Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity

P. ITTIYAVIRAH SIBI, AND T. RAHEES

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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, Tinosporacordilifolia

Advances in molecular biology have revolutionized depending on the requirement of the situation. Immunology and medicine. Initially the use of antibody 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 Tinosporacordifoloid. 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 "AcquiredImmunodeficiency 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.
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, amritti. A variety immunomodulatory activities [6]. Anarabinogalactan of family menispermae is a perennial, wild climber, poly saccharide, isolated from the dried stem of succulent, shrub often attaining a great height and 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 oral creamy white and grey, leaves are membranous and treatment of mice with water and ethanol extracts of chordate. Flowers grow during the summer and fruits T.cordifolia stems, there was a significant increase in during the winter. The viscus sap has a yellow colour, the total of count leucocytes. The aqueous extract of odourand nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various T.cordifolia was found to increase phagocytosis in vitro. The aqueous and ethanolic extract also induced an ailments throughout the centuries. Today the drug and tincture are used for the treatment of general weakness, extracts treatment cause significant reduction in fever, dyspepsia, dysentery, gonorrhea, secondary eosinophil count and improved hemoglobin in HIV syphilis, urinary diseases, impotency, gout, viral patients [5]. Sixty percent patients receiving TCE and hepatitis, skin diseases and anemia. In compound 20% on placebo reported decrease in the incidence of formulation Guduchi is clinically used to treat jaundice, various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered 146 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 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].

eq_{25}^{1}\text{count was observed from day 3 onwards. The}
\text{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 Tinospora cordifolia extract. The IL-8 concentration level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The immunomodulatory activity of the polysaccharides of T. cordifolia, and also it was conclude that the T. cordifolia (stem) possesses antibacterial and polysaccharide with lowest sugar content showed immunomodulatory properties [10].}

Sharma et al. (2012) isolated and characterised the highest activity and with highest sugar content showed. 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 T. cordifolia possesses immunomodulatory activity with an increase in

Table 1. Chemical composition of T. cordifolia plant

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<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
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<td>Alkaloids</td>
<td>Berberine</td>
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<td>Palmatine</td>
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<td>Glycosides</td>
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<td>Palmatoside C</td>
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<td>Palmatoside P</td>
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<td>Steroids</td>
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<td>Giloinsterol</td>
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<td>Diterpenoid lactones</td>
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<td>Sesquiterenoid</td>
<td>Tinocardifolin</td>
<td>Stem</td>
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<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
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<td>Heptacosanol</td>
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<td>Miscellaneous Compounds</td>
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<td>Cordifelon</td>
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<td></td>
<td>Gilonin</td>
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<td>Tinosporic acid</td>
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Neutrophil lymphocyte ratio was recorded in Guduchi supplemented cows in comparison to untreated cows. 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 upregulating 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 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-dihydroxybenzene (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 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, percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylmannoan, 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 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 cladrogene 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 that 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 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, percentage phagocytosis, neutrophil count along with increased

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insulin signaling with mitochondrial function. Inhibition of Fox01 can improve hepatic metabolism during diabetes in DL-bearing mice not only augment the basic function of 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**

diabetic retinopathy due to its the tumor growth and increase the life span of tumor antihyperglycemic, anti-angiogenic, anti-inflammatory, bearing host, thus showing its anti-tumor effect through and anti-oxidant properties. It also prevents the destabilizing the membrane integrity of DL cells. 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-diabetic rats, the aqueous extracts also reduced levels of brain phospholipids, and fatty acid levels. In another study in diabetic rat (2.5 and 5g/kg body weight for 6 weeks) and for their cell differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host (37), activates tumor-associated acts 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 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 phospholipids (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 an anti-neoplastic agent. Further investigation was undertaken to study whether the tumor associated macrophages (TAM) of Daltons lymphoma (DL) alloxan-induced diabetic rats. After 6 weeks, the level spontaneous transplantable T-cell lymphoma, can be 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**

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addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was found to have an anti-inflammatory effect, the drug was inferior to the most effective one [43]. In another study, guduchi exhibited a significant anti-inflammatory effect [48]. The aqueous extract of stem was shown to inhibit the lipid peroxidation in vitro, and it was found to be protective against acute and subacute models of inflammation.

Hepatoprotective effects

The hepatoprotective action was reported in one of the studies. An antioxidant effect of PPI from this plant was found to be similar to indomethacin and its mode of action. The hepatoprotective action was reported in one of the studies. A dose-dependent reduction in infant mortality and in serum and heart lipid peroxide levels was observed with PPI. The 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].

Osteoprotective activity

The stem extract of T. cordifolia that grow on neem-giloe [T. cordifolia] significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A dose of T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone loss in tibia was slower than that in controls. Serum induced arthritis. It also significantly inhibited antibody osteocalcin and cross-laps levels were significantly reduced. This study demonstrates that extract of T. cordifolia has the potential for being used as an antiosteoporotic agent [56].

Anti-allergic activity

The aqueous extract of T. cordifolia showed a significant anti-allergic effect in the cotton pellet granuloma and formalin induced arthritis model, its effect was comparable with indomethacin and its mode of action. The juice is also employed for the treatment of asthma, and the juice is also employed for the treatment of asthma. The juice is also employed for the treatment of asthma. The juice is also employed for the treatment of asthma. The juice is also employed for the treatment of asthma. The juice is also employed for the treatment of asthma. The juice is also employed for the treatment of asthma.
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 15%. Miers and C. asiatica Linn were observed to induce a 12.5% decrease. T. cordifolia significantly decreased all symptoms of allergic rhinitis and was well tolerated [58]. The anti-allergic and bronchodilator properties of T. cordifolia stem and leaves extract prevented the induction of bronchospasms in guinea pigs, capillaritis and the toxic influences of lead on haematological value and the permeability in mice and mast cell disruption in rats [59]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-sensitive of T. cordifolia stem and leaves extract prevented the induced bronchospasms in guinea pigs, capillaritis and the toxic influences of lead on haematological value and the permeability in mice and mast cell disruption in rats [59]. Results suggested that simultaneous supplementation of these showed that it significantly decreased bronchospasms. T. cordifolia protects against lead intoxication [60].

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, antineoplastic, 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 [61]. 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 [62].

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.

REFERENCES


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