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REVIEW ARTICLE

Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity

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ABSTRACT

Immunomodulation is a procedure, which can alter the immune system of an organism by interfering its function. Modulation of immune system may result in suppression or stimulation of immunological reactivity. Recently the effect of immunomodulators in the treatment of various diseases is significant. *Tinosporacordifolia* is a widely used shrub in ayurvedic system of medicine. It is reported to benefit the immune system in a variety of ways. The medicinal properties incorporated with this plant are anti-diabetic, hypolipidemic, anti-neoplastic, anti-oxidant, anti-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 immunology and medicine. Initially the use of antibody as therapeutic agents was limited by their purity and heterogeneity. Immunotherapy derives from the observation from the 19th century, that cancer sometimes regressed after acute bacterial infections, that is, there may be no specific immunostimulant effect. The rapidly expanding discipline of immunology contributes to diagnosis, therapy and prevention of human diseases in many ways. The role of immunocompetents in prevention of malignancy is currently of great interest in experimental science as well as clinical medicine. Interest in the immune response has been stimulated by the alarming increase in a novel epidemic form of immune deficiency, "AcquiredImmunoDeficiency Syndrome" (AIDS).

Immunomodulation relates to potentiation or suppression of the immune responses of the host, depending on the requirement of the situation. Alternative medicine is now recognized as an invaluable resource even by the most intransigent clinicians of advanced countries. Plant extracts have been widely investigated for their possible immunomodulatory properties, *Tinospora cordifolia*, an indispensable medicinal plant, has been used for the treatment of various diseases and has been recommended for improving the immune system. There is great interest in development of new drugs from traditionally used medicinal plants like *Tinosporacordifolia.* Ayurveda refers to *Tinospora cordifolia* as '*Amruth*' or the 'Nectar of Immortality'. The term '*Amruth*' is attributed to this drug in recognition of its ability to impartyouthfulness, vitality and longevity. Immunomodulation can be determined by the capacity of the compounds to influence the cytokine production, mitogenicity, stimulation and activation of immune effector cells.

Fig 1. *Tinospora Cordilifolia* (Courtesy: KottakkalAryavaidyashala)

Panchabhai et al done a study "Validation of therapeutic claims of *Tinospora cordifolia*: a review "on 2008 [1]. As *Tinosporia 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. *Tinosporia 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* of family *menispermaceae* is a perennial, wild climber, succulent, shrub often attaining a great height and sending down long thread like aerial roots. The bark is creamy white and grey, leaves are membranous and chordate. Flowers grow during the summer and fruits during the winter. The viscous sap has a yellow colour, odourand nauseating bitter [2]. It has been used in ayurvedic preparations for the treatment of various ailments throughout the centuries. Today the drug and tincture are used for the treatment of general weakness, fever, dyspepsia, dysentery,gonorrhea,secondary syphilis, urinary diseases, impotency,gout,viral hepatitis, skin diseases and anemia. In compound formulation Guduchi is clinically used to treat jaundice, rheumatoid 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.

CHEMISTRY

A variety of constituents have been isolated from *T.cordifolia*plant. They belongs 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 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.aureaus* 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, CordifoliosidesA&B were identified as the active principle responsible for the anticompliment and immunomodulatoryactivities [6]. Anarabinogalactan polysaccharide, isolated from the dried stem of *T.cordifolia* showed polyclonal mitogenicactivity against beta cell [4]. It was reported that following oral treatment of mice with water and ethanol extracts of *T.cordifolia* stems, there was a significant increase in the total of count leucocytes. The aqueous extract of *T.cordifolia* was found to increase phagocytosis *in vitro*. The aqueous and ethanolic extract also induced an increase in antibody production *in vivo*. *T.cordifolia* extracts treatment cause significant reduction in eosinophil count and improved hemoglobin in HIV patients [5]. Sixty percent patients receiving TCE and 20% on placebo reported decrease in the incidence of various symptoms associated with the disease. All extracts inhibited cyclophosphamide-induced

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Table 1. Chemical composition of *T. cordifolia*plant

Types of chemicals	Active principle	Parts in which present
Alkaloids	Berberine Palmatine Magnoflorine Tinosporine Choline Isocolumbin Tetrahydropalmatine Magnoflorine	Stem Root
Glycosides	Tinocordiside Cordiside Syringin Cordifolioside A Cordifolioside B Cordifolioside C Cordifolioside D Cordifolioside E Palmatoside C Palmatoside P	Stem
Steroids	Beta-sitosterol gama-sitosterol 20B-ecdysone Ecdysone Ecdysterone Makisterone A Giloinsterol	Aerial part Stem
Diterpenoid lactones	Furanolactone Celondane derivatives Tinosporon Tinosporides Jateorine Columbin	Whole plant
Sesquiterenoid	*Tincordifolin*	*Stem*
Aliphatic Compounds	Octacosanol Heptacosanol	Whole plant
Miscellaneous Compounds	Tinosporidine Cordifol Cordifelone Cordifelone Gilonin Tinosporic acid	Root

immunosuppression [7]. The polysaccharide-enriched 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. 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 [10].

Sharma et al (2012) isolated and characterised the immunomodulatory active compounds of *Tinospora cordifolia*. It was found that ethyl acetate, water fractions and hot water extract exhibited significant immunomodulatory activity with an increase in

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percentage phagocyctosis. 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-pyrrolidone, cordifolioside A , magnoflorine , tinocordiside , syringin by nuclear magnetic resonance and mass spectrometry . Cordifolioside A and syringin have been reported to possess immunomodulatory activity. Other five compounds showed significant enhancement in phagocytic activity and increase in nitric oxide and reactive oxygen species generation at concentration 0.1-2.5 µg/ml [11].

Recently, the presence of an immunomodulatory protein (ImP) in guduchi has been investigated.Guduchi ImP showed ~3-fold mitogenic activity compared to untreated murine splenocytes in the 1-10 µg/mL concentration range; 5-7-fold increase in mitogenic activity was seen in the case of murine thymocytes vs control. The purified protein also induced nitric oxide production from macrophages present in isolated murine peritoneal exudates cells. Guduchi ImP displays enhanced phagocytosis of yeast cells by macrophages. Guduchi ImP does not possess 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 dentritic cells [13]. *Tinosporia cordilifolia* 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, lymphocyte, neutrophil count along with increased 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 adose 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 glycolysis [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcome 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 -thiazolidinedione (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

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insulin signaling with mitochondrial function. Inhibition of Foxo1 can improve hepatic metabolism during insulin resistance and the metabolic syndrome [30].

Diabetic retinopathy

T. cordifolia plays role in prevention and management of diabetic retinopathy due to its antihyperglycemic, anti-angiogenic, anti-inflammatory and anti-oxidant properties. It also prevents the progression of cataract and vascular changes, the important symptoms of DR. Although diabetic rats treated with TC do not achieve the status of normal non-diabetic rats, but they achieve significant levels as compared to untreated diabetic rats. T. cordifolia thus acts as a potential therapeutic agent for prevention of the vascular complications of diabetes.

Diabetic neuropathy

Tinospora cordifolia prevents the hyperalgesia in expiremental 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* been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemicactivity. 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 anti-neoplastic agent. Further investigation were undertaken to study whether the tumor associated macrophages (TAM)of Daltons lymphoma (DL) a spontaneous transplantable T-cell lymphoma, can be activated by the aqueos liquid extract of *T.cordifolia* (ALTC) [35]. Intra-peritoneal administration of ALTC 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 the intra-peritoneal administration of ALTC slow down the tumor growth and increase the life span of tumor bearing host, thus showing its anti-tumor effect through destabilizing the membrane integrity of DL cells. *T.cordifolia* was shown effective in several other tumour models including Ehrlich ascites carcinoma (EAC) in mice [36]. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a tumor-bearing host [37], activates tumor-associated 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].

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 histopatholagicalinvestigation [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 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 alloxan-induced diabetic rats. After 6 weeks, the level of plasma barbituric acid reactive substances, 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 the most effective one [43]. In another study, guduchi extract was shown to inhibit the lipid peroxidation superoxide and hydroxyl radical *in vitro*. Earlier studies shows that dry stem crude extract (DSCE) contains a polygonal beta cell mitogen; G1-4A, DSCE as well as 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 antioxidant effect PPI from of this plant was examined against reactive oxygen and nitrogen species (ROS/RNS), generated by photosensitization/peroxynitrite. Oxidative damage induced by peroxynitrite was inhibited by PPI. The degradation of protein due to photosensitization assessed by SDS PAGE was effectively reduced by simultaneous treatment with PPI during photosensitization. Selective inhibitors of ROS-like mannitol, super oxide dismutase (SOD), Sodiumazide, ant-oxidant GSH, and vitamin C brought about significant inhibition of formation of TBARS thus indicating generation of oxygen. Thus the action of PPI may be against oxidative damage through type 1 and type 2 photosensitization mechanism. *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-osteoporotic 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 sub acuteinflammation [46]. The water extract of the stem of neem-giloe [*T. cordifolia* that grow on *Azadirachtaindica (neem)]* significantly inhibited acute inflammatory response evoked by carrageen in a dose of 50 mg/100 g given orally and intraperitoneally. A significant inhibition of primary and secondary phases of inflammation was observed in a model of adjuvant-induced arthritis. It also significantly inhibited antibody formation by typhoid "H" antigen. A mild analgesic effect of its own as well as potentiation of morphine analgesia has been reported [47]. In another study aqueous extract of *T. cordifolia* showed a significant 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* produced significant anti-inflammatory effect in both acute and subacute models of inflammation. *T. cordifolia* was found to be more effective than acetylsalicylic acid in acute inflammation, although in subacute inflammation, the drug was inferior to phenylbutazone [48]. The aqueous extract of stem was reported to exert a significant anti-inflammatory effect in both cotton pellet–induced granuloma (1, 250 and 500 mg/kg given orally) and formalin-induced arthritis (1 mg/kg given orally) rat models.

Hepatoprotective effects

The hepatoprotective action was reported in one of the experiment in which goats treated with *T.cordifolia* have shown significant clinical and hematobiological improvement in CCL_4-induced hepatopathy [49]. Extract of *T.cordifolia* has also exhibited *in vitro* inactivating property against hepatitis B and E surface antigen in 48-72 hours [50]. Oral administration of Tinospora cordifolia stem and leaves extract prevented the occurrence of lead nitrate induced liver damage in Swiss Albino mice [51]. *T. cordifolia* exhibited time-dependent hepatoprotection as reflected in both biochemical and histological examination in a study conducted in Albino Wistar rats against CCl_4-induced hepatic damage. Extract effectively control the ALT, ALP and total bilirubin levels and also, histopathological studies proved the hepatoprotective activity of extract [52].

Cardioprotective activity

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 (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

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 antiosteoporotic agent [56].

Anti-allergic activity

T. cordifolia is traditionally used for the treatment of asthma, and the juice is also employed for the treatment of chronic coughs [57]. In a clinical study, 100% relief was reported from sneezing in 83% of the patients on treatment with *T. cordifolia*. Similarly, the relief from nasal discharge was reported in 69%; from nasal obstructions 61% and from nasal pruritis, in 71%. In

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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 pruritis, in 12%. Thus, T. cordifolia significantly decreased all symptoms of allergic rhinitis and was well tolerated [58]. The anti-allergic and bronchodilator properties of an aqueous extract of the stem evaluated on histamine-induced bronchospasm in guinea pigs, capillary permeability in mice and mast cell disruption in rats showed that it significantly decreased bronchospasm induced by 5% histamine aerosol, decreased capillary permeability and reduced the number of disrupted mast cells.

Antipyretic and anti-infective activity

The water-soluble fraction of 95% ethanolic extract of *T. cordifolia* plant has shown significant antipyretic 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 anti-infective and antipyretic properties of *T. cordifolia*. Pre-treatment 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].

Antifertility & aphroadisiac activity

Oral administration of 70% methanolic extract of *T. cordifolia* stem to male rats at a dose level of 100 mg/d for 60 days did not cause body weight loss but decreased the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner [62]. Gudichi is a natural aphrodisiac in females. Its immunomodulatory action helps to strengthen the immune system and to make the body stronger and hence make a woman more able and ready to enjoy the sex. It is a rejuvenator and a natural herbal aphrodisiac.

Other effects

In a clinical evaluation, a compound preparation 'RUMALAYA' containing *T.cordifolia* was reported to significantly reduce the pain in patient suffering from rheumatoid arthritis. Ether 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-leprotic properties, along with wide use in other types of skin disorders and has been shown to exert antileprotic activity in a combination formulation. Ethanolic 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 gluconeogenic enzymes activity in diabetic rat kidney [66]. The ethanol extracts of the roots of *T. cordifolia* Miers and *C. asiatica* Linn were observed to induce a marked protective action against an 8 h restraint stress induced ulcerization, the activity being comparable to that of diazepam [67]. Concurrent daily administration of *T. cordifolia* stem and leaves extract prevented the toxic influences of lead on haematological value and the results suggested that simultaneous supplementation of *T. 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 posses adaptogenic, antinflamatory, anti-neoplastic, anti-oxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunologic properties. There are limited human studies to support these use. *T. cordifolia* can also be used as an adjuvant drug in the treatment of hyper-reactive malarious splenomegaly [69]. Tinospora cordifolia appears to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome in patients with malignant obstructive jaundice [70].

Toxicology

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

CONCLUSION

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

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