**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 clinician of heterogeneity. Immunotherapy derives from the advanced countries. Plant extracts have been widely observation from the 19th century, that cancer investigators 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 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 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.
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

Immunomodulatory activity of Tinosporacordifolia

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 belongs to different classes such as alkaloids, diterpenoids, lactones, glycosides, steroids, sesquerpenoids, 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, Cordifolsiosides A&B were identified as the active principle responsible for the anticomplement and antiphagocytosis activity of formulation Guduchi is clinically used to treat jaundice, various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered

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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 the lowest sugar content showed the highest activity and with the highest sugar content showed the lowest activity.

Mukherjee et al. evaluated the biological activity of the Tinospora cordifolia extract at standardized dose 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 (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 the 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 phagocytic activity and lysosomal enzyme content of immunomodulatory activity of three polysaccharide-enriched milk polymorphonuclear cells enhanced in the diseased enriched immunomodulatory fractions from Tinospora cordifolia extract. The IL-8 level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The results confirmed the highest activity and with highest sugar content showed Sharma et al. (2012) isolated and characterised the lowest activity. Mukherjee et al. evaluated the immunomodulatory active compounds of Tinospora cordifolia extract.

### 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, Tetrahydropalmatine, Magnoflorine</td>
<td>Stem, Root</td>
</tr>
<tr>
<td>Glycosides</td>
<td>Tincordiside, 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, Giloinsterol</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>Tinosporidine, Cordifol, Cordifelone, Cordifelone, Gilolin, Tinosporic acid</td>
<td>Root</td>
</tr>
</tbody>
</table>

immunosuppression [7]. The polysaccharide-enriched T. cordifolia treatment, significantly caused the fraction from this plant is found to be very effective in reducing in cell count (p < 0.05) on day 15 of the reducing the metastatic potential of B16f-10 melanoma treatment period, however, reduction in total bacterial cells [8].

The count was observed from day 3 onwards. The Sharma et al. (2012) evaluated the phagocytic activity and lysosomal enzyme content of immunomodulatory activity of three polysaccharide-enriched milk polymorphonuclear cells enhanced in the diseased enriched immunomodulatory fractions from Tinospora cordifolia extract. The IL-8 level in milk serum also increased significantly (p < 0.05) in diseased cows treated with the extract. The results confirmed the highest activity and with highest sugar content showed Sharma et al. (2012) isolated and characterised the lowest activity. Mukherjee et al. evaluated the immunomodulatory active compounds of Tinospora cordifolia extract. It was found that ethyl acetate, water standardized dose against bovine subclinical mastitis. Fractions and hot water extract exhibited significant Intramammary infusion of hydro-methanolic extract of immunomodulatory activity with an increase in

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immunomodulatory activity of Tinosporacordifolia

...glucokinase activity, releasing glucose... 

...neutrophil lymphocyte ratio was recorded in Guduchi supplemented cows in comparison... 

...reduce the isolation of... 

...purification of these fraction led to the isolation of... 

...among seven immunomodulatory active compounds belonging... 

...to different classes such as N-formylalanine, 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 concentrations 0.1-2.5 μg/ml [11]. 

... Currently, 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 for 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 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 lipo polysaccharide 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 lymphocyte, neutrophil lymphocyte ratio was recorded in Guduchi supplemented cows in comparison to untreated cows... 

... Although plasma total antioxidant activity was similar between the two groups. Prepartum plasma progesterone concentration was significantly lowered in the treated group however there was no significant change in peripartum plasma total estrogens and PGFM 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 Diabetic mellitus. Oral administration of aqueous T. cordifolia root extract to alloxan-induced diabetic rats caused a significant reduction in blood glucose level and brain lipids [17]. Though the aqueous extract at a dose of 400 mg/kg could elicit significant hypoglycemic effect in different animal model, its effect was equivalent to only one unit/kg of insulin [18]. It was reported that the daily administration of either aqueous or alcoholic extract of T. cordifolia decreases the blood glucose level and increases glucose tolerance in rodents [19, 20]. 

... Berberine, an alkaloid obtained from the stem of T. cordifolia has been tested and used successfully in experimental and human diabetes mellitus. Berberine has been shown to lower elevated blood glucose as effectively as metformin [21]. The mechanisms of action include inhibition of aldose reductase [22], inducing glycosylation [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcomes insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells [26]. Berberine might exert its insulinotropic effect in isolated rat islets by 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-dihydroxybenzocaine (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 diabetes in DL-bearing mice not only augment the basic function of macrophages such as phagocytosis as well as their antigen-presenting ability and secretion of IL-1 and TNF. The results of the investigation also indicate that T. cordifolia plays role in prevention and management of diabetic retinopathy due to its the tumor growth and increase the life span of tumor and 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 tumor models including Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-treated (EAC) in mice. 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, activates tumor-associated acts as a potential therapeutic agent for prevention of macrophages-derived dendritic cells, is effective against various cancers, killing the cancer cells very effectively in vitro, inhibits skin carcinogenesis in mice [39], and inhibits experimental metastasis [8].

**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 debrideiments and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing [32].

**Hypolipidemic effects**

Diabetics are often associated with hyperlipidemia and as T. cordifolia has been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity. An aqueous extract of T. cordifolia root was administered to alloxan-induced diabetic rat (2.5 and 5g/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and fatty acid levels. In another study in rats, the aqueous extracts also reduced levels of brain lipids [33].

**Antineoplastic effects**

Jagetia *et al.* have found that the guduchi killed the HeLa cells very effectively in vitro. In this study, the stem extracts were evaluated in vitro for their cell killing effects [34]. When HeLa cells were exposed to various doses of the extract, a dose-dependent increase in cell killing was observed as compared with non-drug treated controls. The methylene chloride extract was the most potent. The effect of guduchi extract was comparable or better than doxorubicin treatment and thus it indicates that the plant warrants a future study as an anti-neoplastic agent. Further investigation was undertaken to study whether the tumor associated macrophages (TAM)of Daltons lymphoma (DL) alloxa-induced diabetic rats. After 6 weeks, the level of plasma barbital 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 g/kg was found to exert a significant anti-inflammatory effect in vitro. Earlier studies have shown that T. cordifolia contains a significant anti-inflammatory effect.

In another study, the aqueous extract of stem was shown to inhibit the lipid peroxidation and to exert a significant anti-inflammatory effect in vitro. Earlier studies have shown that T. cordifolia contains a significant anti-inflammatory effect.

In a clinical study, T. cordifolia was found to exert a significant anti-inflammatory effect in both acute and subacute models of inflammation. T. cordifolia was found to be more effective than controls.

Hepatoprotective effects

The hepatoprotective action was reported in one of the studies. Antioxidant effect PPI from of this plant was examined in the experiment in which goats treated with T. cordifolia exhibited a significant anti-inflammatory effect in the cotton pellet–induced granuloma (1, 250 and 500 mg/kg given orally) and formalin-induced arthritis. The aqueous extract of stem was shown to inhibit the lipid peroxidation and to exert a significant anti-inflammatory effect in vitro. Earlier studies have shown that T. cordifolia contains a significant anti-inflammatory effect.

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. The stem extract can normalize the alterations in lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats, indirectly benefitting the heart.

Osteoprotective activity

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 osteoporotic agent.

Anti-allergic activity

The aqueous extract of stem was shown to inhibit the lipid peroxidation and to exert a significant anti-inflammatory effect in vitro. Earlier studies have shown that T. cordifolia contains a significant anti-inflammatory effect.

In a clinical study, T. cordifolia was found to be more effective than controls.
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 pruritus, in 15%. Miers and C. asiatica Linn were observed to induce a 12% reduction in sneezing, nasal discharge, and nasal obstruction, respectively, and from nasal pruritus, in 8%. T. cordifolia significantly decreased all these symptoms of allergic rhinitis and was well tolerated [58]. The anti-allergic and bronchodilator properties of T. cordifolia were also studied in rats [59]. Concurrent daily administration of an aqueous extract of the stem evaluated on histamine-induced bronchoconstriction in guinea pigs, capillaries, and mast cells showed that it significantly decreased bronchospasm [60]. T. cordifolia protects against lead intoxication [61].

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 antipyretic, antiproliferative, anti-inflammatory, anti-neoplastic, antihypertensive, antioxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunomodulatory 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 malabsorption syndrome and splenomegaly [62]. Tinospora cordifolia appears to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome improvement in patients with malignant obstructive jaundice [63].

Toxicology

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

Antipyretic and anti-infective activity

The water-soluble fraction of 95% ethanolic extract of T. cordifolia plant has shown significant antipyretic and anti-infective activity [59]. In another experimental study, antipyretic effects have been reported in the hexane- and chloroform-soluble portions of T. cordifolia stems [60]. Various studies show remarkable antipyretic and antipruritic properties of T. cordifolia. Pretreatment with T. cordifolia was shown to impart protection against mortality induced by intra-abdominal sepsis following caecal ligation in rats and significantly reduced mortality from induced by E. coli–induced peritonitis in mice [61].

Other effects

In a clinical study, a compound preparation containing T. cordifolia was reported to significantly reduce the pain in patients suffering from rheumatoid arthritis. Either extract of the steam distillate of aerial part of T. cordifolia has inhibited the in vitro growth of Mycobacterium tuberculosis at 1:50,000 dilutions [63]. It is used for its anti-leprosy properties, along with wide use in other types of skin disorders and has been shown to exert antileprosy activity in combination formulation. Ethanol extract of T. cordifolia has exhibited significant antipyretic activity in rats [64]. 'Septilin syrup' a compound preparation containing T. cordifolia was found to elicit good clinical response in children suffering from upper respiratory tract infection and chronic otitis media. In a scientific study on rats and human volunteers, T. cordifolia was found to have diuretic effects [65]. It was also found effective in modulation of morphology and some

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