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REVIEW ARTICLE

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, hypolipidemico, 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 is 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 investigat ed for their possible immunomodulatory properties, Tinospora cordifolia, an indispensable is, there may be no specific immunostimulant effect. medicinal plant, has been used for the treatment of 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 is 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 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.

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Immunomodulatory activity of Tinosporacordifolia

Fig 1. Tinospora Cordifolia (Courtesy: KottakkalAryavaidyashala)

Panchabhai et al done a study “Validation of therapeutic claims of Tinospora cordifolia: a review “on 2008 [1]. As Tinospora cordifolia is a plant of high pharmacological potential, day by day new studies are conducted and novel therapeutic activities are revealed. Recently, isolation and characterisation of phytoconstituents responsible for the activities are done. So, there is a scope for a new study. Tinospora cordifolia is a plant of high pharmacological potential, day by day new studies are conducted and novel therapeutic activities are revealed. Recently, isolation and characterisation of phytoconstituents responsible for the activities are done. So there is a scope for a new study.

The current survey is aimed to include the updated informations available with special emphasis on immunomodulatory activity, as its name suggests “amruth”.

DESCRIPTION AND HISTORY

T.cordifolia (Fig 1); common name guduchi, amrita of family menispermaceae is a perennial, wild climber, polyasacharide, isolated from the dried stem of succulent, shrub often attaining a great height and showed polyclonal mitogenicactivity 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 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 odourand nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and increase in antibody production in vivo. T.cordifolia tincture are used for the treatment of general weakness, extracts treatment cause significant reduction in fever, dyspepsia, dysentery,gonorrhoea,secondary eosinophil count and improved hemoglobin in HIV syphilis, urinary diseases, impotency,gout,viral patients [5]. Sixty percent patients receiving TCE and 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 treatment had resulted in significant amelioration of symptoms from chemo or radiotherapy.

CHEMISTRY

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

PHARMACOLOGICAL ACTIONS

T.cordifolia benefits the immune system in variety of ways. The alcoholic and aqueous extract of this plant have been tested successfully for immunomodulatory activity [5]. Pretreatment with T.cordifolia lead to protection against mortality induced by intra-abdominal sepsis following caecal ligation in rats. It also significantly reduced mortality from E. coli induced peritonitis in mice [6]. In a clinical study, it was afforded protection in cholestatic patients against E. coli infection. As T.cordifolia is 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.
The polysaccharide-enriched fraction from this plant is found to be very effective in reducing the metastatic potential of B16f-10 melanoma cells. Sharma et al. (2012) evaluated the immunomodulatory activity of three polysaccharide-enriched immunomodulatory fractions from Tinospora cordifolia using the polymorphonuclear leukocyte function test. The results confirmed the immunomodulatory activity of the polysaccharides of T. cordifolia, and also it was concluded that the polysaccharide with lowest sugar content showed highest activity and with highest sugar content showed lowest activity. Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract against bovine subclinical mastitis. Intramammary infusion of hydro-methanolic extract of T. cordifolia treatment, significantly caused the reduction in cell count (<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 (<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.

Sharma et al (2012) isolated and characterised the immunomodulatory active compounds of Tinospora cordifolia. It was found that ethyl acetate, water fractions and hot water extract exhibited significant immunomodulatory activity with an increase in

Table 1. Chemical composition of T. cordifolia plant

<table>
<thead>
<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Berberine, Palmatine, Magnoflorine, Tinosporine, Choline, Isocolumbin, Tetrabaydropalmatine, Magnoflorine</td>
<td>Stem, Root</td>
</tr>
<tr>
<td>Glycosides</td>
<td>Tinosponderide, Cordiside, Syringin, Cordifolioside A, Cordifolioside B, Cordifolioside C, Cordifolioside D, Cordifolioside E, Palmatoside C, Palmatoside P</td>
<td>Stem</td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol, gama-sitosterol, 20B-ecdysone, Ecdysone, Ecdysterone, Makisterone A, Giloistolerol</td>
<td>Aerial part, Stem</td>
</tr>
<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone, Celondane derivatives, Tinosporon, Tinosporides, Jateorine, Columhin</td>
<td>Whole plant</td>
</tr>
<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolio</td>
<td>Stem</td>
</tr>
<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol, Heptacosanol</td>
<td>Whole plant</td>
</tr>
<tr>
<td>Miscellaneous Compounds</td>
<td>Tinospiridine, Cordifol, Cordifelone, Cordifelone, Gilonin, Tinosporic acid</td>
<td>Root</td>
</tr>
</tbody>
</table>
percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylammonium, 11-hydroxymustakone, N-methyl-2-pyrrolidine, cordifolioside A, magnoflorine, tinocordione 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 the isolates were evaluated for their in vitro immunomodulatory activity using mouse bone marrow-derived dientric cells [13]. Tinospora cordifolia had shown a significant level of macrophages activation, 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 hyperglycemic 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, lymphocyte, neutrophil count along with increased progesterone concentration was signif...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during diabetes in DL-bearing mice not only augment the basic function of Foxo1 in the tumor growth and increase the life span of tumor-bearing host. Thus, showing its anti-tumor effect through apoptosis and antioxidant properties. It also prevents the destabilizing the membrane integrity of DL cells. The T.cordifolia extract was shown effective in several other important reactions of DR. Although diabetic rats were administered Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-treated (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host activates tumor-associated macrophages-derived dendritic cells, is effective against various cancers, killing the cancer cells very effectively in vitro, inhibits skin carcinogenesis in mice and inhibits experimental metastasis.

Diabetic retinopathy

T. cordifolia plays role in prevention and management of 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 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 reactions of DR. Although diabetic rats were administered Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-treated (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host activates tumor-associated macrophages, acts as a potential therapeutic agent for prevention of the vascular complications of diabetes. Cognitive effects

Tinospora cordifolia prevents the hyperglycemia in experiential diabetic neuropathy. It has an adaptive reductase inhibitory activity in vitro which may contribute to the beneficial 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 outcome with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing.

Hypolipidemic effects

Diabetics are often associated with hypolipidemia, and as T.cordifolia 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 diabetic rats, the aqueous extracts also reduced levels of brain lipids.

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. 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 were undertaken to study whether the tumor associated macrophages (TAM)of Daltons lymphoma (DL) alloxa-induced diabetic rats. After 6 weeks, the level spontaneous transplanted 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 the level of plasma barbituric acid reactive substances, ceruloplasmin and alpha tocopherol were reduced. In another study in diabetic rats, the aqueous extract of Tinospora cordifolia was shown effective in several other important reactions of DR. Although diabetic rats were administered Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-treated (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host activates tumor-associated macrophages-derived dendritic cells, is effective against various cancers, killing the cancer cells very effectively in vitro, inhibits skin carcinogenesis in mice and inhibits experimental metastasis.

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.

Antioxidant activity

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. The antioxidant properties of T. cordifolia roots were studied by administering the aqueous extract of macrophages (TAM)of Daltons lymphoma (DL) alloxan-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.

Cognitive effects

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In addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was less active in acute inflammation, although it was significant. In another study, guduchi, a plant with anti-inflammatory properties, was used. The aqueous extract of stem was shown to inhibit the lipid peroxidation 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 a significant anti-inflammatory effect in both acute and subacute models of inflammation. Tinospora cordifolia has been found to exert anti-inflammatory activity as well. The oral administration of T. cordifolia (10 mg/kg body weight) showed a significant improvement in CCL-induced hepatitis [49]. The hepatoprotective action was reported in one of the studies. Anti-inflammatory action in models of acute and subacute inflammation. The dried stem of T. cordifolia has been found to exert anti-inflammatory properties. The water extract of the stem of T. cordifolia 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].

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

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 actions in models of acute and subacute inflammation and acute inflammation 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].

Azadirachta indica (neem) significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A study reported that rats treated with T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone loss in tibia was slower than that in controls. Serum osteocalcin and cross-laps levels were significantly reduced. This study demonstrates that extract of T. cordifolia has the potential for being used as an anti-osteoporotic agent [56].

Anti-allergic activity

T. cordifolia is traditionally used for asthma and its mode of action appears to resemble that of non-steroidal anti-inflammatory drugs. In a clinical study, 100% relief in asthma, and the juice is also employed for the treatment of allergic activity. The dried stem of T. cordifolia was reported to reduce 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 16% obstructions 61% and from nasal cilia. In order to explore the possibility of using G1-4A/pp1 to modulate radiation-induced immune suppression, the hepatoprotective effects of T. cordifolia was also examined in vitro. The oral administration of T. cordifolia (10 mg/kg body weight) showed a significant increase in CCL-induced hepatitis [49].
placebo group, there was relief from sneezing only in Tinospora cordifolia extract in human immune deficiency virus positive 21% patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritis, in 19.5%. 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 [58]. The anti-allergic and bronchodilator properties of T. cordifolia was reported to be comparable to that of diazepam [67]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-sensitized mice [59] of T. cordifolia stem and leaves extract prevented the induced bronchospasm in guinea pigs, cpiplary 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 5% histamine aerosol, decreased capillary permeability and reduced the number of disrupted mast cells [62].

**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, 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 not been validated by a remarkable body of modern evidence suggesting that this drug has immense potential in modern pharma-therapeutics.

**REFERENCES**


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