**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*

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Advances in molecular biology have revolutionized depending on the requirement of the situation. Immunology and medicine. Initially the use of antibody as therapeutic agents was limited by their purity and resource even by the most intransigent clinicians of heterogeneity. Immunotherapy derives from the advanced countries. Plant extracts have been widely observed from the 19th century, that cancer investigated for their possible immunomodulatory sometimes regressed after acute bacterial infections, that properties, *Tinospora cordifolia*, an indispensable is, there may be no specific immunostimulant effect. medicinal plant, has been used for the treatment of The rapidly expanding discipline of immunology various diseases and has been recommended for contributes to diagnosis, therapy and prevention of improving the immune system. There is great interest in human diseases in many ways. The role of development of new drugs from traditionally used immunocompetents in prevention of malignancy is medicinal plants like *Tinosporacordifolia*. Ayurveda currently of great interest in experimental science as refers to *Tinospora cordifolia* as 'Amruth' or the 'Nectar well as clinical medicine. Interest in the immune of Immortality'. The term 'Amruth' is attributed to this response has been stimulated by the alarming increase drug in recognition of its ability to impart youthfulness, in a novel epidemic form of immune deficiency, vitality and longevity. Immunomodulation can be 'AcquiredImmunodeficiency 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 Tinosporacordifolia

T.cordifolia

**CHEMISTRY**

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

**PHARMACOLOGICAL ACTIONS**

Immunological effects

T.cordifolia benefits the immune system in variety of ways. The alcoholic and aqueous extract of this plant have been tested successfully for immunomodulatory activity [5]. Pretreatment with T.cordifolia lead to protection against mortality induced by intra-abdominal peritonitis following caecal ligation in rats. It also significantly reduced mortality from E. coli induced sepsis following caecal ligation in rats. It also 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 infection were significant. Syringin, Cordiol, Cordioside, Cordifoliosides A&B were identified as the active principle responsible for the anticomplement and amnethoid activity.

Immunomodulatoryactivity [6]. Anarabinogalactan

**DESCRIPTION AND HISTORY**

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

of family menispermae is a perennial, wild climber, polysaccharide, 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 of T.cordifolia stems, there was a significant increase in during the winter. The viscous sap has a yellow colour, the total of count leucocytes. The aqueous extract of odourand nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various. The aqueous and ethanolic extract also induced an ailments throughout the centuries. Today the drug and increase in antibody production and eosinophil count and improved hemoglobin in HIV tincture are used for the treatment of general weakness, extracts treatment cause significant reduction in fever, dyspepsia, dysentery, gonorrhea, secondary eosinophilic arthritis and diabetes. The root is considered as a powerful emetic and is used for bowel obstruction. T.cordifolia is used as an antidote for snake bite and used in malaria, environmental illness, asthma, upper respiratory tract infection, UTI, general debility and amelioration of symptoms from chemo or radiotherapy.

**PHARMACOLOGICAL ACTIONS**

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immunosuppression [7]. The polysaccharide-enriched T. cordifolia treatment, significantly caused the fraction from this plant is found to be very effective in reducing the metastatic potential of B16f-10 melanoma cells [8]. Sharma et al. (2012) evaluated the immunomodulatory activity of three polysaccharide-enriched immunomodulatory fractions from Tinospora cordifolia using the polymorphonuclear leukocyte function test. The results confirmed the immunomodulatory activity of the polysaccharides of T. cordifolia, and also it was conclude that the polysaccharide with lowest sugar content showed highest activity and with highest sugar content showed lowest activity [9]. Mukherjee et al evaluate the biological activity of the Tinospora cordifolia extract at standardized dose against bovine subclinical mastitis. It was found that ethyl acetate, water fractions and hot water extract exhibited significant 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 and with highest sugar content showed highest activity and with highest sugar content showed lowest activity [10].

### 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</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>Choline</td>
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<td>Tetrabradpalmatine</td>
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<td>Magnoflorine</td>
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<tr>
<td>Glycosides</td>
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<td>Cordiside</td>
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<td>Syringin</td>
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<td>Cordifoliside A</td>
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<td>Cordifoliside B</td>
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<td>Cordifoliside C</td>
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<td>Cordifoliside E</td>
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<td>Palmatiside C</td>
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<td></td>
<td>Palmatiside P</td>
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<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
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<td></td>
<td>gamma-sitosterol</td>
<td>Stem</td>
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<td>20B-ecdysone</td>
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<td>Makisterone A</td>
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<td>Giloinsterol</td>
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<td>Diterpenoid lactones</td>
<td>Furanolactone</td>
<td>Whole plant</td>
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<td>Celondane derivatives</td>
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<td>Tinosporon</td>
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<td></td>
<td>Tinosporides</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>Cordifelone</td>
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<td></td>
<td>Gilonin</td>
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<td></td>
<td>Tinosporic acid</td>
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Immunomodulatory activity of *Tinospora cordifolia*

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]. Although 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 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 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-dihydroxyphenylalanine (THZ), and can partly replace the commercial drugs, which could lead to a reduction in toxicity and side effects of lymphocyte, neutrophil count along with increased the latter. Berberine inhibits Foxo1, which integrates...
insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during fasting in DL-bearing mice not only augment the basic function of insulin resistance and the metabolic syndrome [30].

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 and hyperglycemic, anti-angiogenic, anti-inflammatory, bearing host, thus showing its anti-tumor effect through and 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 symptoms of DR. Although diabetic rats' tumour models including Ehrlich ascites carcinoma treated with TC do not achieve the status of normal non-diabetic (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 neuropathy

Tinospora cordifolia prevents the hyperalgesia in experimental diabetic neuropathy. It has an aldose reductase inhibitory activity in vitro which may contribute to the beneficial effects [31].

Diabetic foot ulcer

Diabetic patients with foot ulcers on T. cordifolia as an adjuvant therapy showed significantly better final outcome with improvement in wound healing. Reduced debridentments 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 rats (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 were undertaken to study whether the tumor associated macrophages (TAM)of Daltons lymphoma (DL) alloxaan-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) alloxaan-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

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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 more effective than the 48 subacute inflammation model, the drug was inferior to the most effective one [43]. In another study, guadixyn phenylbutazone [48]. The aqueous extract of stem was shown to inhibit the lipid peroxidation reported to exert a significant anti-inflammatory effect on superoxide and hydroxyl radical in vitro. Earlier studies in both cotton pellet–induced granuloma (1, 250 and 500 mg/kg) and dry skin crude extract (DSCE) contains as much as 8500 mg/kg given orally) and formalin-induced arthritis in polygonal beta cell mitogen; G1–4A, DSCE as well as 69 (1 mg/kg given orally) rat models.

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 hepatoprotective action was reported in one of the recent studies. The experiment in which goats treated with T. cordifolia against reactive oxygen and nitrogen species have shown significant clinical and hematobiological effects. T. cordifolia seed leaves extract prevented simultaneous treatment with PPI during 7 days of the occurrence of liver damage induced by peroxynitrite. Selective inhibitors of ROS-like 80 Swiss Albino mice [51]. T. cordifolia exhibited time-dependent 381 hepatoprotection as reflected in both antioxidant activity against hepatic B and E surface degradation of protein due to photosensitization. 777 antigen in 48–72 hours [50]. Oral administration 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-arthritic and anti-osteoartritic 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 [46]. The water extract of the stem of neem-giloe [T. cordifolia] that grow on alloxan-induced diabetic rats [55].

Azadirachtaindica (neem) significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A 502 Rats treated with T. cordifolia (10 mg/kg body weight) showed an osteoprotective effect, as the bone formation, and serum and heart lipid peroxide levels was observed with prior treatment with T. cordifolia in ischemia-reperfusion–induced myocardial infarction in rats [53]. The stem extract can normalize the alterations in lipid metabolism caused by diabetes mellitus in streptozotocin-induced diabetic rats, indirectly benefitting 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

501 Anti-allergic activity

The aqueous extract of T. cordifolia showed a significant anti-inflammatory effect in the cotton pellet granuloma and formalin induced arthritis model, its effect was comparable with indomethacin and its mode of action appeared to resemble that of non-steroidal anti-inflammatory agent. The dried stem of T. cordifolia was reported from sneezing in 83% of the patients on produced significant anti-inflammatory effect in both acute and subacute models of inflammation. T. cordifolia was found to be more effective than nasal discharge was reported in 69% from nasal cordifolia was found to be more effective than nasal discharge was reported in 69% from nasal pruritis, in 71%. In acute and subacute inflammation, although in a recent study, 100% relief from sneezing in 83% of the patients. The dried stem of T. cordifolia was reported from sneezing in 83% of the patients on produced significant anti-inflammatory effect in both acute and subacute models of inflammation. T. cordifolia was found to be more effective than nasal discharge was reported in 69% from nasal pruritis, in 71%. In...
The ethanol extracts of the roots of *T. cordifolia* Linn were observed to induce a
activity in diabetic rat kidney
was shown to impart protection
T. cordifolia protects against lead intoxication [68].
induced the number of disrupted mast
Clinical uses
*T. cordifolia* is used clinically in the Indian system
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*
effect 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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