Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity

P. ITTIYAVIRAH SIBI*, AND T. RAHEES

For author affiliations, see end of text.

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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-inflammatoire, immunomodulator, 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 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 Tinospora cordifolia. 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 in recognition of its ability to impart youthfulness, in a novel epicdemic 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.
DESCRIPTION AND HISTORY

T. cordifolia (Fig 1); common name guduchi, amritha. it 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.

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 peritonitis 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 amruth.

Panchabhai et al done a study “Validation of therapeutic claims of Tinospora cordifolia: a review”. 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”.

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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. 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 evaluated 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 (p < 0.05) on day 15 of the treatment period, however, reduction in total bacterial count was observed from day 3 onwards. The phagocytic activity and lysosomal enzyme content of milk polymorphonuclear cells enhanced in the diseased cows treated with the T.cordifolia extract. The IL-8 level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The results suggest that the hydro-methanolic extract of T.cordifolia, and also it was conclude that the T.cordifolia (stem) possesses antibacterial and immunomodulatory properties [10].

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 biological activity of the Tinospora cordifolia extract at.

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, Palmitine, Magnoflorine, Tinosporine, Choline, Isocolumbin, Tetrabryopalmitine, Magnoflorine</td>
<td>Stem, Root</td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol, gama-sitosterol, 20B-ecdysone, Ecdysone, Ecdysterone, Makisterone A, Gitolinsterol</td>
<td>Aerial part, Stem</td>
</tr>
<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone, Celondane derivatives, Tinosporon, Tinosporides, Jateorine, Columbin</td>
<td>Whole plant</td>
</tr>
<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolin</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>Tinosporine, Cordiol, Cordifelone, Cordifolone, Gilonin, Tinosporic acid</td>
<td>Root</td>
</tr>
</tbody>
</table>

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percentage phagocytosis. Chromatographic purification of these fraction led to the isolation of seven immunomodulatory active compounds belonging to different classes such as N-formylmonanion, 11-hydroxymustakone, N-methyl-2-pyrrolidone, 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 range 5-10 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 haemagglutinatory 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 another 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, 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 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 levels due to Guduchi supplementation [16].

**Antidiabetic effects**

The stem of *T. cordifolia* has long been used in Indian Ayurvedic Medicine for the treatment of type 2 diabetes 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, a alkaloid obtained from the stem of *T. cordifolia* has been tested and used successfully in experimental and human diabetes mellitus. Berberine has been shown to lower elevated blood glucose as effectively as metformin [21]. The mechanisms of action include inhibition of aldose reductase [22], inducing glycolysis [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcomes insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells [26]. Berberine might exert its insulinotropic effect in isolated rat islets by up-regulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge [27].

Berberine also seems to inhibit human dipeptidyl peptidase-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 disaccharidases 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'-dihydroxydiphenyldione (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of the latter. Berberine inhibits Foxo1, which integrates...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during 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

Adaptogenic effects

Antineoplastic effects

Tinospora cordifolia

Cognitive effects

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 and anti-oxidant properties. It also prevents 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- EAC in mice [36]. It induces proliferation and myeloid diabetic rats, but they achieve significant levels as differentiation of bone marrow precursor cells in a compared to untreated diabetic rats. T. cordifolia thus tumor-bearing host [37], activates tumor-associated 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 retinopathy

Diabetic neuropathy

Hypolipidemic effects

Antioxidant activity

T. cordifolia was shown to have hypoglycemic reduces the inhibitory activity in vitro which may contribute to the beneficial effects [31].

Diabetic foot ulcer

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 diabetic rats, the aqueous extracts also reduced levels of brain lipids [33].

34 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) or 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

32 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 outcome with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing [32].

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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 less effective than the subacute inflammation, although in the most effective one [43]. In another study, guduchi [46] and phenylbutazone [48]. The aqueous extract of stem was shown to inhibit the lipid peroxidation reported to exert a significant anti-inflammatory effect. The aqueous extract was shown to significantly inhibit the anti-inflammatory effect of its own as well as potentiation of morphine in the carrageen-induced arthritis model. It also significantly inhibited antibody formation by the hemorrhagic and hyperalgesic activity of the experiment in which goats treated with T. cordifolia reduced. This study demonstrates that extract of T. cordifolia may be against oxidative damage through type I and ALP and total bilirubin levels and also, type II photosensitization mechanism. T. cordifolia histopathological studies proved the hepatoprotective activity of extract [52].

Hepatoprotective effects

The hepatoprotective action was reported in one of the studies conducted in Albino Wistar rats against CC 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].

Cardioprotective activity

A dose-dependent reduction in infarct size and in serum and heart lipid peroxide levels was observed with a 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 extract of T. cordifolia showed a significant effect on 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. The water extract of the stem of neem-giloe [T. cordifolia] that grow on cotton pellets was observed with oxygen radicals. The extract was shown to significantly inhibit the anti-inflammatory effect of its own as well as potentiation of morphine in the carrageen-induced arthritis model. It also significantly inhibited antibody formation by the hemorrhagic and hyperalgesic activity of the experiment in which goats treated with T. cordifolia reduced. This study demonstrates that extract of T. cordifolia may be against oxidative damage through type I and ALP and total bilirubin levels and also, type II photosensitization mechanism. T. cordifolia histopathological studies proved the hepatoprotective activity of extract [52].

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Tinospora cordifolia: a review.

The immunologically active
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Sainis K
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The ethanol extracts of the roots of
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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

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, anti-neoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunologic properties. There are limited human studies to support these use. T. cordifolia can also be used as an adjuvant drug in the treatment of hyper-reactive malarious splenomegaly [69]. Tinospora cordifolia appears to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome in patients with malignant obstructive jaundice [70].

Toxicology
The ayurvedic literature reports that T. cordifolia can cause constipation, if taken regularly in high doses. It has no side effect and toxicity. When T. cordifolia extract was administered to rabbit up to the highest oral doses of 1.6 g/kg, there were no predictable adverse drug effects.

Conclusion
The pharmacological actions attributed to T. cordifolia in ayurvedic texts and folk medicine have been validated by a remarkable body of modern evidence suggesting that this drug has immense potential in modern pharmacotherapeutics.

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Immunomodulatory activity of *Tinosporacordifolia*

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