Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity

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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, Tinosporacordifolia

Advances in molecular biology have revolutionized depending on the requirement of the situation. immunology and medicine. Initially the use of antibody as therapeutic agents was limited by their purity and resource even by the most intransigent clinicians of heterogeneity. Immunotherapy derives from the advanced countries. Plant extracts have been widely observed from the 19th century, that cancer investigated for their possible immunomodulatory sometimes regressed after acute bacterial infections, that properties, Tinospora cordifolia, an indispensable is, there may be no specific immunostimulant effect. medicinal plant, has been used for the treatment of The rapidly expanding discipline of immunology various diseases and has been recommended for contributes to diagnosis, therapy and prevention of improving the immune system. There is great interest in human diseases in many ways. The role of development of new drugs from traditionally used immunocompetents in prevention of malignancy is medicinal plants like Tinosporacordifolia. Ayurveda currently of great interest in experimental science as refers to Tinospora cordifolia as 'Amruth' or the 'Nectar well as clinical medicine. Interest in the immune of Immortality'. The term 'Amruth' is attributed to this response has been stimulated by the alarming increase drug in recognition of its ability to impartyouthfulness, 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” in 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, amrita. It belongs to family menispermaceae as a perennial, wild climber, succulent, shrub often attaining a great height and sending down long thread like aerial roots. The bark is creamy white and grey, leaves are membranous and chordeate. Flowers grow during the summer and fruits. T. cordifolia stems, there was a significant increase in during the winter. The viscous sap has a yellow colour, the total of count leucocytes. The aqueous extract of guduchi contains a nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and tincture are used for the treatment of general weakness, fever, dyspepsia, dysentery, gonorrhea, secondary syphilis, urinary diseases, impotency, gout, viral hepatitis, skin diseases and anemia. In compound 20% on placebo reported decrease in the incidence of symptoms associated with the disease. All 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 sepsis 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. 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, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticomplement and therapeutically claims of T. cordifolia: a review “on T. cordifolia”

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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 the immunomodulatory activity of the polysaccharides of T. cordifolia, and also it was conclude that the polysaccharide with lowest sugar content showed highest activity and with highest sugar content showed lowest activity [9]. Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. It was found that ethyl acetate, water fractions and hot water extract exhibited significant immunomodulatory activity with an increase in

| Table 1. Chemical composition of T. cordifolia plant |
|-----------------|------------------|----------------|
| Types of chemicals | Active principle | Parts in which present |
| Alkaloids | Berberine | Stem |
| | Palmatine | Root |
| | Magnoflorine | Stem |
| | Tinosporine | Root |
| | Choline | Stem |
| | Isocolumbin | Root |
| | Tetrabutyldipalmitate | Stem |
| Glycosides | Tincordiside | Stem |
| | Cordaside | Stem |
| | Syringin | Stem |
| | Cordifolioside A | Stem |
| | Cordifolioside B | Stem |
| | Cordifolioside C | Stem |
| | Cordifolioside D | Stem |
| | Cordifolioside E | Stem |
| | Palmatoside C | Stem |
| | Palmatoside P | Stem |
| Steroids | Beta-sitosterol | Aerial part |
| | gama-sitosterol | Stem |
| | 20B-ecdysone | Stem |
| | Ecdysone | Stem |
| | Ecdysterone | Stem |
| | Makisterone A | Stem |
| | Gilonolsterol | Stem |
| Diterpenoid lactones | Furanolactone | Whole plant |
| | Celondane derivatives | Whole plant |
| | Tinosporon | Whole plant |
| | Tinosporides | Whole plant |
| | Jateorine | Whole plant |
| | Columbin | Whole plant |
| Sesquiterenoid | Tincordifolin | Stem |
| Aliphatic Compounds | Octacosanol | Whole plant |
| | Heptacosanol | Whole plant |
| Miscellaneous Compounds | Tinosporidine | Root |
| | Cordifol | Root |
| | Cordifelone | Root |
| | Gilonin | Root |
| | Tinosporic acid | Root |
percentage phagocytosis. Chromatographic
 purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylmannonain, 11-
hydroxymustakone, N-methyl-2-pyrrrolidone, cordifolioside A , magnoflorine , tinocordiside , 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 an methanol-soluble extract of the stems of Tinospora cordifolia. The structures of the new compounds were determined on the basis of spectroscopic data, 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 denticritic cells [13]. Tinospora cordifolia had shown a significant level of macrophages activation, 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

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 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 insulinitropic 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 boast the effects of metformin and 2,4 - dihydroxiphenylalanine (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of lymphocyte, neutrophil count along with increased the latter. Berberine inhibits Foxo1, which integrates
insulin signaling with mitochondrial function. Inhibition of FoxO1 can improve hepatic metabolism during diabetes in diabetic rats [30].

**Diabetic retinopathy**

*T. cordifolia* plays a role in prevention and management of diabetic retinopathy due to its antioxidant properties, anti-hyperglycemic, anti-angiogenic, anti-inflammatory properties. It also prevents the progression of cataract and vascular changes, the aqueous extract of *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-drug (EAC) in mice [36]. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a comparable to untreated diabetic rats. *T. cordifolia* thus acts as a potential therapeutic agent for prevention of vascular complications of diabetes.

**Diabetic neuropathy**

*Tinospora cordifolia* prevents the hyperalgesia in experimental diabetic neuropathy. It has an aldose reductase inhibitory activity in vitro which may contribute to the beneficial effects [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 hypolipidemia, and as *T. cordifolia* has been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity in vitro. 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 rat (2.5 and 5g/kg body weight for 6 weeks), the hypolipidemic activity of *Tinospora cordifolia* 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 behavioural 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].

**Antineoplastic effects**

Jaegla 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) were induced diabetic rats. After 6 weeks, the level of plasma barbituric acid reactive substances, 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 administered to the rats, the drug was inferior to the most effective one [43]. In another study, guduchi-phenylbutazone [48]. The aqueous extract of stem was shown to inhibit the lipid peroxidation and reported to exert a significant anti-inflammatory effect in vitro. Earlier studies in both cotton pellet-induced granuloma (1, 250 and 500 mg/kg) and dry stem crude extract (DSCE) showed a significant inhibition of formation of TBARS thus highlighting the anti-inflammatory action of T. cordifolia.

Hepatoprotective effects

The hepatoprotective action was reported in one of the antioxidant effect PPI from this plant was examined the experiment in which goats treated with T. cordifolia against reactive oxygen and nitrogen species have shown significant clinical and hematological (ROS/RNS), generated by PPI during the occurrence of lead nitrate induced liver damage in photodermatitis. Selective inhibitors of ROS-like Swiss Albino mice [51]. T. cordifolia exhibited time in the hay mannanol, super oxide dismutase (SOD), Sodiumazide, dependent hepatoprotection as reflected in both the 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 CCL4-induced indicating generation of oxygen. Thus the action of PPI on hepatic damage. Extract effectively control the ALT, may be against oxidative damage through type 1 and ALP and total bilirubin levels and also, type 2 photosensitization mechanism. T. cordifolia histopathological studies proved the hepatoprotective activity of extract [52].

Cardioprotective activity

A dose-dependent reduction in infarct size and in serum and heart lipid peroxides 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. cordifoliaroots (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 neem-giloe T. cordifolia that grow on alloxan-induced diabetic rats [55].

Osteoprotective activity

501 Rats treated with T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone turnover was observed in a model of adjuvant-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 osteoprotective agent [56].

Anti-allergic activity

T. cordifolia is traditionally used for the treatment of asthma, and the juice is also employed for the treatment of chronic coughs as well as asthma, and the juice is also employed for the treatment of asthma. The dried stem of T. cordifolia was reported from sneezing in 83% of the patients on treatment with T. cordifolia. Similarly, the relief from acute and subacute models of inflammation. T. cordifolia was found to be more effective than 61% obstructions 61% and from nasal 71%.
placebo group, there was relief from sneezing only in gluconeogenic enzymes activity in diabetic rat kidney patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritus, in 75%. Miers and C. asiatica Linn were observed to induce a 12%. Thus, T. cordifolia significantly decreased all marked protective action against an 8 h restraint stress symptoms of allergic rhinitis and was well tolerated. The activity being comparable to [58]. The anti-allergic and bronchodilator properties of that of diazepam [67]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-sensitivity of T. cordifolia stem and leaves extract prevented the induced bronchospasm in guinea pigs, capillaries [80] toxic influences of lead on haematological value and the permeability in mice and mast cell disruption in rats. 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.

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, antiinflammatory, anti-neoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimarial, 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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