismutase (SOD), Sodiumazide, independent hepatoprotection as reflected in both antioxidant GSH, and vitamin C brought about biochemical and histological examination in a study significant inhibition of formation of TBARS thus conducted in Albino Wistar rats against CCL2-induced type 1 and type 2 photosensitization mechanism. T. cordifolia histopathological studies proved the hepatoprotective activity of extract [52]. A dose-dependent reduction in infant 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 benefiting the heart [54]. Administration of the extract of T. cordifolia roots (2.5 and 5.0 g/kg body weight) for 6 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids and free fatty acids in alloxan-induced diabetic rats [55].

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Hepatoprotective effects

Cardioprotective activity

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

Osteoprotective activity

Anti-allergic activity
placebo group, there was relief from sneezing only in 73 glucocorticogenic enzymes activity in diabetic rat kidney 518 21% patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritis, in 519 Miers and C. asiatica Linn were observed to induce a 520 12%. Thus, T. cordifolia significantly decreased all 521 symptoms of allergic rhinitis and was well tolerated: 522 induced ulcerization, the activity being comparable to 523 the anti-allergic and bronchodilator properties of 524 that of diazepam [67]. Concurrent daily administration 525 of an aqueous extract of the stem evaluated on histamine-S19 of T. cordifolia stem and leaves extract prevented the 526 induced bronchospasm in guinea pigs, capillary 80 toxic influences of lead on haematological value and the 527 permeability in mice and mast cell disruption in rats. 528 Results suggested that simultaneous supplementation of 529 T. cordifolia and histamine aerosol, decreased capillary 530 permeability and reduced the number of disrupted mast 531 cells.

**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 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].

**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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Immunomodulatory activity of Tinospora cordifolia

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