Immunomodulation relates to potentiation or depression of the immune responses of the host, "Acquired ImmunoDeficiency Syndrome" (AIDS). The term 'Amruth' is attributed to this response has been stimulated by the alarming increase of drug in recognition of its ability to impartyouthfulness, in a novel epidemic form of immune deficiency, "Acquired ImmunoDeficiency Syndrome" (AIDS). Immunomodulation can be determined by the capacity of the compounds to 39 Immune modulation relates to potentiation or 40 influence the cytokine production, mitogenicity, 41 suppression of the immune responses of the host, 42 stimulation and activation of immune effector cells.

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, Tinosporacordilifolia

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. 47 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 53 of Immortality'. The term 'Amruth' is attributed to this response has been stimulated by the alarming increase of drug in recognition of its ability to impartyouthfulness, in a novel epidemic form of immune deficiency, 55 vitality and longevity. Immunomodulation can be "Acquired ImmunoDeficiency Syndrome" (AIDS). 56 determined by the capacity of the compounds to 39 Immune modulation relates to potentiation or 57 influence the cytokine production, mitogenicity, 40 suppression of the immune responses of the host, 58 stimulation and activation of immune effector cells.
Immunomodulatory activity of Tinosporacordifolia

T.cordifolia is a perennial, wild climber, of family menispermaceae is a perennial, wild climber. It has been used in ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and its extracts treatment cause significant reduction in fever, dyspepsia, dysentery, gonorrhea, secondary syphilis, urinary diseases, impotency, gout, viral hepatitis, skin diseases and anemia. In various symptoms associated with the disease. All rheumatoid arthritis and diabetes. The root is considered 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.

DESCRIPTION AND HISTORY

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

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”.

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. It was also observed that following oral drug administration there was a significant increase in the number and percentage of phagocytes 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, Cordifiolosides were identified as the active principle responsible for the activities.

CHEMISTRY

A variety of constituents have been isolated from T.cordifolia plant. They belong to different classes such as alkaloids, diterpenoids, lactones, glycosides, steroids, sesquieterpenoids, 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].

Fig 1. Tinospora Cordifolia (Courtesy: Kottakkal Aryavaidyashala)
immunosuppression [7]. The polysaccharide-enriched 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 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 immunomodulatory active compounds of Tinospora cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanolic extract of T. 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cordifolia, and also it was conclude that the hydro-methanolic extract of T. cordifolia, and also it was conclude that the hydro-methanological activity of the Tinospora cordifolia extract at 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

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>Tinospoline</td>
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<td></td>
<td>Choline</td>
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<td></td>
<td>Isocolumbin</td>
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<td></td>
<td>Tetrabropalmatine</td>
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<tr>
<td></td>
<td>Magnoflorine</td>
<td></td>
</tr>
<tr>
<td>Glycosides</td>
<td>Tinocordiside</td>
<td>Stem</td>
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<tr>
<td></td>
<td>Cordiside</td>
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<tr>
<td></td>
<td>Syringin</td>
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<tr>
<td></td>
<td>Cordrifolioside A</td>
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<td></td>
<td>Cordrifolioside B</td>
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<td></td>
<td>Cordrifolioside C</td>
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<td></td>
<td>Cordrifolioside D</td>
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<tr>
<td></td>
<td>Cordrifolioside E</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palmatiside C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palmatiside P</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Beta-sitosterol</td>
<td>Aerial part</td>
</tr>
<tr>
<td></td>
<td>gamma-sitosterol</td>
<td>Stem</td>
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<td></td>
<td>20B-ecdysone</td>
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<td></td>
<td>Ecdysone</td>
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<tr>
<td></td>
<td>Ecdysterone</td>
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<td></td>
<td>Makisterone A</td>
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<td></td>
<td>Giloistemon</td>
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<tr>
<td>Diterpenoid lactones</td>
<td>Furanolactone</td>
<td>Whole plant</td>
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<tr>
<td></td>
<td>Celondane derivatives</td>
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<tr>
<td></td>
<td>Tinosporon</td>
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<tr>
<td></td>
<td>Tinosporides</td>
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<tr>
<td></td>
<td>Jateorine</td>
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<td></td>
<td>Columbin</td>
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<tr>
<td>Sesquiterenoid</td>
<td>Tincordifolin</td>
<td>Stem</td>
</tr>
<tr>
<td>Aliphatic Compounds</td>
<td>Octacosanol</td>
<td>Whole plant</td>
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<tr>
<td></td>
<td>Heptacosanol</td>
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<tr>
<td>Miscellaneous Compounds</td>
<td>Tinosporine</td>
<td>Root</td>
</tr>
<tr>
<td></td>
<td>Cordifol</td>
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<tr>
<td></td>
<td>Cordifelone</td>
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<tr>
<td></td>
<td>Cordifelone</td>
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<tr>
<td></td>
<td>Gilonin</td>
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<td></td>
<td>Tinosporic acid</td>
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</table>
Berberine suppresses intestinal disaccharides (h-aldose reductase insulin resistance-diabetes) and human incretins. Berberine might act like metformin and 2,4-dinitrophenol which are known to be toxic to the pancreas and therefore lead to a reduction in toxicity and side effects of the latter. Berberine inhibits Foxo1, which integrates the reproductive performance of crossbred cows by its immunomodulatory activity using mouse bone marrow derived dendritic cells. The structure of the new compound is 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. Tinospora cordifolia had shown a significant level of macrophage activation, which leads to increase in GM-CSF which leads to leucocytosis and improved neutrophil function. 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.

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. 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. 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.

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. The mechanisms of action include inhibition of aldose reductase, inducing glycosylation, preventing insulin resistance through increasing insulin receptor expression, and acting like incretins. Berberine also overcomes insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells. Berberine might exert its insulino-mimetic 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. 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.

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. Berberine has been shown to boost the effects of metformin and 2,4-dihydroxyphenylalanine (DHA), 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 performance postpartum. A higher total leukocyte, neutrophil lymphocyte ratio was recorded in Guduchi supplementation cows in comparison to untreated cows. Although plasma total antioxidant activity was similar to different classes such as N-formylmannosan, 11-hydroxymustakone, N-methyl-2-pyrrolidone, cordifoliol A, magnoflorine, tinocordiside, syringin by nuclear magnetic resonance and mass spectrometry. Cordifoliol 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 1-2.5 μg/ml.
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 activity and secretion of IL-1 and TNF. The results of the investigation also indicate that T. cordifolia has successfully reversed the hippocampal neuronal degeneration histopathologically, T. cordifolia has successfully reversed the hippocampal neuronal degeneration histopathologically, and T. cordifolia is a potent immunomodulator and cognitive enhancer.

Cognitive effects

Diabetic retinopathy

T. cordifolia displays role in prevention and management of diabetic retinopathy due to its hypoglycemic, anti-angiogenic, anti-inflammatory properties. It also prevents the loss of retinal pigment epithelium and cellular changes, the T. cordifolia was found effective in several other important symptoms of DR. Although diabetic rats treated with TC did not achieve the status of normal non-diabetic mice (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a tumor-bearing host, thus stabilizing the membrane integrity of DL cells.

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

Hypolipidemic effects

Diabetics are often associated with hyperlipidemia and as T. cordifolia has been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity. An aqueous extract of 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]

Antineoplastic effects

Jaegia et al. have found that the guduchi killed the HeLa cells very effectively in vitro. In this study, the stem extracts were evaluated in vitro for their cell killing effects.[34] When HeLa cells were exposed to various doses of the extract, a dose-dependent increase in cell killing was observed as compared with non-drug treated controls. The methylene chloride extract was the most potent. The effect of guduchi extract was comparable or better than doxorubicin treatment and thus it indicates that the plant warrants a future study as an anti-neoplastic agent. Further investigation was undertaken to study whether the tumor associated macrophages (TAM) of Daltons lymphoma (DL) were sensitive to the guduchi extract. After 6 weeks, the level of plasma barbituric acid reactive substances, activated by the aqueous liquid extract of T. cordifolia, ceruloplasmin and alpha tocopherol were reduced. In
addition, the level of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was found to exert a significant anti-inflammatory effect in acute inflammation, although in one study, guduchi (Tinospora cordifolia) was shown to inhibit the lipid peroxidation induced by phenylbutazone [48]. The aqueous extract of stem was shown to have significant anti-inflammatory effect on superoxide and hydroxyl radical in vitro. Earlier studies reported that extract of Tinospora cordifolia exhibited time-dependent hepatoprotective effect [49]. Extracts of Tinospora cordifolia have shown significant clinical and hematobiological activity, as the bone marrow damage was inhibited by peroxynitrite. The root extract at a dose of 5 g/kg given orally and intraperitoneally was found to exert a significant anti-inflammatory effect in acute and subacute models of inflammation. The hepatoprotective action was reported in one of the studies [50]. The hepatoprotective activity of Tinospora cordifolia was evaluated in vitro by measuring the level of glutathione and vitamin C brought about by treatment with PPI [51]. Administration of the extract of Tinospora cordifolia to rats undergoing chemotherapy was found to be beneficial in reducing the levels of glutathione and vitamin C [52]. The herb also exhibited strong free radical-scavenging properties against reactive oxygen and nitrogen species as studied by electron paramagnetic resonance spectroscopy [45].

**Cardioprotective activity**

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 activities in models of acute and subacute inflammation. The water extract of the stem 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-osteoarthritic activities**

A dose-dependent reduction in infarct size and in 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 benefiting the heart [54]. Administration of the extract of T. cordifolia roots to rats 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**

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Concurrent daily administration of *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, antinflammatory, antineoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunomodulatory 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].

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, antinflammatory, antineoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunomodulatory 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.

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Immunomodulatory activity of Tinosporacordifolia

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