**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. *Tinospora cordifolia* 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 antidiabetic, 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, *Tinospora cordifolia*
Immunomodulatory activity of *Tinospora cordifolia*

**Fig 1. Tinospora Cordifolia (Courtesy: Kottakkal Aryavaidyashala)**

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

**CHEMISTRY**

99 A variety of constituents have been isolated from 100 *T.cordifolia* plant. They belongs to different classes such 101 as alkaloids, diterpenoids, lactones, glycosides, steroids, 102 sesquiterpenoids, 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**

108 *T. cordifolia* benefits the immune system in variety 109 of ways. The alcoholic and aqueous extract of this plant 110 have been tested successfully for immunomodulatory 111 activity [5]. Pretreatment with *T. cordifolia* lead to 112 protection against mortality induced by intra-abdominal 113 sepsis following caecal ligation in rats. It also 114 significantly reduced mortality from *E. coli* induced 115 peritonitis in mice [6]. In a clinical study, it was 116 afforded protection in cholestatic patients against *E. coli* 117 infection. Those activities were not due to its 118 antibacterial activity as shown by the negative *in vitro* 119 antibacterial activity of the plant extract. It was reported 120 that treatment in rats had resulted in significant 121 leucocytosis and predominant neutropenia. It has been 122 also observed that it stimulated the macrophages as 123 evidenced by an increase in the number and percentage 124 phagocytosis of *S. aureus* by peritoneal macrophages in 125 rats. The phagocytic and intercellular killing capacity of 126 polymorphs in rats, tested at 3.5 hours after *E. coli* 127 infection were significant. Syringin, Cordiol, 128 Cordioside, Cordifoliosides A&B were identified as the 129 active principle responsible for the anticomplication and 130 immunomodulatory activities [6]. Anarabinogalactan

**DESCRIPTION AND HISTORY**

131 T. cordifolia (Fig 1); common name guduchi, amrutha 132 131 immunomodulatory activities [6]. Anarabinogalactan

133 of family *Menispermaceae* is a perennial, wild climber, 134 polycarcinare, isolated from the dried stem of 135 succulent, shrub often attaining a great height and 136 *T. cordifolia* showed polyclonal mitogenic activity 137 sending down long thread like aerial roots. The bark is 138 against beta cell [4]. It was reported that following oral 139 creamy white and grey, leaves are membranous and 13139 treatment of mice with water and ethanol extracts of 13135 stems, there was a significant increase in 13133 during the winter. The viscus sap has a yellow colour, 13137 the total of count leucocytes. The aqueous extract of 13139 astringent and nauseating bitter [2]. It has been used in 13138 *T. cordifolia* was found to increase phagocytosis *in vitro*. 13136 ayurvedic preparations for the treatment of various 13130 formulations. Guduchi is clinically used to treat jaundice, 13139 The aqueous and ethanolic extract also induced an 13134 various symptoms associated with the disease. All 13137 fever, dyspepsia, dysentery, gonorrhea, secondary 130 rheumatoid arthritis and diabetes. The root is considered 13136 eosinophil count and improved hemoglobin in HIV 13139 various extracts treatment cause significant reduction in 13137 syphilis, urinary diseases, impotency, gout, viral patients [5]. Sixty percent patients receiving TCE and 13134 during the winter. The viscus sap has a yellow colour, 13139 in a placebo reported decrease in the incidence of 13137 the total of count leucocytes. The aqueous extract of 13132 formulation is a powerful emetic and is used for bowel 13138 patients reported decrease in the incidence of 13138 astringent and nauseating bitter [2]. It has been used in

13137 astringent and nauseating bitter [2]. It has been used in
Table 1. Chemical composition of T. cordifolia plant

<table>
<thead>
<tr>
<th>Types of chemicals</th>
<th>Active principle</th>
<th>Parts in which present</th>
</tr>
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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>Tinosporine</td>
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<td>Choline</td>
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<td>Tetrabxpathalamin</td>
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<td>Magnoflorine</td>
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<td>Glycosides</td>
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<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>Cordifolioside B</td>
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<td>Cordifolioside E</td>
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<td></td>
<td>Palmatocide C</td>
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<td>Palmatocide P</td>
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<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
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<td>gama-sitosterol</td>
<td>Stem</td>
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<td>20B-ecdysone</td>
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<td>Ecdysone</td>
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<td>Ecdysterone</td>
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<td>Makisterone A</td>
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<td>Giloninsterol</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>Jateorine</td>
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<td>Columbin</td>
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<td>Sesquiterenoid</td>
<td>Tinocordisolin</td>
<td>Stem</td>
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<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
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<td>Heptacosanol</td>
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<td>Miscellaneous Compounds</td>
<td>Tinosporidine</td>
<td>Root</td>
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<td>Cordifol</td>
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<td>Cordifelone</td>
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<td>Gilonin</td>
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<td>Tinosporic acid</td>
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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-formylannonain, 11-hydroxymustakone, N-methyl-2-pyryldione, Tinosporidine 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 0.1-2.5 μg/ml [11].

Recently, the presence of an immunomodulatory protein (ImP) in guduchi has been investigated. Guduchi ImP in untreated murine splenocytes in the 1-10 μg/mL concentration range; 5-7-fold increase in mitogenic activity was seen in the case of murine thymocytes vs control. The purified protein also induced nitric oxide production from macrophages present in isolated murine peritoneal exudates cells. Guduchi ImP displays enhanced phagocytosis of yeast cells by macrophages. Guduchi ImP does not possess haemagglutination activity indicating that the immunomodulatory protein is not a lectin. The confirmation of an immunomodulatory protein in guduchi stem showing lymphoproliferative and macrophage-activating properties reinforces the rationale of the use of guduchi preparations for immunomodulation [12].

Cordifolide A, a novel unprecedented sulfur-containing clerodane diterpene glycoside, together with other two new diterpene glycosides, cordifolides B and C, and four known analogues, were isolated from a methanol-soluble extract of the stems of Tinospora cordifolia. The structures of the new compounds were determined on the basis of spectroscopic data. 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 denticrine 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 lymphocyte, neutrophil count along with increased

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 models, 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 challenges [27]. Berberine also seems to inhibit human dipeptidyl peptidase-4 (DPP-4) activity, 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-dihydroxybenzoic acid (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
plays role in prevention and... for their cell... a... were exposed to... in vitro... cholesterol, neurons and immunosuppression... have found that the guduchi killed the... in vitro... 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 tetracloride or serum, thus it satisfied the definition of most potent. The effect of guduchi extract was comparable or better than doxorubicin treatment and... anti-neoplastic agent. Further investigation were... Antioxidant activity

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addition, the level of glutathione and vitamin C were 463-acetylsalicylic acid in acute inflammation, although in 40 increased. The root extract at a dose of 5 g/kg was the464-subacute inflammation, the drug was inferior to 40 most effective one [43]. In another study, guduchi465-phenylbutazone [48]. The aqueous extract of stem was 40 extract was shown to inhibit the lipid peroxidation466-reported to exert a significant anti-inflammatory effect. 40 superoxide and hydroxyl radical in vitro. Earlier studies467-in both cotton pellet–induced granuloma (1, 250 and 40 shows that dry stem crude extract (DSCE) contains a468500 mg/kg given orally) and formalin-induced arthritis 40 superior action is comparable with indomethacin and 469-polygonal beta cell mitogen; G1-4A, DSCE as well as69(1 mg/kg given orally) rat models. 40 G1-4A also enhance immune response in mice [44]. In 40 order to explore the possibility of using G1-4A/pp1 to 470 Hepatoprotective effects 40 modulate radiation-induced immune suppression, the471 The hepatoprotective action was reported in one of 40 antioxidant effect PPI from of this plant was examined472 the experiment in which goats treated with T. cordifolia 40 against reactive oxygen and nitrogen species have shown significant clinical and hematobiological 40 (ROS/RNS), generated by74 improvement in CCL4-induced hepatopathy [49]. 40 photosensitization/peroxynitrite. Oxidative damage475 Extract of T. cordifolia has also exhibited in vitro 40 induced by peroxynitrite was inhibited by PPI. The76 inactive property against hepatitis B and E surface 40 degradation of protein due to photosensitization77 antigen in 48-72 hours [50]. Oral administration of 40 assessed by SDS PAGE was effectively reduced by78 Tinospora cordifolia stem and leaves extract prevented 40 simultaneous treatment with PPI during79 the occurrence of lead nitrate induced liver damage in 40 photosensitization. Selective inhibitors of ROS-like80 Swiss Albino mice [51]. T. cordifolia exhibited time81 mannotol, super oxide dismutase (SOD), Sodiumazide,82 independent hepatoprotection as reflected in both 40 significant inhibition of formation of TBARS thus83 conducted in Albino Wistar rats against CCL4-induced 40 indicating generation of oxygen. Thus the action of PPI84 hepatic damage. Extract effectively control the ALT, 40 may be against oxidative damage through type 1 and85 AP and total bilirubin levels and also, type 2 photosensitization mechanism. T. cordifolia86 histopathological studies proved the hepatoprotective 40 has also been reported to elevate GSH levels, expression87 activity of extract [52]. 40 of the gamma-glutamylcysteine ligase and Cu-Zn SOD 40 Anti-inflammatory, anti-arthritis and anti-88 Cardioprotective activity 40 genes. The herb also exhibited strong free radical- 40 scavenging properties against reactive oxygen and 40 nitrogen species as studied by electron paramagnetic 40 resonance spectroscopy [45]. 40 inflammatory actions in models of acute and sub-40 acute inflammation [46]. The water extract of the stem of 40 neem-giloe [T. cordifolia] that grow on500 allaxan-induced diabetic rats [55]. 40 Azadirachta indica (neem)] significantly inhibited acute 40 inflammatory response evoked by carrageen in a dose of 40 50 mg/100 g given orally and intraperitoneally. A502 Rats treated with T. cordifolia (10 mg/kg body 40 significant inhibition of primary and secondary phases503 weight) showed an osteoprotective effect, as the bone 40 of inflammation was observed in a model of adjuvant504 loss in tibia was slower than that in controls. Serum 40 induced arthritis. It also significantly inhibited antibody505 osteocalcin and cross-laps levels were significantly 40 inflammation by typhoid "H" antigen. A mild analgesic506 reduced. This study demonstrates that extract of T. 40 effect of its own as well as potentiation of morpheine507 cordifolia has the potential for being used as 40 analgesia has been reported [47]. In another study508 antiosteoportor agent [56]. 40 Aqueous extract of T. cordifolia showed a significant 40 inflammatory effect in the cotton pellet granuloma and 40 formalin induced arthritis model, its effect was510 T. cordifolia is traditionally used for the treatment of 40 comparable with indomethacin and its mode of action511 asthma, and the juice is also employed for the treatment 40 appeared to resemble that of non-steroidal anti-512 of chronic coughs [57]. In a clinical study, 100% relief 40 inflammatory agent. The dried stem of T. cordifolia513 was reported from sneezing in 83% of the patients on 40 produced significant anti-inflammatory effect in both514 treatment with T. cordifolia. Similarly, the relief from 40 acute and subacute models of inflammation. T.515 nasal discharge was reported in 69%; from nasal 40 cordifolia was found to be more effective than516 obstructions 61% and from nasal pruritis, in 71%. In
placebo group, there was relief from sneezing only in 73% of patients with nasal discharge, in 16.2%; from nasal pruritis, in 74% [66]. The ethanol extracts of the roots of *T. cordifolia* were observed to induce a 12% decrease in nasal obstruction, in 17%; and from nasal pruritis, in 75% of patients [67]. These effects were noted within 1 h, and the symptoms disappeared within 4 h. The ethanol extracts were also found to be effective against allergic rhinitis and were well tolerated [68]. The anti-allergic and bronchodilator properties of *T. cordifolia* were studied in guinea pigs, pigs, and rats. The plant was shown to impart protection against the effects of histamine, 20% [69]. Tinospora cordifolia protects against lead intoxication [70]. The aqueous extract of the stem evaluated on histamine- and diazepam-induced bronchospasm showed that the plant significantly decreased bronchospasm [71]. Tinospora cordifolia protects against lead intoxication [68].

**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 antiprostaglandin, antinflammatory, anti-neoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic, and immunologic properties. There are limited human studies to support these uses. *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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