**Review Article**

**Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity**

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Received June 25, 2012; Revised October 2, 2012; Accepted November 12, 2012

This paper is available online at [http://ijpt.tums.ac.ir](http://ijpt.tums.ac.ir)

**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 many 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 impart youthfulness, in a novel epidemic form of immune deficiency, vitality and longevity. Immunomodulation can be "Acquired ImmunoDeficiency Syndrome" (AIDS). determined by the capacity of the compounds to Immunomodulation relates to potentiation or influence the cytokine production, mitogenicity, suppression of the immune responses of the host, stimulation and activation of immune effector cells.
Immunomodulatory activity of *Tinospora cordifolia*

**Fig 1. Tinospora Cordifolia (Courtesy: Kottakkal Ayurvedic Hospital)**

93 as a powerful emetic and is used for bowel obstruction.
94 *T. cordifolia* is used as an antidote for snake bite and
95 used in malaria, environmental illness, asthma, upper
96 respiratory tract infection, UTI, general debility and
97 amelioration of symptoms from chemo or radiotherapy.

**CHEMISTRY**

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

**PHARMACOLOGICAL ACTIONS**

107 **Immunological effects**

109 *T. cordifolia* benefits the immune system in variety
110 of ways. The alcoholic and aqueous extract of this plant
111 have been tested successfully for immunomodulatory
112 activity [5]. Pretreatment with *T. cordifolia* lead to
113 protection against mortality induced by intra-abdominal
114 sepsis following caecal ligation in rats. It also
115 significantly reduced mortality from *E. coli* induced
116 peritonitis in mice [6]. In a clinical study, it was
117 afforded protection in cholestatic patients against *E. coli*
118 infection. Those activities were not due to its
119 antibacterial activity as shown by the negative in vitro
120 antibacterial activity of the plant extract. It was reported
121 that treatment in rats had resulted in significant
122 leucocytosis and predominant neutropenia. It has been
123 also observed that it stimulated the macrophages as
124 evidenced by an increase in the number and percentage
125 phagocytosis of *S. aureus* by peritoneal macrophages in
126 rats. The phagocytic and intercellular killing capacity of
127 polymorphs in rats, tested at 3.5 hours after
128 *E. coli* infection were significant. Syringin, Cordiol,
129 Cordioside, Cordifoliosides A&B were identified as the
130 active principle responsible for the anticomplement and
131 immunomodulatory activities [6]. Anarabinogalactan
132 of *T. cordifolia* (Fig 1); common name *guduchi, amrita*;
133 as a powerful emetic and is used for bowel obstruction.
134 *T. cordifolia* is used as an antidote for snake bite and
135 used in malaria, environmental illness, asthma, upper
136 respiratory tract infection, UTI, general debility and
137 amelioration of symptoms from chemo or radiotherapy.

**DESCRIPTION AND HISTORY**

139 *T. cordifolia* (Fig 1); common name *guduchi, amrita*;
140 family *menispermaceae* is a perennial, wild climber, 141
142 succulent shrub often attaining a great height and 143
144 *T. cordifolia* showed polyclonal mitogenic activity
145 sending down long thread like aerial roots. The bark is 146
147 against beta cell [4]. It was reported that following oral
148 creamy white and grey, leaves are membranous and 149
150 treatment of mice with water and ethanol extracts of
151 chordeate. Flowers grow during the summer and fruits 152
153 *T. cordifolia* stems, there was a significant increase in
154 during the winter. The viscous sap has a yellow colour, 155
156 the total of count leucocytes. The aqueous extract of
157 gum and nauseating bitter [2]. It has been used in
158 ayurvedic preparations for the treatment of various 159
160 The aqueous and ethanolic extract also induced an
161 complaints throughout the centuries. Today the drug and 162
163 increase in antibody production in vivo. *T. cordifolia*
164 tincture are used for the treatment of general weakness, 165
166 extracts treatment cause significant reduction in
167 fever, dyspepsia, dysentery, gonorrhea, secondary 168
169 syphilis, urinary diseases, impotency, gout, viral 160
169 patients [5]. Sixty percent patients receiving TCE and
169 hepatits, skin diseases and anemia. In compound 165
169 various symptoms associated with the disease. All
169 rheumatoid arthritis and diabetes. The root is considered 166
169 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 reducing the metastatic potential of B16F-10 melanoma [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 Intramammary infusion of hydro-methanolic extract of 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 standardized dose against bovine subclinical mastitis. Fractions and hot water extract exhibited significant

Table 1. Chemical composition of T. cordifolia

<table>
<thead>
<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
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<tbody>
<tr>
<td>Alkaloids</td>
<td>Berberine</td>
<td>Stem</td>
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<td></td>
<td>Palmatine</td>
<td>Root</td>
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<td></td>
<td>Magnoflorine</td>
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<td></td>
<td>Tinosporine</td>
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<td></td>
<td>Choline</td>
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<td>Isocolumbin</td>
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<td></td>
<td>Tetrahydropalmatine</td>
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<td></td>
<td>Magnoflorine</td>
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<tr>
<td>Glycosides</td>
<td>Tinocordiside</td>
<td>Stem</td>
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<td></td>
<td>Cordiside</td>
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<td></td>
<td>Syringin</td>
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<td></td>
<td>Cordifolioside A</td>
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<td></td>
<td>Cordifolioside B</td>
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<td>Cordifolioside C</td>
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<td>Cordifolioside E</td>
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<td></td>
<td>Palmatosis C</td>
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<td></td>
<td>Palmatosis P</td>
<td></td>
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<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
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<td></td>
<td>gama-sitosterol</td>
<td>Stem</td>
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<td>20β-ecdysone</td>
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<td></td>
<td>Ecdysone</td>
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<td></td>
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<td>Makisterone A</td>
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<td></td>
<td>Giloinsterol</td>
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<td>Diterpenoid lactones</td>
<td>Furanolactone</td>
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<td>Celondane derivatives</td>
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<td>Tinosporon</td>
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<td>Jateorine</td>
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<td>Columbin</td>
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<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
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<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
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<td></td>
<td>Heptacosanol</td>
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<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporidine</td>
<td>Root</td>
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<td></td>
<td>Cordifol</td>
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<td></td>
<td>Cordifelone</td>
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<td></td>
<td>Gilonin</td>
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<td>Tinosporic acid</td>
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Immunomodulatory activity of Tinosporacordifolia

percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylammonian, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tincordicline, 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 spleenocytes 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 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, 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].

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. cordifolialdecreases 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 glycosylisis [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcomes insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells [26]. Berberine might exert its insulinotropic effect in isolated rat islets by up-regulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge [27]. Berberine also seems to inhibit human dipeptidyl peptidase-4 (DPP IV), as well as the pro-diabetic target human protein tyrosine phosphatase 1B (h-PTP 1B), which explain at least some of its anti-hyperglycemic activities. Berberine suppresses intestinal disaccharides with beneficial metabolic effects in diabetic states [28].

A recent comprehensive metabolomics method, applied to type 2 diabetes, suggested administration of berberine down-regulates the high level of free fatty acids which are known to be toxic to the pancreas and cause insulin resistance. These results suggest berberine might play a pivotal role in the treatment of type 2 diabetes [29]. Berberine has been shown to boost the effects of metformin and 2,4 -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 into the reproductive process of crossbred cows by its periparturient 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...
insulin signaling with mitochondrial function. Inhibition of FoxO1 can improve hepatic metabolism during diabetes in the liver of mice not only augment the basic function of insulin resistance and the metabolic syndrome [30].

Diabetic retinopathy

*T. cordifolia* plays a role in the prevention and management of diabetic retinopathy due to its anti-hyperglycemic, anti-angiogenic, anti-inflammatory and anti-oxidant properties. It also prevents the 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-treated controls. The results of the investigation also indicate that *T. cordifolia* is also effective in reducing the levels of plasma barbituric acid reactive substances, ceruloplasmin and alpha tocopherol were reduced in diabetic rats, but they achieve significant levels as compared to untreated diabetic rats. *T. cordifolia* has been shown to be a potential therapeutic agent for prevention of the 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 a 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 the root was administered to alloxan induced diabetic rat (2.5 and 5g/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. In another study in diabetic rats, the aqueous extracts also reduced levels of brain lipids [33].

Antineoplastic effects

Jaegia 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) and 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. 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) and 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. In
addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 mg/kg was tested for subacute inflammation, and 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 on superoxide and hydroxyl radical in vitro. Earlier studies showed that dry stem crude extract (DSCE) contains anti-oxidant and formalin-induced arthritis. The polygonal beta cell mitogen; G1-4A, DSCE as well as 69 (1 mg/kg given orally) rat models.

12. G1-4A also enhance immune response in mice [44]. In order to explore the possibility of using G1-4A/pp1 to modulate radiation-induced immune suppression, the experiment was performed in mice [47]. The hepatoprotective action was reported in one of the antioxidant effect PPI from of this plant was examined [47]. The experiment in which goats treated with T. cordifolia against reactive oxygen and nitrogen species have shown significant clinical and hematobiological effects [46]. In vitro studies have shown significant inhibition of formation of TBARS thus conducted in Albino Wistar rats against CCl4-induced indicating generation of oxygen. Thus the action of PPI against hepatic damage. Extract effectively control the ALT, may be against oxidative damage through type 1 and type 2 photosensitization mechanism. T. cordifolia histopathological studies proved the hepatoprotective activity of extract [52].

13. 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].

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

15. 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 [46]. The water extract of the stem of neem-giloe [T. cordifolia] that grow on allophan-induced diabetic rats [55].

16. Azadirachta indica (neem), significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A502 Rats treated with T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone of inflammation 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 antigen in 72 hours. Oral administration of T. cordifolia showed significant anti-inflammatory activity [52]. In another study [58], antosteoporotic agent [56].

17. Osteoprotective activity

18. Anti-allergic activity

19. T. cordifolia is traditionally used for the treatment of asthma, and the juice is also employed for the treatment of chronic coughs [57]. In a clinical study, 100% relief of allergic activity. The dried stem of T. cordifolia was reported from sneezing in 83% of the patients on anterior and subacute models of inflammation. T. cordifolia was found to be more effective than 616 obstructions 61% and from nasal discharge in 69%; from nasal pruritis, in 71%. In
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 75%. Miers and C. asiatica Linn were observed to induce a 12% decrease in the T. cordifolia significantly decreased all marked protective action against an 8 h restraint stress symptoms of allergic rhinitis and was well tolerated by induced ulceration, the activity being comparable to [58]. The anti-allergic and bronchodilator properties of T. cordifolia stem and leaves extract prevented the induced bronchospasm in guinea pigs, capillary protective effects in mice and mast cell disruption in rats. Results suggested that simultaneous supplementation of T. cordifolia showed that it significantly decreased bronchospasm [62]. 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 antioxidant, antinflammatory, anti-neoplastic, anti-hemolytic, 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 malignant 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.

REFERENCES


Immunomodulatory activity of Tinospora cordifolia


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