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TINOSPORA CORDIFOLIA: A CLIMBING SHRUB IN HEALTH CARE MANAGEMENT

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ABSTRACT

Tinospora cordifolia is a deciduous climbing shrub described as '*the one who protects the body against diseases*'. It is one of the most versatile rejuvenating shrub also known as 'Giloya' in Indian vernacular having many therapeutic applications. The pharmaceutical significance of this plant is mainly because of the leaves, barks and roots contain various bioactive compounds such as alkaloids, glycosides, lactones, steroids, polysaccharides and aliphatic compounds having various medicinal importance viz. immunomodulatory or immunostimulatory, antitumor, cognition, anti-inflammatory, anti-neoplastic, antihyperglycemia, antihyperlipidemia, antioxidant, anti-tuberculosis, gastrointestinal and hepatoprotection, anti-osteoporotic, anti-angiogenic, anti-malarial, anti-allergic and side effects prevention of the cancer chemotherapy. The bitter priniciples present in the leaves, stems, roots and barks viz. tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, berberine, cordifolioside A, B. C, amritosides A, B, C, and columbin which act as therapeutic agents and play vital role in many therapeutic applications. Various parts of the plant are being prescribed in Ayurveda and other systems of medicine as a monoherbal or polyherbal preparation. The climbing shrub has shown a great potential for the development of industrial products and commercial exploitation of biopharmaceuticals for the treatment of various diseases. The focus of the present review is to galvanize the potential of medicinal importance of this shrub for health care management.

KEYWORDS: Tinospora cordifolia, climbing shrub, immunomodulation, anti-tumor, tinosporine, cordifolide.

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INTRODUCTION

Medicinal plants since times immemorial have been used in virtually all cultures as a source of medicine. The widespread use of herbal remedies and healthcare preparations as those described in ancient texts such as the Vedas and the Bible and obtained from commonly used traditional herbs and medicinal plants have been traced to the occurrence of natural products with medicinal properties. *Tinospora cordifolia* (Willd.) Miers exHook. F. & Thoms (Menispermaceae) is a large deciduous climbing shrub found throughout India, especially tropical part of India and also in certain parts of China. It is describe as '*the one who protects the body against disease*'. According to the 1918 United States Dispensatory, the plant has a long history of use in India as a medicine and in the preparation of a starch known as gilae-ka-sat or as palo. Its therapeutic strength lies in its rejuvenating and strengthening properties while also detoxifying and cleansing the whole system, specifically via liver. It is widely used as anti-bacterial, analgesic, antipyretic and also for the treatment of jaundice, skin diseases, anemia etc. The stem is used in dyspepsia, fever and urinary diseases[1]. The biter principle present shows several medicinal applications viz. antiperiodic, antispasmodic, anti-inflammatory, immunomodulatory or immunostimulatory, antitumor, cognition, anti-neoplastic, antihyperglycemia, antihyperlipidemia, antioxidant, anti-tuberculosis, gastrointestinal and hepatoprotection, anti-osteoporotic, anti-angiogenic, anti-malarial, anti-allergic and antipyretic properties (Fig 1)[2]. The root is a powerful emetic and used for visceral obstructions; its water extract used in leprosy also has antidiabetic effect. The extracts of stem, leaves, barks and roots show strong antioxidant activities. This wonderful Ayurvedic herb helps in raising the efficiency of protective WBC (white blood cells) and builds up the body's own immune system. Some of the health experts and Ayurvedic doctors also prescribe Tinospora for some sexually transmitted diseases such as gonorrhea. The shrub is useful in treating various skin diseases and in some cases, hyperacidity too. Guduchi has been systematically formalized by several clinical studies to maximize benefits. Its formulations have been subjected to the contemporary examination of clinical testing to prove its benefits in lightly addressing the health concerns, and its quality is controlled by the most advanced chromatographic techniques. The pharmaceutical significance of this shrub is mainly because of various bioactive compounds found in this plant such as glucoside, alkaloidal constituents including berberine, three fatty alcohol, a bitter glucoside giloin, a nonglucosidic bitter substance gilonin[3]. This review mainly gives a bird view of the chemical constituents and bioactive components, biological activities, therapeutic or pharmacological actions and medicinal applications of *T. cordifolia* extracts.

PHYTOCHEMISTRY AND BIOACTIVE COMPOUNDS

A variety of constituents have been isolated from *T. cordifolia* plant and their structures were well elucidated. They belongs to different classes such as alkaloids, diterpenoid lactones, glycosides, sesquiterpenoid, aliphatic compounds, phenolics, polysaccharides, steroids like tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furanolactone tinosporidine, columbin and β-sitosterol. Leaves of the plant are rich in protein (11.2%) and are fairly rich in calcium and phosphorus[4]. Studies on the physical characteristic and chemical composition of the starch obtained from *T. cordifolia* (extract) were carried out and the polysaccharide was found to consist chiefly of 1→4 linked glucan with occasionally branched points[5]. The aqueous extract of guduchi stem has shown the presence of arabinogalactan that showed immunological activity[6]. An arabinogalactan had been isolated from the dried stems of *T. cordifolia.* The methanolic extract of the plant contains

phenylpropanoids, norditerpene furan glycosides, diterpene furon glycosides and plytoecdysones[7].

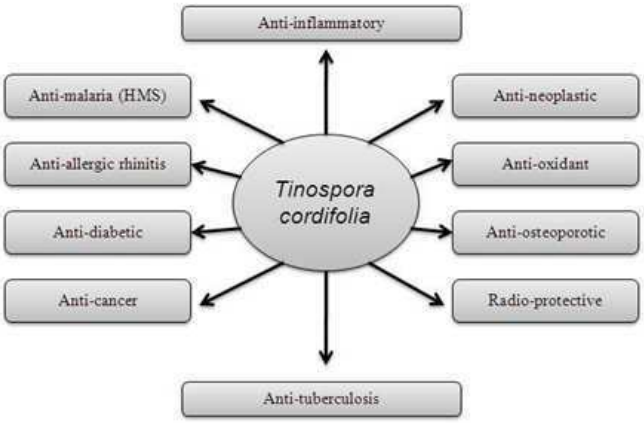

***Figure 1 Medicinal uses of* Tinospora cordifolia**

(I) Alkaloids

A great deal of chemical investigation on this plant is already on record and a number of protoberberine and aporphine alkaloids have been reported to occur on it. Based on some spectral evidence occurrence of terahydropalmatin and jatrorhizine were reported[8,9,10]. Kiem *et al.*[11] isolated and elucidated the structure of two new aporphine alkaloids (Fig 2). A berberin and palmatine had been isolated from the stem of *T. cordifolia*[12]. Studies showed that berberine induced apoptosis in human tongue cancer SCC-4 cells *in vitro*[13]. Tembetarine, Choline, Tinosporin, Isocolumbin, Palmatine, Tetrahydropalmatine and Magnoflorine were also isolated from root extract of *T. cordifolia*.

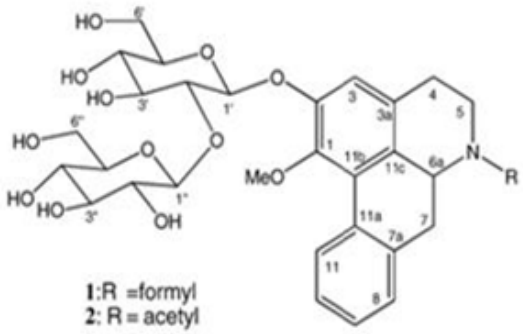

Figure 2 *Structure of aporphine alkaloids*

(II) Glycosides

Kiem *et al.*[11] isolated and elucidated the structure of eleven compounds including two new aporphine alkaloids, a new clerodane diterpene (3), and a new phenylpropanoid (7) from the methanol extract of *T. cordifolia* aerial parts. The known compounds were identified as borapetoside F (4)[14], borapetoside B (5)[15], polypodine B 20,22-acetonide (6)[16], syringin (8)[17], angelicoidenol 2-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (9), secoisolariciresinol-9′ O-β-D-glucopyranoside (1)[18], and pinoresinol-di-O-glucoside (2)[19] by comparison of their NMR and ESI-MS data with the literature values (Fig 3 A). Gangan *et al.*[20] investigated and elucidated the three new compounds cordifolioside A, cordifolioside B and Cordifolioside C in tetraacetate forms 1a, 2a and 3a respectively (Fig 3 B). In 1995, they also characterize two more norditerpene furan glycosides, cordifoliside D (1) and cordifoliside E (2), in the tetra acetate forms la and 2a, respectively (Fig 3 C). The four new clerodane furano diterpene glucosides, designated as amritosides A, B, C and D (1–4), in the acetate forms (1a–4a), respectively have been isolated from the plant[21] (Fig 4 A). A new diterpene glucoside named cordioside (1) together with four known compounds tinosporaside (7), syringin (8),

columbin (9) and 2 were investigated from stems of the plant (Fig 4 B)[22]. Later Maurya *et al.*[23] isolated and elucidated the structure of two new clerodane diterpenoids tinosponone (1) and tinocordioside (4) from the plant (Fig 4 C).

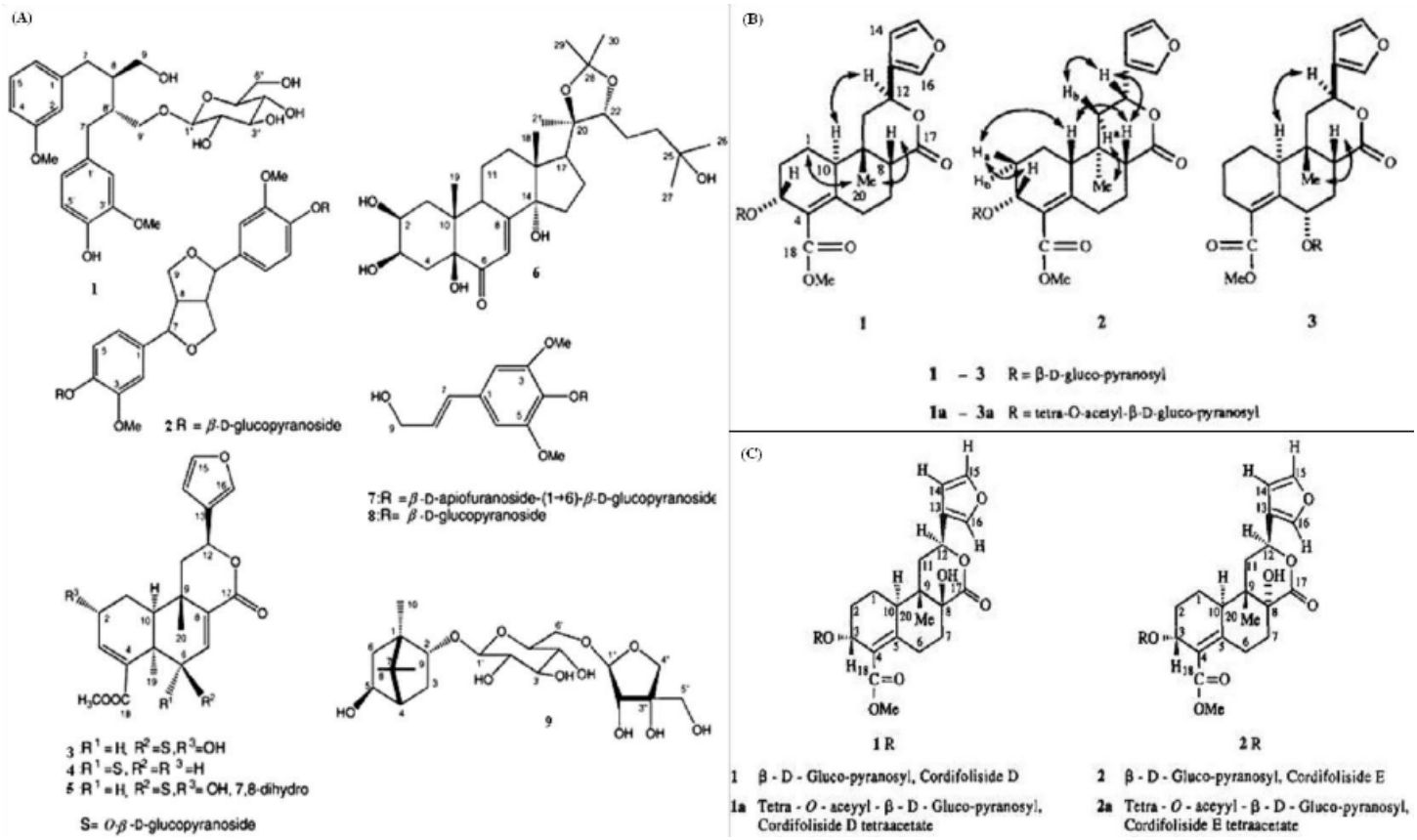

Figure 3 Structure of glycosides and cordifolisides (A) Structures of glycosides 1-9 (B) Structures of cordifolioside A, B and C in tetracetate forms 1a-3a (C) Cordifoliside D (1) & Cordifoliside E (2), in the tetra acetate forms Ia and 2a

In the recent past years photo- reactivity of synthetic drugs has been intensively studied for their phototoxicity and phototherapeutic value. Plant materials are well known for their biological activity and medicinal values. Iqbal *et al.*[24] investigated photooxidation of tinosponone, a clerodane diterpene isolated from *T. cordifolia* under different combinations of sensitizer dyes and solvents.

(III) Diterpenoid Lactones

The whole parts of the plant *T. cordifolia* contain diterpenoid lactones i.e. Furanolactone[25], Jateorine, Tinosporides and Columbin etc[26]. Swaminathan *et al.*[26] elucidated the structure of tinosporide. Two terpene rings, two delta-lactones, two methyl groups, a tertiary hydroxyl group and a beta-substituted furan ring are present in the structure. The H atoms at C (12) and C (8) are alpha-and beta-oriented. The terpene ring A is locked into a boat conformation by the C (1)-C (4) lactone bridge. The furan ring is attached equatorially at atom C (12). The hydroxyl group is involved in intramolecular hydrogen bonding. Later, they also elucidated the structure of columbin and found two terpene rings, two delta-lactones, two methyl groups, a tertiary hydroxyl group and a beta-substituted furan ring in the structure. The H atoms at C (12) and C (8) are alpha-and beta-oriented. The terpene ring A is locked into a boat conformation by the C (1)-C (4) lactone bridge. The furan ring is attached equatorially at atom C (12). The hydroxyl group is involved in intramolecular hydrogen bonding.

(IV) Steroids

Dixit and Khosa[27] investigated β-sitosterol, δ-sitosterol, 20β- hydroxyl ecdysone from the aerial part of the plant. Later Gangan *et al.*[7] elucidated the structure of Makisterone and Ecdysterone from the stem of the *T. cordifolia*.

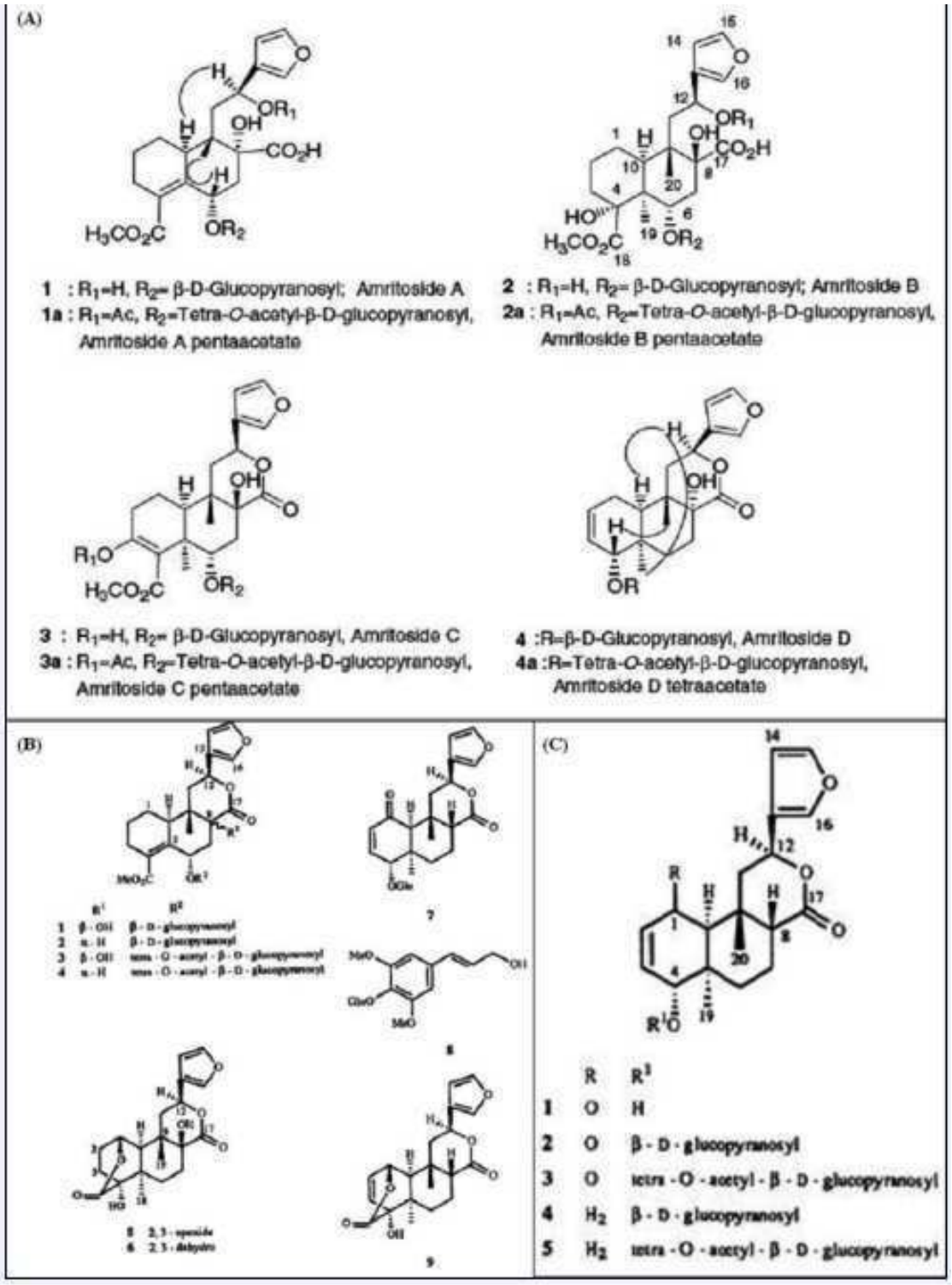

Figure 4 Structures of secondary metabolites. (A) Structures of Amritosides A, B, C and D (B) Structure of Cordioside (1) along with four know compounds tinosporaside (7), syringin (8), columbin (9) and (2) (C) Structure of tinosponone and tinocordioside (1, 4)

(V) Aliphatic compound

It can be cyclic, like cyclohexane, or acyclic, like hexane and also can be saturated or unsaturated. In aliphatic compounds, carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (in which case they are called alicyclic). They can be joined by single

bonds (alkanes), double bonds (alkenes), or triple bonds (alkynes). Besides hydrogen, other elements can be bound to the carbon chain, the most common being oxygen, nitrogen, sulfur, and chlorine. Octacosanlo Heptacosanol and Nonacosan-15-one were found in the whole parts of the plant *T. cordifolia*[27].

(VI) Other compounds

In addition to Alkaloids, Glycosides, diterpenoid lactones, steroids and aliphatic compounds, *T. cordifolia* having more compounds have been investigated. 3, (α, 4-di hydroxy-3-methoxy-benzyl)-4-(4-hydroxy-3-methoxy-benzyl)-tetrahydrofuran[27], Jatrorrhizine[8] Cordifelone[28], N-trans-feruloyl tyramine as diacetate[7], Giloin, Giloinin and Tinosporic acid[29] are found in the whole parts of the plant as well as Tinosporidine and Cordifol[28] are found in the root of the plant**.**

ETHNOMEDICINAL USES

Guduchi (*T. cordifolia*) is commonly known as rasayana plant and its rejuvenating property is well reported in Ayurvedic and other ancient literature. Various parts of the plant are being prescribed in Ayurveda and other systems of medicine as a monoherbal or polyherbal preparation. In India, various extracts of the plant are traditionally used as a remedy for many diseases and are included in various polyherbal preparations used for the treatment of diabetes, hepatitis, etc.

The leaves are beaten with honey and applied to ulcers. Dried and powdered fruit, mixed with ghee or honey, is used as a tonic and also in the treatment of jaundice and rheumatism. The root is powerful emetic and used for visceral obstructions; its watery extract is used in leprosy. A decoction of the leaves is used for the treatment of gout, and young leaves, bruised in milk, are used as a liniment in erysipelas. Guduchi or Giloy also improve the functioning of protective cells, macrophages and improve body's resistance to infection. Guduchi or amrita is a very good and helpful diuretic agent that helps removing renal stones and reducing blood urea from the blood.

The whole plant is used in scabies in swine. The vine is used as an apetizer and for internal parasites in ruminants as well as for diarrhea in poultry. It is also used in stomach trouble. Stem, root and whole plant are used in sprain, abscess, tumor, wound, broken horn, cracked tail, anthrax, as a galactagogue and in the treatment of pneumonia, asthma, cough, swelling of lungs colic, constipation, tetanus, pox and compound fracture.

PHARMACOLOGICAL IMPORTANCE

T. cordifolia is one of the indispensable medicinal plants used in veterinary folk medicine/Ayurvedic system of medicine for the treatment of diverse diseases and recommended for improving the immune system by means of body resistance. Authors group previously described some medicinal plants and biological entities (macrofungus) as golden gift for human kind[29-32]. In continuation, *T. cordifolia* has been the subject of extensive phytochemical and bioactive investigations due to its importance in traditional folk and Ayurvedic system of medicine. In Ayurvedic medicine, it is used for treatment of jaundice, rheumatism, urinary diseases, lever and intestinal disorders, diabetes, skin diseases and anaemia. The extracts of this plant have also exhibited anti-inflammatory and anti-allergic properties. Some of the pharmacological activities are described below:

(I)Immunomodulatory/Immunostimulatory Activity

Acquired immune-deficiency syndrome (AIDS) is a fatal illness caused by human immune-deficiency virus (HIV), which break down the host immune system, leaving the subject vulnerable to life-threatening opportunistic infections, neurological disorders and malignancies. Once infected, it

is probable that a person will be infected for life. It has been suggested that when routinely used pharmacological interventions fail to relieve the symptoms, immunotherapy may be effective. It is therefore, worth looking for a natural product that is safer, affordable, effective, better tolerated and devoid of side effects. *T. cordifolia* is well documented for its immunomodulatory activities since many years; some compounds are being isolated, characterized and subjected for their possible mode of immunomodulatory activity. Kalikar *et al.*[34] investigated the Immunomodulatory effect of *T. cordifolia* extract in human immuno-deficiency virus positive patients. For this, they assessed the efficacy of *T. cordifolia* extract (TCE) in HIV positive patients in randomized double blind placebo controlled trial. 68 HIV positive participants are randomly assigned to two groups to receive either TCE or placebo for six months. After clinical examination TLC, DLC, ESR, platelet count, hemoglobin and CD4 count were done. The results showed that TCE treatment caused significant reduction in eosinophil count and hemoglobin percentage. 60% patients receiving TCE and 20% on placebo reported decrease in the incidence of various symptoms associated with disease. Their findings suggest that *T. cordifolia* extract, a plant derived immunostimulant, significantly affected the symptoms of HIV. This was validated by clinical evaluation. However not all of the objective parameters studied by them, back this up. *T. cordifolia* could be used as an adjunct to HIV/AIDS management.

Sudhakaran *et al.*[35] investigated the immunostimulatory effect of leaf extract of *T. cordifolia* on (a) specific immunity (antibody response), (b) non-specific immunity (neutrophil activity) and (c) disease resistance against *Aeromonas hydrophila* in *O. mossambicus* using ethanol and petroleum ether extracts of the leaves. They observed that the fish injected with both the extract at a dose of 8 mg/kg were protected against experimental infection with virulent *A. hydrophila* and concluded that the potentiality of *T. cordifolia* leaf extracts for use as an immunoprophylactic to prevent diseases in finfish aquaculture. Immunological activity of extract of *T. cordifolia* has also been reported by several researchers[36-42].

According to recent reports, arabinogalactan polysaccharide (G1-4A) from the stem, appear to induce tolerance against endotoxic shock by modulation of cytokines and nitric oxide. In addition, it also modulates the release of nitric oxide by marine macrophages[38]. Nair *et al.*[39,40] reported the immunostimulating signaling mechanism of the novel (1, 4)-alpha-d-glucan through the activation of macrophages that occurs through TLR6 signaling, NF-kappa B translocation and cytokine production.

(II) Anti-cancer/Anti-tumor Activity

Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. Cancer of the oral cavity is a common disease in Asian country and oral squamous cell carcinoma (OSCC) is clinically the most common in Indian males. Treatment with *T. cordifolia* extracts (TCE) *in vitro* inhibited cell proliferation and induced cell death in a dose-dependent (25-75µg/ml) and time dependent (24-120 hours) manner in oral squamous cell carcinoma cell line along with a significant cytostatic effect. Hence; it may have therapeutic potential in cancer[44]. Singh *et al.*[2] reported differentiation and anti-tumor functions of tumor-associated macrophages (TAM) derived dendritic cells (DC) obtained from tumor-bearing host administered with alcoholic extract of *T. cordifolia* (ALTC). In another report by Singh *et al.*[44] who investigated the effect of *in vivo* administration of alcoholic extract of *T. cordifolia* whole plant (ALTC) on the proliferation and myeloid differentiation of bone marrow hematopoietic precursor cells in mice bearing a transplantable T cell lymphoma of spontaneous origin designated as Dalton's lymphoma (DL). Their study indicates that the *T. cordifolia* can influence the myeloid differentiation of bone marrow progenitor cells and the recruitment of macrophages in response to tumor growth *in situ*.

Recent reports have claimed that many anticancer drugs or cancer chemo-preventive agents act through the induction of

apoptosis to prevent tumor promotion and progression. Thippeswamy and Salimath[45] reported the mechanism of cell death exhibited by the hexane extract fraction of *T. cordifolia* (TcHf) against Ehrlich ascites tumor (EAT) in mice. They concluded that the hexane fraction of *T. cordifolia* is capable of inducing apoptosis in EAT cells *in vivo*. Metastasis is also a major problem of treatment failure in cancer patients. Administration of the polysaccharide fraction from *T. cordifolia* was found to be very effective in reducing the metastatic potential of B16F-10 melanoma cells. There was a 72% inhibition in the metastases formation in the lungs of syngeneic C57BL/6 mice, when the drug was administered simultaneously with tumour challenge. Biochemical parameters such as lung collagen hydroxyproline, hexosamines and uronic acids that are markers of neoplastic development were reduced significantly ($P < 0.001$) in the treated animals compared with the untreated control animals. The treatment could also reduce serum γ-glutamyltranspeptidase (γ-GT) and sialic acid levels as compared to the control animals[46]. Several researchers report the anti-tumor activity of *T. cordifolia* but the mechanism of action of *T. cordifolia* extract (TCE) is not yet understood. Jagetia and Rao[47] elucidated the possible mechanism underlying the cytotoxic effects of dichlormethane extracts of TCE, after selecting optimal duration and concentration for treatment. Their results suggest that the cytotoxic effect of TCE may be due to lipid peroxidation and release of LDH and decline in GST.

(III)Cognition (Learning and Memory) Activity

Dementia is a syndrome of failing memory and other intellectual functions with little or no disturbance in consciousness[48]. Degeneration of the cerebral neurons is one of the commonest and vital causes for dementia with increasing age, there by leading to deterioration in quality of life in elderly. *T. cordifolia* (TC) extract effects on learning and memory in normal and cyclosporine induced memory deficit rats. Alcoholic and aqueous extracts of the whole plant of *T. cordifolia* was administered orally for 15 days in two groups of rats. Cyclosporine 15, 25 mg/kg, *i.p.* was administered on alternate days for 10 days. Combination of cyclosporine 25 mg/kg, *i.p.* for 10 days and TC alcoholic 200 mg/kg and TC aqueous 100 mg/kg were administered in two different groups of rats. Both alcoholic and aqueous extracts of TC produced a decrease in learning scores in Hebb William maze and retention memory indicating enhancement of learning and memory. However, cyclosporine at both the doses increased the learning scores in Hebb William maze and decrease in retention time in the passive avoidance task suggesting a memory deficit. The combination of cyclosporine and TC produced a decrease in learning scores in Hebb William maze and increase latency in passive avoidance task compared to cyclosporine alone treated rats. Their results indicated that TC enhances cognition (learning and memory) in normal rats. Cyclosporine induced memory deficit was successfully overcome by TC[49].

(IV)Anti-inflammatory and Wound Healing Activity

The aqueous extract of *T. cordifolia* exerted a significant anti-inflammatory effect on cotton pellet granuloma and formalin induced arthritis models. Its effect was comparable with Indomethacin and its mode of action appeared to resemble that of a non-steroidal anti-inflammatory agent. The dried stem of *T. cordifolia* produced significant anti-inflammatory effect in both acute and sub acute models of inflammation. *T. cordifolia* has been found to be more effective than acetylsalicylic acid in acute inflammation but in sub acute inflammation, the drug is inferior to phenylbutazone[50]. Meravanige and Priyadarshini[51] investigated the effect of TC on wounds healing in albino rats. They revealed that TC promotes wound healing, peri-operative use of TC leads to healing of surgical wounds. They concluded that TC may be attributed to the phytoconstituents present in it, which may be either due to their individual or additive effect that hastens the process of wound healing. The component(s)

of the extract that is responsible for this effect has not been investigated.

(V) Anti-neoplastic Activity

Jagetia *et al.*[52] have found that guduchi killed the HeLa cells very effectively *in vitro* and thus it indicates that guduchi needs attention as an anti-neoplastic agent. In the study exposure of HeLa cells to 0, 5, 10, 25, 50 and 100 mg/ml of guduchi extract (methanol, aqueous and methylene chloride) resulted in a dose dependent but significant increase in cell killing when compared to non-drug treated controls.

(VI) Anti-tuberculosis Activity

Ether extract of the stem distillate of aerial part of *T. cordifolia* has inhibited the *in vitro* growth of *Mycobacterium tuberculosis* at 1:50,000 dilutions. Its ethanolic extract has exhibited significant antipyretic activity in experimental rats. 'Septilin' syrup, a compound preparation containing *T. cordifolia* (7.82% in 5 ml of syrup) has been found to elicit good clinical response in children suffering from upper respiratory tract infection and chronic otitis media[53].

(VII) Hepatoprotective and Anti-oxidant Activity

T. cordifolia is very well documented for hepatoprotective and antioxidant activity. Crude extract of TC showed protective effect on drug induced liver injury and immunosuppression by isoniazid, rifampicin and pyrazinamide. Aerial root extract has protective action against liver injury induced by the above-mentioned anti-tubercular drugs and it prevents immunosuppression. It is suggested that consumption of hepatoprotective herbs like TC with the above said drugs could minimize the liver toxicity[54]. The hepatoprotective action of *T. cordifolia* has been reported in which goats treated with *T. cordifolia* have shown significant clinical and hemato-biochemical improvement in CCl_4 induced hepatopathy. Extract of *T. cordifolia* has also exhibited *in vitro* inactivating property against Hepatitis B and E surface antigen in 48-72 hrs[55]. Pepticare, a herbomineral formulation that contains Amrita has antiulcer and antioxidant activity. This formulation at a dose of 125, 250, 500 and 1000 mg/kg, p.o produces a significant antiulcer activity in the pylorus ligated rat model. It is postulated that antioxidant mechanism of the formulation is responsible for the possible anti ulcer activity[56]. One more polyherbal formulation has hepatoprotective effect on a day-old broiler chicken in paracetamol induced hepatic injury[57].

The aqueous extract of roots of *T. cordifolia* has shown the anti-oxidant action in alloxan diabetes rats. The administration of the extract of *T. cordifolia* roots (25, 50 mg/kg body weight) for 6 weeks resulted in a significant reduction of serum and tissue cholesterol, phospholipids and free fatty acids in alloxan diabetic rats[58]. It is reported that the alcoholic root extract normalizes the antioxidant status of heart, brain, liver and kidney at a dose of 100 mg/kg orally for six weeks and the effect is more prominent than glibenclamide and insulin[59,60]. The possibility of using proven antioxidant climbing shrub *T. cordifolia* for the ischemic brain damage has also been reported. The climbing shrub has strong free radical scavenging properties against reactive oxygen and nitrogen species as revealed by electron paramagnetic resonance spectroscopy, diminishing the expression of iNOS gene, therefore attenuating oxidative stress mediated cell injury during oxygen glucose deprivation and exerting the above effects at both the cytosolic as well as at gene expression levels. Hence *T. cordifolia* may be an effective therapeutic tool against ischemic brain damage[61-63].

A polyherbal formulation "HIMOLIV" is useful in hepatitis, jaundice and biliary dysfunction. It produces protective effect on the carbon tetrachloride and paracetamol induced liver necrosis at the dose of 0.5 and 1.0 ml/kg, p.o[64]. Another polyherbal formulation "HP-1", possess strong hepatoprotective and antioxidant activity, when administered orally[65]. Significant reduction in thiobarbituric acid reactive substances and an increase in reduced glutathione, catalase and superoxide dismutase activity in alloxan induced diabetic rats are the results of aqueous root extracts.

This effect has been found to be more than glibenclamide[66,67]. Extract of this climbing shrub prevents the toxic effects produced in mice hematological system attributed to the free radical generated due to the administration of cyclophosphamide[68].

(VIII) Anti-osteoporotic Activity

On the basis of inflammation as one of the major causes of bone loss and profound use of the plant *T. cordifolia* in preparation of several immunomodulatory and anti inflammatory medicines, anti-osteoporotic potential of *T. cordifolia* ethanolic stem extract in ovariectomized rat model of osteoporosis has been investigated[69]. Ovx rats treated with TC (10 mg/kg b.wt) showed an osteoprotective effect. They found serum osteocalcin and cross-laps levels have been significantly reduced as well as alkaline phosphatase activity significantly higher in TC treatment groups. Total cholesterol and LDL levels remained unaltered but HDL levels has significantly lowered with TC (50 mg/kg b.wt) treatment. Uterus and mammary gland showed no signs of proliferation after treatment with TC extract. TC extract showed estrogen like effects in bone but not in reproductive organs like uterus and mammary gland.

In another report by Abiramasundari et al.[70], investigated the effects of the alcoholic TCE on the proliferation, differentiation and mineralization of bone like matrix on osteoblast model systems in vitro. Results showed that the alcoholic extract of TC at a dosage of 25µg/ml stimulated the growth of osteoblasts, increased the differentiation of cells, increase the cell numbers into osteoblastic lineage and increased the mineralization of bone like matrix on the osteoblast model systems. Their finding suggests that TCE has a potential influence on osteogenesis and hence its use could be explored as a potential anti-osteoporotic agent.

(IX) Anti-angiogenic Activity

The antiangiogenic activity of *T. cordifolia* has been studied using *in vivo* as well as *in vitro* models. *In vivo* study done using B16F10 melanoma cell-induced capillary formation in animals. Intraperitoneal administration of the extract at a concentration of 20 mg/kg significantly inhibited the tumor directed capillary formation induced by melanoma cells. Analysis of the serum cytokine profile showed a drastic increase of proinflammatory cytokines such as IL-1b, IL-6, TNF-a, granulocyte monocyte-colony stimulating factor (GM-CSF) and the direct endothelial cell proliferating agent vascular endothelial cell growth factor (VEGF) in the angiogenesis-induced control animals. Administration of Tinospora extract could differentially regulate these cytokine's elevation. The differential regulation is further evidenced by the increased production of antiangiogenic agents IL-2 and tissue inhibitor of metalloprotease-1 (TIMP-1) in the B16F10-injected, extract-treated animals. Moreover, using an *in vitro* rat aortic ring assay, it is observed that the extract at nontoxic concentrations inhibited the production of proangiogenic factors from B16F10 melanoma cells. Direct treatment of the extract also inhibits the microvessel outgrowth from the aortic ring. Hence, the observed antiangiogenic activity of the plant *T. cordifolia* is related, at least in part, to the regulation of the levels of these cytokines and growth factors in the blood of the angiogenesis-induced animal[46].

(X) Anti-malaria (HMS) Activity

Hyper-reactive malarious splenomegaly (HMS) is thought to be the result of immunological dysfunction due to recurrent episodes of malaria. HMS is treated by chloroquine (CQ)/ proguanil/pyrimethamine prophylaxis. There is paucity of clinical trials to compare the efficacy of different antimalarial drugs in HMS. The effect of aqueous extract of *T. cordifolia* along with chloroquine in the treatment of three cases of HMS was studied[2]. Aqueous extract of *T. cordifolia* (500mg) added to CQ base (300mg) weekly and CQ prophylaxis including spleen enlargement, Hb, serum IgM and well-being have been observed up to six months. The results showed regression of spleen by 37-50% after six weeks and 45-69% after six months. Likewise decrease in IgM and increase in Hb as well as well being

were observed. Their findings required large-scale trial to confirm the beneficial effect of *T. cordifolia* extract in combination with chloroquine.

(XI) Anti-allergic rhinitis Activity

Allergic rhinitis is the commonest atopic disease with prevalence of 5–22%. It is the sixth most prevalent condition in the US, outranking cardiac disease. Allergic rhinitis implies hypersensitive response following exposure to allergens including pollens of grass, weeds, trees, animal dander's, house dust and food. Rhinitis symptoms impair patient's quality of life[71]. It has been suggested that when routinely used pharmacological interventions fail to relieve the symptoms, allergen immunotherapy may be effective[72]. Efficacy of TCE in patients of allergic rhinitis in a randomized double blind placebo controlled trial is reported. For this, seventy-five patients are randomly given either TC or placebo for 8 weeks. With TC treatment 100% relief reported from sneezing in 83% patients, in 69% from nasal discharge, in 61% from nasal obstruction and in 71% from nasal pruritus. In placebo group, there was no relief in 79% from sneezing, in 84.8% from nasal discharge, in 83% from nasal obstruction, and in 88% from nasal pruritus. The difference between TC and placebo groups was highly significant. After TC, eosinophil and neutrophil count decreased and goblet cells were absent in nasal smear. After placebo, decrease in eosinophil and neutrophil count was marginal and goblet cells were present. TC significantly decreased all symptoms of allergic rhinitis.

(XII) Anti-diabetic Activity

Diabetes mellitus (DM) is a metabolic disorder, which affects the people of all age groups and from all walks of life. There are estimated 150 million people worldwide sufferings from diabetes. Attempt has been made to test the anti-diabetic activity of *T. cordifolia* and to study its effect in modulating the kidney morphology and some gluconeogenic enzymes in STZ diabetic rats' kidneys since diabetic nephropathy is one of the major complications in long-term diabetes mellitus. Efficacy of these effects is compared with standard drug insulin. Further effect of *T. cordifolia* (Willd.) stem extracts (both aqueous and alcoholic) in different dosages (200 and 400 mg/ kg b.w) on kidney weight, morphology, serum creatinine, renal gluconeogenic enzymes Glucose-6-phosphatase and Fructose 1, 6-bisphosphatase activity in streptozotocin induced diabetic albino rats has investigated[73]. Drug treated diabetic animals showed a significant effect ($p< 0.05$) of TC on all these parameters except renal morphology, compared to untreated animals. Moreover, the drug administration in control animals did not induce significant change in any one of these parameters, indicates that *T. cordifolia* administration is safe in normal animals. Same study on STZ induced diabetic rats has also been reported by Rajalakshmi *et al.*[74].

Grover *et al.*[75] reported the hypoglycemic action of aqueous extract of *T. cordifolia* at different time intervals from 21-120 days in mice. The extract at a dose of 400 mg/kg per day, exhibits a significant (70.37%) decrease in the plasma sugar level in mild diabetes (plasma sugar levels > 180 mg/dl, duration 21 days) but the hypoglycemic effect is decreased to 48.81 and 0% in moderate diabetes (plasma sugar levels > 280 mg/dl, duration 120 days) and severe diabetes (plasma sugar >400 mg/dl, duration 60 days) respectively.

T. cordifolia has been evaluated for hypoglycemic and hypolipidaemic actions in the alloxan induced diabetic rats. Data showed a significant reduction in blood glucose and brain lipids, also induced an increase in body weight, total haemoglobin and hepatic hexokinase. It also decreased hepatic glucose-6-phosphatase and serum acid phosphatase, alkaline phosphates and lactate dehydrogenase[76]. It also significantly reduced serum and tissue cholesterol, phospholipids and free fatty acids at the dose of 2.5 and 5.0 g/kg body weight for 6 weeks[58]. It is interesting to note that, the aqueous, alcoholic and chloroform extracts of the TC leaves has significant hypoglycemic activity, which is postulated to be an insulin

like action and it has no significant hypolipidaemic activity[77].

Diabetes during pregnancy increases the incidences of congenital anomalies, morbidity and mortality in the mother and her fetus/newborn. Shivananjappa and Muralidhara[78] evaluated the abrogation of maternal and fetal oxidative stress in streptozotocin-induced diabetic rat. Their data revealed that T. cordifolia during pregnancy may provide significant protection against diabetes-induced oxidative stress and thus serve as an effective therapeutic supplement.

(XIII) Radio-protective

Recently, it is found that the aqueous extract of the dried stem of the plant has a pure radio- protecting compound arabinogalactan polysachharide (TP)[6] that is polyclonally mitogenic to mouse B-lymphocytes. Since many of the radio-protective compounds operate via their immunomodulatory activity, it is interesting to assess the potential of the TP enriched polysaccharide preparation (CTP) from *T. cordifolia*, in preventing radiation-induced damages to biomacromolecules and organism. Subramanian *et al.*[79] taken into account and isolate the TP and CTP from the *T. cordifolia* and analyzed the radio-protecting activity using *Saccharomyces cerevisiae* X2180 strain as the *in vivo* test model. It is well known that endogenous antioxidant enzymes like catalase and superoxide dismutase (SOD) act as endogenous defense mechanism against the reactive oxygen species (ROS)-mediated biological damages. Any radioprotectant thus can exert its action by ROS scavenging and/or inducting the generation of the above enzymes *in vivo*. The effects of 12 hr incubation of the yeast cell with CTP (10mg/ml) on the levels of SOD and catalase showed that the CTP treatment did not have any significant effect on the levels of the protective enzymes in the yeast cells. Thus, the radioprotective activity of CTP can be entirely attributed to its superior radical scavenging activity.

(XIV) Cardio-protective

Ethanolic extract of *T. cordifolia* at various dose levels showed dose dependent reduction in infarct size and in lipid peroxide levels of serum and heart tissue[80]. The cardioprotective activity of an herbal formulation "Caps HT2", which contains methanol extract of *T. cordifolia,* has antioxidant, anticoagulant, platelet antiaggregatory, lipoprotein lipase releasing, anti-inflammatory and hypolipidaemic activity in rats[81]. Administration of 2.5 and 5.0 g/kg body weight of aqueous root extract for 6 weeks results in a significant reduction of serum and tissue cholesterol, phospholipids and free fatty acids in alloxan induced diabetic rats[58].

TOXICITY AND SIDE EFFECTS

The Ayurveda literature reports that it can cause constipation, if taken regularly in high doses; it has no side effect and toxicity. However, there is little known about the toxicology of *T. cordifolia* in humans. No adverse reactions have been noted when *T. cordifolia* stem extract was administered to rabbits up to the highest oral doses of 1.6 g/kg, [52,82] and in rats at doses of 1,000 mg/kg of the whole plant extract[80]. However, 40% mortality resulted after mice has given 500-mg/kg body weight of an extract of the stems of *T. cordifolia*[83].

MARKET POTENTIAL

The world is now moving towards the herbal medicine or phytomedicines that repair and strengthening bodily systems (especially the immune system, which can then properly fight foreign invaders) and help to destroy offending pathogens without toxic side effects. A number of National and International Company come into the force for manufacturing and supplying *T. cordifolia* extract due to its high value of pharmacological importance. The products are in the form of plant specific part or whole plant extract on the basis of specific treatment and use of users. The number of herbal products likes *Guduchi, Herbal One, Giloyi Ghanvati, HIMOLIV* and other that made up from *T. cordifolia* or in combination with another herbal extract are supplies by

large number of company like Rajasthan Herbals International, Himalaya, Gurukul, Baidyanath, and Sambex Drugs Pharma etc.

CONCLUSION AND FUTURE PROSPECTS

T. cordifolia is widely used in Ayurveda for treatment of several diseases and used as general tonic, antispasmodic, anti-inflammatory, antiarthritic, antiallergic and antidiabetic. Various parts of the plant are being prescribed in Ayurveda and other systems of medicine as a monoherbal or polyherbal preparation. In India, various extracts of the Plants are used as a remedy for many diseases. Since each part of *T. cordifolia* has some medicinal property, it is very much commercially exploitable. During the last few decades considerable progress has been achieved regarding its biological activity and medicinal applications. Hence, it can be chosen as a source for the development of industrial products for treatment of various diseases. Medicinal value of this climbing shrub has become a matter of great significance particularly some severe diseases like anti-tumor activity which is reported by several researchers but the mechanism of action of *T. cordifolia* extract (TCE) is not yet understood. However, there are currently no standard protocols for guaranteeing its product for quality and efficacy. From a pharmacological point of view, safety is a relative concept and it should be clear by further appropriate research in this direction. A systematic research should be undertaken to develop a modern drug using compounds isolated from this climbing shrub. A modern effective and safe drug can be developed after extensive investigation of its pharmacodynamics, kinetics, proper standardization and clinical trials. *T. cordifolia* has a great potential for the production of useful bioactive metabolites and that they are a prolific resource for drugs. Search for the drugs effective against cancer, aging, hypercholesterolemia, hyper-lipidemia, diabetes, stress etc. and without side effects is the focal point of the research throughout the world. Traditional medicine system provided effective platform for the discovery of many new drugs. Some more therapeutically useful preparations can be marketed, which generates enough encouragement among the scientists in exploring more information about this plant. An extensive research should be undertaken on this climbing shrub and its products including standardization of various parts and subparts as well as drug development program using *T. cordifolia* compounds for their better economic and therapeutic utilization. Further research is needed to establish content and bioactivity of the many compounds present, their mode of actions and the effect of preparation and consumption differences on their medicinal activity.

ABBREVIATION

TC- *Tinospora cordifolia*
HMS- Hyper-reactive malarious splenomegaly
TCE- *T. cordifolia* extract
ALTC- Alcoholic extract of *T. cordifolia*

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