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MEDICINAL USES OF *TINOSPORA CORDIFOLIA* MIERS– A REVIEW

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Medicinal plants have been used to cure human illness since time immemorial. Some of these are believed to promote positive health and maintain organic resistance against infection by re-establishing body equilibrium and conditioning the body tissues. The folk use of plants in medicine is as old as the existence of mankind. *Tinospora cordifolia*, member of family Menispermaceae, is a large glabrous deciduous climbing succulent shrub. It climbs on any big or small tree, in the vicinity of which it grows. Giloe, which is climbing on a margosa tree is called as "Neem Giloe", Leaves are chordate and flowers are greenish yellow, fruits are of pea size and red in colour. Mainly fresh juice has medicinal value than the dry one which is extremely bitter in taste. Stem is succulent with long filiform aerial roots arising from branches. Bark is papery thin, wood is soft, flowers are unisexual, fruit is one seeded and fleshy and seeds are curved.

Keywords : Common names - English-Heart leaf moon seed; Sanskrit - Jetvatica, Guduchi, Amrita and Amrtavalli; Assamese - Siddhilata, Amarlata; Bengali - Gulancha; Gujarati - Galac, Garo; Hindi - Giloe, Gurcha; Punjabi -Gilo; Tamil - Seendal, Seendil Kodi; Telgu - Thippateega; Urdu-Gilo; Botanical name –*Tinospora cordifolia* Miers.

Tinospora cordifolia is a native to India and distributed throughout the tropical India, tropics of Asia, Africa and Australia[1]. It is being used in Indian medicine as Tridosh shamak (Vata, Pitta, Kapha), Rasa (Taste) (tikta, madhura, kashaya), Six flavours : *Madhura* (Sweet), *Amla* (Sair), *Lavana* (Salty), *Katu* (Pungent), *Tikta* (Bitter) and *Kashaya* (Astringent).

Ayurveda (Ayur-life, Veda-knowledge), Indian system of medicine, offers certain plant products (known as Rasayana) to strengthen the tissue resistance to disease[2]. *T. cordifolia* is one of such plants which possess Rasayan (tonic) property. It is used for general adaptogenic and prohost immuno-modulatory activity in fighting infections. The starch from the stems and the roots (Giloe Satwa) is a nutrient and used in chronic diarrhoea and dysentery. Juice of the fresh plant is used as a powerful diuretic and is also used in gonorrhoea with advantage. It is a part of almost all decoctions mentioned in Ayurvedic text books for use in diseases of joint[3-4]. The root of *Tinospora cordifolia* is known for its antistress, antileprotic and antimalarial activities[5]. Its root extract (aqueous) has antioxidant property in alloxan diabetic rats[6]. In combination with other plants such as *Asparagus racemosus, Withania sominifera* and *Picrorhiza kurrooa* it is found to enhance host resistance and rduce the side effects of other toxic agents[7]. It is mentioned in Ayurvedic literature as a constitutent of several compound preparations used in general debility, dyspepsia, fever and urinary diseases. Extract of the leaves have insulin like action and can significantly reduce the blood glucose level. The root is a powerful emetic and is used for visceral obstruction. *T. cordifolia* was studied against the hepatic damage induced by a standard hepatotoxin-Carbon tetrachloride[8]. Watery extract of its leaves is used in leprosy. Pulverized fruit is used as a tonic and also for the treatment of jaundice and rheumatism. The stem is bitter, stomachachic, diuretic, stimulates bile secretion, causes constipation, allays thirst, burning sensation, vomiting, enriches the blood and cures jaundice (Ayurveda). The root and stem are prescribed in combination with other drugs as an anti-dote to snake bite (Charak, Shusrut, Vagbhatia) and scorpion sting (Sushrut). It has shown immunomodulating activities also[9].

Guduchi has been reported to be active against throat cancer in man[10]. Stanely[11]. found that *T. cordifolia* root extract has hypoglycaemic and hypolipidaemic effect.

Chemical Composition- Chemical constitutents of *Tinospora cordifolia* can be broadly categorised as alkaloids, glycosides, sterols, lactones, fatty acids, etc.

The alkaloids – main components are generally the protoberberine bases. Berberine, Palmatine, Tembeterine, Magnoflorine, Choline and Tinosporin are reported from its stem[12-14].

Glycosides – 18-Norclerodane glucosides. Clerodane

furnoditclvene glucoside (TC-1), Cordioside (TC-2), Cordifolioside A (TC-5) and Cordifolioside B (TC-6) and Cordiole (TC-7) were isolated from *T. cordifolia* by Wazir *et al.*[15]. The petroleum ether extract of the plant contained β-Sitosterol, Octacosanol, Heptacosanaol, Nonacosan-15-one and a new phenolic Lignin, 3-(α4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxy benzyl) tetrahydrofuran.

Lactones – Diterpenoid Furenolactone (VII) a Clerodane derivative (5R, 10R)-4R-8R dihydroxy-2S-3R : 15, 16-diepoxy cleroda-13 (16), 14-dieno-17, 12S : 18, 1S-dilactone (VIII)[16] and Tinosporin[17]. Tinosporide, which was identical with jeteorine and columbin were also isolated.

Starch and other polysaccharides were found to consist chiefly of a 1-4-linked Glucan with occasional branch point. Leaves are rich in protein (11.2%) and fairly rich in Calcium and Phosphorus. The root of *T. cordifolia* is known for its antileprotic, antimalarial and antistress activities[5].

Anti-Inflammatory effects- Water extract of *T. cordifolia* was investigated for anti inflammatory activities using albino rats of either sex[18]. The aqueous extract of it exerted a significant anti-inflammatory effect in cotton pellet granuloma and formalin induced arthritis models. Its effect was comparable with Indomethacin and its mode of action appears to resemble that of a non steroidal anti-inflammatory agent. In a clinical evaluation, a compound preparation Rumalaya, containing *T. cordifolia* was reported to significantly reduce the pain and morning sickness in patients suffering from rheumatoid arthritis.

Antistress and immunomodulatory activity - The alcoholic and aqueous extracts of *T. cordifolia* have been tested with success to evaluate its Immuno-modulatory activity[19,20].

Pretreatment with *T. cordifolia* was found to impart protection against mortality induced by intraabdominal sepsis following caecal ligation in rats. It has also significantly reduced the mortality from *E. coli* induced peritonitis in mice. This showed inhibitory effects on the haemolytic activity of the complement system towards antibody coated sheep erythrocyte by guinea pig serum. Immuno-modulating agents have been reported to act primarily on cellular rather than humoral immune response and to restore the immunocompetency of impaired hosts without hyperstimulating the normal animals.

The active principles of *T. cordifolia* were found to possess anticomplementary and immunomodulatory activities. Syringin (TC-4) and Cordiol (TC-7) inhibited *in vitro* immunohaemolysis of antibody coated sheep erythrocytes by guinea pig serum. The reduced immunohaemolysis was found to be due to inhibition of the C-3-convertase of the classical complement pathway. However, higher concentrations showed constant inhibitory effects. The compounds also gave rise to significant increases in IgG antibodies in serum. Humoral and cell mediated immunity were also enhanced depending upon the given dose. Macrophage activation was reported for Cardioside (TC-2), Cordifolioside A (TC-5) and Cordiol (TC-7) and this activation was more pronounced with increasing incubation times[20]. It augments macrophage chemotaxis, phagocytosis and promotes interaction with other immunoregulatory lymphoid cells, In a clinical study, it has afforded protection in cholastatic patients against *E. coli* infection. These activities are not due to antibacterial activity of the plant extract[19].

An arabinoglactan M(r) 2.2 x 10(6) has been isolated from the dired stem of *Tinospora cordifolia* and examined by methylation analysis, partial hydrolysis and carboxyl reduction. Purified polysaccharide showed polyclonal mitogenic activity against B-cell, their proliferation did not require macrophage[21].

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Alpha-D-glucan separated from TC exhibits immunoprotective and and immunostimulatory effects[22].

The antistress and tonic property of the plant was clinically tested wherein it brought about good response in children with moderate degree of behavioural disorders and mental deficit. It has also significantly improved the I.Q. levels.

Anti-diabetic activity- Though the aqueous extract, at a dose of 400 mg/kg body weight could elicit significant anti-hyperglycaemic effect in different animal models. Its effect was equivalent to only one unit/kg of insulin. It is reported that the daily administration of either alcoholic or aqueous extracts caused reduction in fasting blood glucose level and increased glucose tolerance in albino rats[23,24]. Aqueous extract also caused a reduction in blood sugar in alloxan-induced hyperglycaemia in rats and rabbits at the dose of 400 mg/kg body weight. Aqueous extract of *T. cordifolia* root at doses of 2.5, and 5.0 g, decreased blood and urine glucose when compared to diabetic rats.

T. cordifolia root extract also caused an increase in bodyweight, total haemoglobin and hepatic hexokinase at the dose-rate of 2.5 and 5.0 g/kg[25]. Administration of *T. cordifolia* root extract (aqueous) 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 acid in alloxan diabetic rats[6].

T. cordifolia is also reported to decrease intestinal hydraulic permeability of nutrients[26].

Histological examination of pancreas did not reveal any evidence of regeneration of β–cells of islets of Langerhans and the possible mode of action of the plant is in the control of glucose metabolism. The aqueous extract has also exhibited some inhibitory effect on adrenaline induced hyperglycaemia. This effect could be due to some effect on glucose metabolism, through some enzyme system inhibiting gluconeogenesis[27]. Ethyl acetate extract has afforded a pyrolidine, derivative with hypoglycaemic activity in rabbits.

Hepatoprotective activity -Goats treated, with extract of *T. cordifolia,* have shown significant clinical and hematobiochemical improvement in CCl_4 induced hepatopathy. Thus, indicating hepatoprotective action[28]. *In vitro* experiment have shown that extract of *T. cordifolia* has also exhibited inactivating property against Hepatitis-B surface antigen in 48-72 hours.

Mice administered 10 doses of cyclophosphamide had a drastically suppressed bone marrow cell population. Treatment with Cyclophosphamide and together with *T. cordifolia* extract (50 mg, iv) entirely blocked the cyclophosphamide-induced cytotoxicity in bone marrow cells and in lymphocytes of mice. *T. cordifolia* extract reduced lipid peroxidation due to drug exposure in the liver of test animals. Concentration needed for 50% inhibition was 6 mg and 12.5 mg/ml respectively. The extract was also found to reduce the toxic side effects of cyclophosphamide administration (25 mg/kg wt, 10 days) in mice[29].

Miscellaneous experimental studies- The active constituent in the *T. cordifolia* was found to inhibit in vitro growth of mycobacterium tuberculi. Chauhan[30] reported that *T. cordifolia* was active against throat cancer in man. Samy[31] observed antimicrobiol activity of TC.

It has also been reported to be non toxic in acute toxicity studies with almost no side effect[30].

Ethanolic extract of *T. cordifolia* exhibited significant antipyretic activity in experimental rats[31]. 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.

Antihepatotoxic activity of *T. cordifolia, Phyllanthus niruri,* and *Ricinus communis* was studied in albino rats intoxicated with CCl_4[32]. The effect of *T. cordifolia,* was evaluated on Kupffer cell function in rats using carbon clearance test[33].

Exposure of HeLa cells 0.5, 10, 25, 50 and 1.00 mg/ml of *T. cordifolia* extract (Methanol, aqueous and Methylene chloride) resulted in a dose-dependent but significant increase in cell killing[34,35]. It has also shown nitric oxide scavenging activity[35].

Oral administration of an aqueous *T. cordifolia* root extract have been tested with success to evaluate its antioxidant activity. Administration of it (2.5 and 5.0 g/kg) for 6 weeks resulted in a decrease in the level of plasma thiobarbituric acid reactive substances, ceruloplasmin, and α–tocopherol in alloxan diabetic rat. Extract of *T. cordifolia* has been shown to inhibit the lipid peroxidation and superoxide and hydroxyl radicals *in vitro*[36]. According to Singh *et al.*[37] TC is potent chemopreventive agent against various diseases including cancer as it induces engymes of carcinogen/drug metabolism and antioxidant system.

Japetia and Rao[38,39] observed antitumor properties of Dichloromethane extract of Guduchi and reported that cytotoxic effect of this extract may be due to lipid peroxidation and release of LDH and decline in GST.

Alcoholic extract of TC can influence the myeloid differentiation of bore marrow progenitor cells and the recuitment of macrophages in response to tumor growth *in situ*[40].

Badar *et at.*[41] assessed the efficacy of *T. cordifolia* extracts in patients of allergic rhinitis in a controlled trial. Here TC significantly decreased all the symptoms of allergic rhinitis and nasal smear cytology and leucocyte count correlated with it.

The plant extract in combination with *Picrorhiza kurrooa* was found to enhance host resistance and reduce the side effect of other toxic agents[7].

Oral administration of *Tinospora cordifolia* 5 mg/kg body wt. to Swiss albino mice one hour prior to whole body irradiation (8 Gy) showed radioprotective effect in Swiss albino mice[42]. It also protected various body tissues including testis and intestine.

Administration of CCl_4 (0.7 ml/kg body weight for 7 days) produces damage in the liver as evident by estimation of enzymes. *T. cordifolia* extract (100 mg/kg body weight for 15 days) in CCl_4 intoxicated rats was found to protect the liver, as indicated by enzyme level in serum. A significant reduction in serum levels of SGOT, SGPT, ALP and Birirubin were observed following *T. Cordifolia*

treatment. It may be a critical remedy for the adverse effects of CCl_4 in liver function as well as immune function[43].

The antioxidant activity of an Arabinogalactan polysacchride (TSP) isolated from *T. cordifolia* was studied. The polysaccharide showed good protection against Iron-mediated lipid peroxidation of rat brain homogenate as revealed by the Thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxidase. TSP also provide significant protection to protein against Gamma-ray induced damage. The protective action can possibly be explained by its very high reactivity towards DPPH, superoxide radicals and the most damaging of radical, hydroxyl radicals[44]. Prince *et at.*[45] reported that oral administration of it increased concentration of TBARS in liver and kidney. They also reported decreased concentration of GSH and decreased activities of superoxide dismutase and catalase in liver and Kidney.

Manjrekar *et al.*[46] reported that water and Ethanol extracts of stems of *T. cordifolia* and *T. Sinensis* inhibit immunosuppression produced by Cyclophosphamide. Ethanol extracts of stems of both the plants inhibit cyclophosphamide-induced anemia. The water extract of *T. Sinensus* was found to be more potent than the other extracts.

Singh *et al.*[47] observed that *in vivo* administration of alcoholic extract of TC to mice bearing a spontaneous T cell lymphoma designated as Dalton's lymphoma prevented tumor growth dependent regression of thymus. It restores thymus homeostasis and increases survival of tumor bearing mice.

Goel and Prem Kumar[48] have reported that aqueous extract of *T. cordifolia* inhibited fenton ($FeSO_4$) reaction and radiation mediated 2DR degradation. It also inhibited the formation of Fe^{2+} lipridyl complex and formation of camet tail by chelating Fe^{2+} ions in a dose dependent manner. It inhibited fereus sulphate mediated lipid peroxidation.

Levon and Kuttan[49] studied antiangiogenic activity of TC *in vivo* and *in vitro* models. They observed that administration of TC extract regulate cytokine's regulation. It also inhibits microvessel outgrowth from the aortic ring after intraperitoneal administration at the rate of 20 mg/kg.

Rao *et al.*[50] tested TC alcoholic extract in a rat model in which surgically myocardial ischemia was induced. They observed that TC pretreatment is cardioprotective and limits ischemia reperfusion induced myocardiol infarction.

Immunosuppression associated with deranged hepatic function and sepsis results in poor surgical outcome in extra hepatic obstructive jaundice. The patients were given TC (16 mg/kg/day orally) during the period of biliary drainage alongwith vitamin K and antibiotics. It was concluded that TC improves the drainage by strengthening host defenses[51]. Kupffer cell function is suppressed in liver damage. It is protected by TC pretreatment[52].

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