**ABSTRACT**

Immunomodulation is a procedure, which can alter the immune system of an organism by interfering its function. Modulation of immune system may result in suppression or stimulation of immunological reactivity. Recently the effect of immunomodulators in the treatment of various diseases is significant. *Tinosporacordifolia* is a widely used shrub in ayurvedic system of medicine. It is reported to benefit the immune system in a variety of ways. The medicinal properties incorporated with this plant are anti-diabetic, hypolipidemic, anti-neoplastic, anti-oxidant, anti-inflammatory, immunomodulatory, cognitive, adaptogenic, aphrodisiac, cardioprotective and hepatoprotective effect. Many compounds belonging to different classes such as alkaloids, diterpenoids, phenol, aliphatic compounds and polysaccharides have been isolated from this plant. But it is not well known that which of these compounds are responsible for various activities. Therefore, it needs further exploration of its components, pharmacological action and mechanism of action. This review presents a detail survey of literature on immunomodulatory properties of *T. cordifolia*. The main aim of the survey is to reinforce scientific reconfirmation of its immunological activities and human studies.

**Keywords:** Immunomodulation, Immunomodulating agent, *Tinosporacordifolia*
Immunomodulatory activity of Tinosporacordifolia

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, amrta is a perennial, wild climber, succulent, shrub often attaining a great height and sending down long thread like aerial roots. The bark is showy, creamy white and grey, leaves are membranous and cordate. Flowers grow during the summer and fruits (stem of T. cordifolia stems, there was a significant increase in phagocytic activity during the winter. The viscous sap has a yellow colour, the total of count leucocytes. The aqueous extract of stem of T. cordifolia was found to increase phagocytosis in vivo.

Ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and its tincture are used for the treatment of general weakness, fever, dyspepsia, dysemacia, gonorrhea, secondary dysentery, goitre, children’s diseases, syphilis, urinary diseases, impotency, gout, viral, secondary dysentery, goitre, children’s diseases, syphilis, urinary diseases, impotency, gout, viral, and various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered 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 amelioration of symptoms from chemo or radiotherapy.

CHEMISTRY

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

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 infection in a variety of animal models. E. coli 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, Cordiol, Cordioside, Cordifolioside, A&B were identified as the active principle responsible for the anticomplement and anti-IgG effects.

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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].

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 that 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 standardised dose against bovine subclinical mastitis. Fractions and hot water extract exhibited significant 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, and also it was conclude that the T. cordifolia (stem) possesses antibacterial and polysaccharide with lowest sugar content showed immunomodulatory properties [10].

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<th>Types of chemicals</th>
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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-formylmonanoin, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tinocordiside and 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 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 dentritic 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 plasma progesterone concentration was significantly lowered in the treated group however there was no significant change in peripartum plasma total estrogens and PGFM levels due to Guduchi supplementation [16].

**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 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 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-IV (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-dihydroxydinedione (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter. Berberine inhibits Foxo1, which integrates...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during caloric restriction [30]. It also prevents the progression of type 2 diabetes mellitus and obesity [31].

**Diabetic retinopathy**

*T. cordifolia* plays role in prevention and management of diabetic retinopathy due to its antihyperglycemic, anti-angiogenic, anti-inflammatory, bearing host, thus showing its anti-tumor effect through anti-oxidant properties. It also prevents the destabilizing the membrane integrity of DL cells. *T. cordifolia* was shown effective in several other important symptoms of DR. Although diabetic rats tumor models including Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-TC (EAC) in mice [36]. It induces proliferation and myeloid diabetics, 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 [37], activates tumor-associated macrophages as a potential 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 experimential diabetic neuropathy. It has an adolsecent or 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**

Jagetta *et al.* have found that the guduchi killed the *HeLa* cells very effectively in vitro. In this study, the cells 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 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 were undertaken to study whether the tumor associated macrophages (TAM) of Daltons 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

**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.cordifolia* is known to be used traditionally for its anti-stress activity. The pure aqueous extract of the root was found to enhance verbal learning and logical memory. Both the alcoholic and aqueous extracts of *T. cordifolia* produced a decrease in learning scores in Hebb William maze and retention memory, indicating enhancement of learning and memory [41].

**Adaptogenic effects**

The aqueous extract not only reversed the effect of cisplatin on gastric emptying, but also normalized cisplatin-induced hypermotility. The plant was also found to normalize the phagocytic function of peritoneal macrophages after exposure of rats to either carbon tetrachloride or serum, thus it satisfied the definition of adaptogen [42].

**Antioxidant activity**

The antioxidant properties of *T. cordifolia* roots were studied by administering the aqueous extract of macrophages (TAM) of Daltons 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
addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was the most effective one [43]. In another study, guduchi showed a significant clinical and hematobiological effect when administered orally at a dose of 1 mg/kg given orally. The herb 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 [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-inflammatory activities in models of acute and subacute inflammation [46]. The water extract of the stem of neem-giloe [47] that grow in 5000 alloxan-induced diabetic rats [55].

Osteoprotective activity

A dose-dependent reduction in infant risk in size and in serum and heart lipid peroxide levels was observed with prior treatment with T. cordifolia in ischaemia-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 to rats (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 non-alcoholic-induced diabetic rats [55].

Anti-allergic activity

T. cordifolia is traditionally used for the treatment of asthma, and the juice is also employed for the treatment of asthma. In a clinical study, 100% relief was reported for non-steroidal anti-inflammatory agent [56]. The dried stem of T. cordifolia was reported significant anti-inflammatory effect in both acute and subacute models of inflammation. T. cordifolia was found to be more effective than 50% nasal discharge was reported in 69% from nasal
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 76 marked protective action against an 8 h restraint stress symptoms of allergic rhinitis and was well tolerated.777 induced ulcerization, the activity being comparable to [58]. The anti-allergic and bronchodilator properties of T. cordifolia have been found to be equal to that of diazepam [67]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-sensitized guinea pigs, capillary toxic influences of lead on haematological value and the permeability in mice and mast cell disruption in rats.61 results suggested that simultaneous supplementation of showed that it significantly decreased bronchospasm. T. cordifolia protects against lead intoxication [68].

induced by 5% histamine aerosol, decreased capillary permeability and reduced the number of disrupted mast cells.

Antipyrctic and anti-infective activity

The water-soluble fraction of 95% ethanolic extract of T. cordifolia plant has shown significant antipyrctic activity [59]. In another experimental study, antipyretic effects have been reported in the hexane- and chloroform-soluble portions of T. cordifolia stems [60]. Various studies show remarkable anti-inflammatory and antipyretic properties of T. cordifolia. Pre-treatment with T. cordifolia was shown to impart protection against mortality induced by intra-abdominal sepsis following caecal ligation in rats and significantly reduced mortality from induced by E. coli–induced peritonitis in mice [61].

Antifertility & aphrodisiac activity

Oral administration of 70% methanolic extract of T. cordifolia stem to male rats at a dose level of 100 mg/kg for 60 days did not cause body weight loss but decreased the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner [62].

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

Other effects

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

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 posses adaptogenic, antinflamatory, 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].

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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