

Tinospora cordifolia (Amruthballi): Medicinal plant with Anticancer activity

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Abstract

This review paper highlights the therapeutic properties of *Tinospora cordifolia* (Amruthballi), Giloy' or 'Guduchi' particularly anticancer activity. Nine species of *Tinospora* are naturalized in the different states of India. *Tinospora cordifolia* is one such plant and has shown to exhibit anti-carcinogenic properties. *Tinospora cordifolia* herbal supplements have recently gained prominence due to their promising immunomodulatory, and anticancer properties. **Berberine** (BBR) is a natural active principle with potential antitumor activity. Significant anti-carcinogenic properties were exhibited by *Tinospora cordifolia*-derived phytochemicals including palmatine, berberine, new clerodane furanoditerene glycoside, arabinogalactan, phenolic compounds and epoxy cleodane diterpene. Cancer is an extreme metabolic disorder that has seen significant advancement in treatment plans and preventative remedies. It is also called neoplastic disease, characterized by the uncontrolled proliferation followed by the constant multiplication of human cells. This leads to the development of tumors of harmful malignant cells with the capacity to be metastatic. These plant derived natural resources have proved to be non-toxic and are potential modes of cancer management and therapy. *Tinospora cordifolia* extracts demonstrated the potent analogs possess multiple effects on numerous molecular targets of malignant cells. These analogs can be developed as non-toxic and therapeutically effective drug products to combat various malignancies.

Keywords: Amruthballi; Antitumor activity; *Ayurveda*; Berberine; Cancer; Giloy; Guduchi; Malignant cells; *Tinospora cordifolia*

1. Introduction

Tinospora cordifolia (Thunb.) and other species belongs to the family *Menispermaceae* is one of the important medicinal plant of pharmaceutical interest [1-46, 47-172]. *Tinospora cordifolia* is also known as Amruthballi (Kannada), 'Giloy' or 'Guduchi' is a genetically diverse plant found in the Indian subcontinent particularly in Western Ghats region of Karnataka, Kerala, and Tamilnadu [1-46, 47-175]. The use of this medicinal plant has been described in detailed manner in Vedic and *Ayurvedic* scriptures. *Tinospora cordifolia* is also found growing in North Indian hilly regions (Uttarakhand, Bihar, UP, Punjab, Sikkim, Meghalaya, Manipur, Assam, and Arunachal Pradesh) and also found in Myanmar, Australia, Sri Lanka, and China [1-46, 47-175]. Amruthballi (*Tinospora cordifolia*) is found growing abundantly in Dharwad, Mysore, Belagavi, Mangalore, Karwar districts of Karnataka state, India [1-46, 47-175]. Total 34 species of *Tinospora* genus are found in Africa, Australia, Asia, Madagascar and Pacific regions of the World [1-43, 47-172]. Nine species of *Tinospora* are naturalized in the different states of India [1-46, 47-172]: 1) *Tinospora cordifolia*, 2) *Tinospora baenzigeri*, 3) *Tinospora glabra*, 4) *Tinospora crispa*, 5) *Tinospora formanii*, 6) *Tinospora maqsoodiana*, 7) *Tinospora sinensis* 8)

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Tinospora smilacina, 9) *Tinospora subcordata* are naturalized in the different states of India [1-46, 47-175]. In traditional medicine, different parts of *Tinospora* are used in the treatment of cancer, syphilis, ulcers, bronchitis, jaundice, urinary disease, piles, skin and liver diseases [1-46, 47-172]. Amruthballi or Guduchi, or Giloy, or *Tinospora cordifolia*, belongs to the menispermaceae family of universal drugs used to treat various diseases in traditional Indian literature. It has received attention in recent decades because of its utilization in folklore medicine for treating several disorders [1-46, 47-175]. Lately, the findings of active phytoconstituents present in herbal plants and their pharmacological function in disease treatment and control have stimulated interest in plants around the world.

Tinospora cordifolia herbal supplements have recently gained prominence due to their promising immunomodulatory and antiviral effects against SARS-CoV-2 [43-149, 170]. During the outbreak of Covid-19, different extracts of *Tinospora cordifolia* was used as a herbal medicine for controlling fever, cough, immunity modulator and throat infections [1-46, 47-172]. The first clinical evidence of HIF-1 reduction in COVID-19 patients receiving AV herbal extract treatment was documented [149, 170]. This study concluded that the use of oral medication of Vasa ghan, Guduchi ghan, and Vasa Guduchi ghan are effective treatment for mild COVID-19 patients [149, 170]. All three treatment arms prevented the disease's progression to its more severe stages [1-46, 47-172]. Immunomodulatory activity of Guduchi, anti-inflammatory, anti-hypoxic, and anti-thrombotic effects were observed for Adhatoda at preclinical levels and clinical study [149, 170]. This is also the first report of in-depth analysis of clinical outcomes of *Ayurvedic* interventions on COVID-19 mild cases, assessed through multiple parameters analyzed at different time points [1-46, 47-172]. Taken together, the results of viral clearance and other systemic beneficial outcomes of host response established the potential of AV, TC, and AV+TC to be safe and efficacious interventions for COVID-19 at doses tested [1-46, 47-172]. One of the study showed the pharmacological effects of the aqueous extracts of *Tinospora cordifolia* (willd.) Hook. f. and Thomson in the form of Giloy Ghanvati (GG) tablets against SARS-CoV-2 spike-protein induced disease phenotype in a humanized Zebra fish model [149, 170]. Treatment with Giloy Ghanvati (GG) tablets reversed the pro-inflammatory cell infiltration in the swim bladder and also rescued the tubule damage and necrosis seen in the kidney [149, 170]. Covid-19 spike-protein induced in fish demonstrated behavioral fever indicative of higher body temperature. This was reversed upon treatment with the test formulation [149, 170]. Taken together, the morphological, cytological, and behavioral changes observed with induction of SARS-CoV-2 spike-protein were rescued to near normal levels with GG treatment [149, 170]. *Tinospora cordifolia* has helped to save the life of people and recovered from covid-19 [149, 170]. Guduchi is ethnobotanically used for jaundice, diabetes, urinary problems, stomach aches, prolonged diarrhea, skin ailments, and dysentery. The treatment with Amruthballi or Guduchi extracts was accredited to phytochemical constituents, which include glycosides, alkaloids, steroids, and diterpenoid lactones [1-149, 170]. *Tinospora cordifolia* (TC) a potential medicinal herb, has been ethnobotanically used as an eco-friendly supplement to manage various diseases, including cerebral fever [1-46, 47-175]. Earlier studies have shown that TC exhibits diverse beneficial effects, including hepatoprotective and neuroprotective effects. Another study in 2024 revealed promising insights on the protective effects of TC against Hepatic encephalopathy [1-46, 47-175]. The findings clearly demonstrated that the significant inhibition of MAPK/NF- κ B signaling and glial cell activation could be responsible for the observed beneficial effects of TC in TAA-induced Hepatic encephalopathy rats [1-46, 47-175].



Figure 1 The wild growth of *Tinospora cordifolia*

Herbal medicine in the form of *Ayurveda*, is a well-documented and widely accepted traditional medical system in India. The use of traditional and complementary medicine is often seen in chronic illness and a general improvement of

wellness. India with its rich plant biodiversity and enormous knowledge of Ayurvedic, Himeopathic, Siddha, Unani system of medicines, provide a strong base for the utilization of plants in general healthcare and common complaints of the people. In a traditional **Indian Ayurvedic** system of medicine, plants and plant-based constituents have been extensively used for the treatment and management of different types of viral and other diseases including cancer. **Ayurveda** is a holistic approach to health and wellness that emphasizes balance between body, mind, and spirit. It is one of the oldest and the most respected Indian herbal medicinal traditions in the world [105-142]. **Ayurveda means 'Science of life'**. It provides a complete system to have a long and healthy life. India has the exclusive distinction of its own recognized traditional medicine; **Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (AYUSH)**. Many safe traditional formulations of **AYUSH**, which are well known immunity modulators, have been used for centuries to control the viral disease, cancer, respiratory disorders, and in allergic conditions. Indian *Tinospora* species possess various pharmacological attributes such as anticancer, antitumor, antioxidant, hepatoprotective, radioprotective, neuroprotective, antidiabetic, anthelmintic, antimicrobial, analgesic, antifertility, antiarthritic, antistress, anti-inflammatory, immunomodulatory, wound healing, and antiulcer activities [1-46, 47-175]. These biological activities of Indian *Tinospora* species can be attributed to the presence of a wide range of phytoconstituents including alkaloids (tinoscorsides A-B, palmatine, tembetarine, jatrorrhizine, magnoflorine, berberine, isocolumbin), clerodane furano diterpene glucosides (amritosides A-D, tinoscorside C, borapetoside B and F, and cordifolide C), flavonoids (diosmetin, genkwanin, genkwanin 7-glucoside, and rutin), lignans (Secoisolariciresinol, syringaresinol, makisterone C), and sterols (campesterol, b-sitosterol, stigmasterol) [1- 43, 44-175].

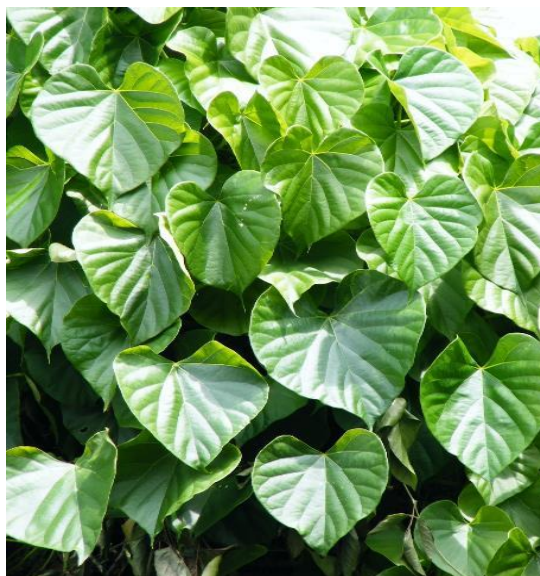


Figure 2 Heart shaped leaves of *Tinospora cordifolia*



Figure 3 The stem of *Tinospora cordifolia*

2. Indian *Tinospora* species

Following are the nine species of *Tinospora* that are naturalized in the different states of India.

1) *Tinospora cordifolia* is a large deciduous dioecious (male and female plants are separate) climber, grows on wide range of hedges and trees. Its stem is green, and contains succulent bark [43] (Figure, 1, 2, 3). The pendulous fleshy roots hang from branches, and its roots have pale shining or glabrous bark. On dryness, stem shrinks and bark separates from the wood. Leaves are membranous, round, cordate or heart shaped, contain 2.5–7.0 cm long petiole. The flowers bloom in the summer season. Inflorescence is of raceme type. Male flowers are small, yellow or green in colour, and occur in clusters in the axils of small subulate bracts [43]. Female flowers are solitary, sepals green, margins not reflexed, staminode short; ovary has 1–3 carpels, widely separated on the short fleshy gynophores, and dorsally convexed [43]. *T. cordifolia* stem is used in the stimulation of gastric activity, bile secretions, enrichment of blood composition and to treat skin diseases, spleen enlargement, vaginal and urethral discharges [1-46, 47-175]. Stem decoction is used for washing of eyes and syphilitic sores, acts as an antidote to treat snakebites and scorpion stings, and in the treatment of cancer, pyorrhoea, malaria, chronic diarrhoea, asthma, dysentery, urinary, skin diseases and respiratory complaints [1-46, 47-172]. The aqueous extract of roots is used as an emetic and analgesic agent, and also useful in the treatment visceral pain [43]. The crushed leaves are mixed with honey and used to cure cancer, ulcers, gout and bacterial skin infections [43]. Decoction of leaves is useful in malaria and enhancement of women's fertility [1-46, 47-172]. Dried fruit powder is mixed with ghee or honey and used as a tonic as well as in the treatment of jaundice and rheumatic complaints [1-46, 47-175]. The combination of ripened fruit juice and honey is recommended daily (for 3–5 days) for treatment of cold in children. Whole plant extract is useful in diarrhoea, stomach complaints, and anemia. The stem is a rich source of copper, calcium, phosphorus, iron, zinc, manganese hence, used in the treatment of metabolic disorders of humans [1-46, 47-175].

2) *Tinospora baenzigeri* is a woody climber, grows up to 15 m high, and stem with scattered pustular-lenticels. Leaves are broadly ovate to orbicular, apex usually long-acuminate, base shallowly to deeply cordate [43]. Male inflorescence appears from the older, leafless stems, pseudo-racemose, long (7–20 cm), flowers in 1–3 flowered clusters [43]. Fruits are drupes, yellow and orange, radiating from sub-globose carpophore, pericarp very thin and endocarp thinly bony [43]. In a traditional medicine, it is useful in curing of headache, cold, fever, diarrhoea, ulcer, indigestion, and rheumatoid arthritis [1-46, 47-175].

3) *Tinospora glabra* is a climber, seriate stem, with thin papery bark. Leaves oblong-ovate or narrowly to broadly ovate, base cordate to truncate, and apex acuminate [43]. Male inflorescence is axillary, pseudo-racemose type, 10–20 cm, flower solitary, and female inflorescence is similar to male [43]. Fruit is drupe red, radiating from un-branched, short to columnar carpophore, endocarp thinly bony, and keeled at apex [43].

4) *Tinospora crispa* is an herbaceous vine, with brownish and fleshy stem [43]. The leaves are large (6–12 cm long and 7–12 cm wide), both surfaces glabrous and heart shaped. Flowers are 2–3, small, and yellowish or green in colour [43]. Male inflorescence is slender, longer (5–10 cm), flowers six, green, sepals in two whorls (outer three ovate and inner three obovate) The female inflorescence is long (2–6 cm), and one flower per node [43]. Fruits are drupe and long (7–8 mm). As per Vietnamese and Indian traditional medicine system, it is useful in malaria, cough, poor digestion, colitis, and diabetes and also used in the treatment of jaundice, rheumatism, bone fractures, scabies, and hypertension [43]. It is taken in the management of thirst, hunger resistance and heat clearing, and used in curing of diabetes [1-46, 47-175].

5) *Tinospora formanii* is a woody dioecious vine, with thick stem (4 cm), clear concentric rings, brown, smooth papery bark, and peeling off into scales [43]. Leaves are alternate, large (6–14 x 4–8 cm), ovate to elliptic-lanceolate, coriaceous, glabrous, acuminate at apex, and cordate at base [43]. Male inflorescences and flowers unknown but, female inflorescence is a compound elongated pseudoraceme type long (5–18 cm) [43]. Fruits are drupes, globose, across (2–3 cm), red on maturity; pericarp thin [43]. Seeds are oblong, subellipsoid and dorsally convex [43].

6) *Tinospora maqsoodiana* is similar to *T. cordifolia* but different in its young stems, papillose-glandular [43]. The leaf shape is triangular-ovate, broad and long, ovate deltoid, elliptic, basal lobes slightly lobed, lamina base cordate to cuneate, endocarp with papillose surface [43].

7) *Tinospora sinensis* is a large fleshy deciduous climber with shiny stem and papery bark. Its young parts are covered with densely matted woolly hairs [43]. The leaves are broadly ovate to sub-orbicular, membranous, beneath with glandular patches at basal nerve axils [43]. Flowers are greenish yellow. Inflorescence is of raceme type, panicles 3–12 cm long, and slender [43]. Female flowers are tri-carpellary, 2-lobed stigma, gynophore 1 mm long [43]. Fruit is drupe, globose (1–3, 10–13 mm across), red, scarlet or orange red [43] and flowering occurs in December–February [43]. Leaf

and stem juice are used in the treatment of chronic rheumatism, ulcerated wounds and piles [43]. Aqueous extract of whole plant is useful in debility, dyspepsia, fever, inflammation, syphilis, ulcers, bronchitis, jaundice, urinary disease, skin disease and liver disease [1-46, 47-172]. The juice or powder of *T. sinensis* stem is useful in the treatment of diabetes and gastritis. *T. sinensis* possesses adaptogenic and anti-inflammatory, and anti-diabetic activities [1-46, 47-175].

8) ***Tinospora smilacina*** Benth is a semi-deciduous herb, with woody climber stem (7 cm diameter) [43]. Leaves are alternate, size 4-5- 12 x 4-11 cm, long petioles (2.5-9 cm), five veins, including the midrib, radiate from the base of the leaf blade [43]. Inflorescence, slender, male flower sepals arrange in two whorls of three. Female flowers also arrange in two whorls of three, outer sepals about 2 mm long, inner sepals petaloid. Fruit is drupe, globular to ellipsoid (6-10 x 6-9 mm) in shape [43]. As per Australian traditional medicine, whole plant is used in the treatment of pain, wounds, swelling, rheumatism, severe colds, infections and snake bites [1-46, 47-172].

9) ***Tinospora subcordata*** is a small woody climber, glabrous, stem with lenticels [43]. Leaves with petioles, and long (2.5-8 cm) [1-46, 47-175]. Pseudo-racemose, long, flowers arrange on slender pedicels, sepals white, outer 3 ovate [43]. The female inflorescence is pseudo-racemose, flowers arrange on pedicels, sepals and petals similar to male but slightly smaller and petals thin. Fruit are drupe, red, endocarp bony, and elliptic in outline [1-46, 47-175-208].

The alkaloids, glycosides, diterpenoid lactones, flavonoids, steroids and sesquiterpenoids have been isolated and identified from 4 species (*T. baenzigeri*, *T. cordifolia*, *T. crispa* and *T. sinensis*) [43] of Indian *Tinospora* while other 5 species have not been investigated for the presence of phytochemicals [43-208]. No compound is reported from 5 Indian *Tinospora* species (*T. formanii*, *T. glabra*, *T. maqsoodiana*, *T. smilacina* and *T. subcordata*) [43].

Different parts of Indian *Tinospora* species are used in the treatment of fever, urinary diseases, asthma, gout, diabetes, diarrhoea, and skin infections [1-46, 47-175-208]. The presence of various bioactive compounds provides the plant for its antidiabetic, antioxidant, anticancer, antimicrobial, antifertility, hepatoprotective, radioprotective, antiarthritic antioxidant, hypolipidemic, and anti-inflammatory activities [1-46, 47-175]. The clerodane furano diterpene glycosides showed promising anticancer and isoquinoline alkaloids exhibited antidiabetic activities in different models [1-46, 47-175]. *T. cordifolia* stem has been used by Indian people in the treatment of diabetes [1-46, 47-175]. Antidiabetic efficacy and safety of *T. cordifolia* stem capsules (dry powder) in diabetic patients has proven in clinical trial as well as in Indian people [1-46, 47-175-208]. This attribute of *T. cordifolia* may be exploited by commercialization of these plants for the identification of potential compounds for the treatment of diabetes [1-46, 47-175]. *T. cordifolia* capsules (300 mg/kg/day) showed a significant decrease in mean systolic blood pressure on fixed workload exercise when compared to placebo and also improved the physical performance [1-46, 47-175]. Capsules significantly changed the neutrophil, and eosinophil counts ($P < 0.05$) and were found effective in relieving the clinical symptoms in cases of allergic rhinitis, cold and fever [1-46, 47-175]. Although, some studies have done to reveal the antidiabetic activities of *T. cordifolia*, its true potential is yet to be acknowledged [1-46, 47-175]. But there is still a need to conduct further scientific-based study to explore the chemical characterizations and pharmacological evaluations of 5 Indian *Tinospora* species (*T. formanii*, *T. glabra*, *T. maqsoodiana*, *T. smilacina*, and *T. subcordata*) [1-46, 47-175-208]. Some *Tinospora* formulations are used in preclinical and clinical preparations with hepatoprotective, antioxidant, pancreatic islet superoxide dismutase, antiatherogenic, antiarthritic, immunomodulatory, antihyperglycemic, antihyperlipidemic, antidepressant, antiamebic, and antistress properties [1-46, 47-175-208]. More scientific studies are to be conducted on therapeutic and toxicological properties of *Tinospora* that will help in the development of new therapeutic products in the future [1-46, 47-175]. Clerodane diterpenes are a large group of plant-derived secondary products of pharmaceutical interest found in thousands of plant species from many plant families including *Tinospora* species [1-46, 47-175-208].

3. *Tinospora cordifolia*: Botany

Tinospora cordifolia is a medicinal plant whose status in the field of natural medicine and *Ayurveda* is of the highest order (Figure, 1, 2, 3). Vernacularly speaking, *Tinospora cordifolia* is known "*Guduchi*" whose origin is rooted to Sanskrit; and is known as "Amruthaballi" in Kannada and is an important drug of the Indian System of Medicine (ISM) [1-46, 47-175-208]. *T. cordifolia* is an esteemed medicinal plant whose uses and application with reference to human benefits have been praised to indescribable heights in various *Ayurvedic* and Vedic scriptures and the practices [1-46, 47-175-208]. *Tinospora cordifolia*, a climber plant of great medicinal property which is widely and popularly used in the *Ayurvedic* and local forms of medicine is studied in the phytochemical and different components that exhibit the properties that have been celebrated and upheld in the age old traditions and medicinal practices [1-46, 47-175]. The plant is known as Guduchi or Amrita in Sanskrit which points to the nature of this plant in the rejuvenating and the retainment of youth and life span of the consumer [1-46, 47-175-208].

The climbing plant is seen to bear lots of spreading slender branches which grab on to the nearby objects for support (Figure, 1, 2, 3). The flowers that are seen are observed are small and unisexual. Female and male flowers are seen in different plants. On the flowering season, the plants bear no leaves and the flowers bear yellowing green color and the flowers are positioned at the apex and terminal racemes. The differentiations in the sexes are seen in the form that the male flowers are usually clustered and the female flowers are solitary in positioning. The seeds are curved and pea sized and are transverse dehiscent in nature. The roots which are present in this plant are seen in both underground and aerial form [1-46, 47-175].

It grows at high altitude and bears flowers that are greenish to yellow. It is a large deciduous, extensively spreading climbing shrub with several coiled branches with a different type of morphology [1-46, 47-175]. The stem of the plant is filiform, fleshy and climbing in nature. The bark is white to gray. Powder of the stem is creamish brown or dark brown, characteristic odour, bitter taste and it is used in cancer treatment, dyspepsia, fever, and urinary diseases. The starch obtained from the stem known as "Guduchi-satva." It is highly nutritive and digestive [1-46, 47-175-208]. Its fruits are single-seeded, fruits during the winter and flowers grow during the summer. The chemical constituents of *T. cordifolia* belong to different classes such as alkaloids, glycosides, steroids, phenolics, aliphatic compounds, polysaccharides, leaves are rich in protein (11.2%), calcium and phosphorus. The stem contains clerodane furano diterpene glucoside (amritoside A, B, C, and D) and the structure has been established by different spectroscopic studies [1-46, 47-175-208].

4. *Tinospora cordifolia*: Phytochemistry

T. cordifolia is a medicinal plant having various type of compounds [1-46, 47-175-208]. The different bioactive compounds, including alkaloids, steroids, glycosides, and sesquiterpenoids, etc. Amruthballi contains phenolics, polysaccharides, diterpenoid lactones, aliphatic compounds, and alkaloids [1-46, 47-175]. The main compound of this plant is berberine and furanolactone. Furthermore other compounds like tinosporone, tinosporic acid, cordifolisides A to E, giloin gilenin, crude giloininand, arabinogalactan polysaccharide, picrotene, bergenin, gilosterol, tinosporol, tinosporidine, sitosterol, cordifol, heptacosanol, octacosonal, tinosporide, columbin, chasmanthin, palmarin, palmatosides C and F, amritosides, cordioside, tinosponone, ecdysterone, makisterone A, hydroxyecdysone, magnoflorine, tembetarine, syringine, glucan polysaccharide, syringine apiosylglycoside, isocolumbin, palmatine, tetrahydropalmatine, jatrorrhizine are few of the compounds that have been isolated from *Tinospora cordifolia* [1-46, 47-175-208]. The presence of three compounds like cyclo euphordenol, Cyclohexyl-11-heneicosanone and 2-Hydroxy-4-methoxy- benzaldehyde has been isolated from the plant and has been seen to be present in various other plants. The presence of proteins and miscellaneous compounds has been attributed to the medicinal properties of the plant [1-46, 47-175-208]. The plant contains a high amount of fiber totaling to an total estimate of 15.9%, and the protein content to about 4.5-11.2%, and the total carbohydrate estimate to about 61.7. Further, a low fat amount estimating to about 3.2% and the mineral content totaling to about 0.845% of potassium, 0.006% chromium, 0.28% of Iron and 0.131% of calcium. All these compounds are involved directly or indirectly in the pathways or regulatory, metabolic and cellular nature [1-46, 47-175-208].

5. *Tinospora cordifolia*: Pharmacy

According to *Auyverda*, the *Tinospora cordifolia* herbal preparations were used for the management of several diseases and discomfort including pyrexia, dyspepsia, syphilis, gonorrhoea, diseases of the urinary tract, gout, viral hepatitis, anemia, general weakness, urinary tract infections, dermatological diseases, loss of appetite, and asthma [1-46, 47-208]. It is considered as an essential herbal plant of Indian system of medicine (ISM) and has been used in the treatment of fever, urinary problem, dysentery, skin diseases leprosy, diabetes, and many more diseases [1-46, 47-175]. The plant is known for anticancer, antioxidant, antiinflammatory, anti-tuberculosis; wound healing, immunomodulatory, immunoprotective, hepatoprotective, anti-osteoporotic, antitumour, antimalaria, cardio protective nature and many more properties that make as the best medicinal plant [1-46, 47-175-208]. The presence of biologically active phytocompounds like berberine, an alkaloidic compound and the bitter compounds like tinosporin, tinosporic acid, tinosporal, and a complex mixture of fatty acids. The essential oils that are responsible for the expression of the antibacterial or the general antimicrobial activity of the plant extract [1-46, 47-175]. The most admirable character of the plant extract is the effect it bears in the cognitive field [1-46, 47-175]. Its ability to affect the learning and memory cortex of the human intelligence is an admirable trait and this trait has attracted the interest of various scientific and industrial bodies [1-46, 47-175]. The plant has been titled to many properties that have been used from time immemorial. Few of them include curative properties against jaundice, fever, gout, urinary and upper respiratory infections and preventive measures against skin infections, chronic diarrhoea, bleeding piles, dysentery, itching and erysipelas [1-46, 47-175]. *Tinospora cordifolia* is also known for its potent aphrodisiac nature and its rejuvenating nature. The plant extract influences the secretion of bile liquids and is known to enrich the blood constituents. The

plants show antidiabetic properties due to the presence of tannins, alkaloids, flavonoids, glycosides, saponins and steroids. The plant has seen to have effect on both the sexual arousal and the sexual performance of the biological systems, and these drugs have stimulatory effect on the co-pulatory behavior and thereby entitled to aphrodisiac activity [1-46, 47-175]. The plant is known for the artistic antifungal activity, antioxidant activity, antimicrobial activity, antibacterial activity, hypolipidaemic effect, hepatic disorder, anticancer, anti HIV potential, antiosteoporotic effects, antitoxic effects, wound healing, anticomplementary activity, immunomodulating activity, systemic infection and Parkinson s disease of *T. cordifolia* [1-46, 47-175-208].

Antimicrobial activity of the *T. cordifolia* with different solvents on different micro-organism, showed good antifungal and antibacterial activity. The antidiabetic activities is due to alkaloids (Magnoflorine, Palmetine, Jatrorrhizine), tannins, cardiac glycosides, flavonoids, saponins, etc [1-46, 47-175-208]. In *Ayurveda*, it acts as Medhya Rasayana or brain tonic by increasing mind power like memory and recollection. The dose of root extract 5.0 g/kg body weight showed the highest hypolipidaemic effect. The ability of *T. cordifolia* root extract to reduce the level of serum or tissue lipids in diabetics animals have been reported. Protective effects of *Tinospora cordifolia* water extract (TCE) on hepatic and gastrointestinal toxicity has been reported. One of the study demonstrated that the root extract of *T. cordifolia* affects the immune system of HIV positive patient [1-46, 47-175]. The stem extract of *Tinospora cordifolia* reduces the ability of eosinophil count, stimulation of B lymphocytes, macrophages, level of hemoglobin, and polymorphonuclear leucocytes. Incision, excision, and dead space of the wound models were employed to investigate the wound healing potential of the plant increased tensile strength extract of *T. cordifolia* may be attributed to the promotion of collagen synthesis. The extract of *T. cordifolia* did not reverse dexamethasone suppressed wound healing [1-46, 47-175]. Another study reported that *T. cordifolia* affect the proliferation, differentiation, and mineralization of bone-like matrix on osteoblast model systems in-vitro. Hence finds potential application as an antiosteoporotic agent [1-46, 47-175]. *T. cordifolia* extracts have been reported to induce a significant increase in the thickness of joint cartilage, induce the osteogenic differentiation in mouse mesenchymal stem cells and to relieve osteoporosis in osteoporotic animal models. Further 20-OH- β -Ecd isolated from *T. cordifolia* has been reported for its anti-osteoporotic effects, thus highlighting the role of *Tinospora cordifolia* in the treatment of osteoporosis and osteoarthritis [1-46, 47-175-208].

The root of Giloya (*T. cordifolia*) is used as potent emetic and for bowel obstruction. The starch of this plant serves a beneficial household remedy for chronic fever, relieves burning sensation, increases energy and appetite [1-46, 47-175]. Giloya is useful in the treatment of helminthiasis, heart diseases, leprosy, rheumatoid arthritis, support the immune system, the body's resistance to infections, supports standard white blood cell structure, function, and levels. It also helps in digestive ailments such as hyperacidity, colitis, worm infestations, loss of appetite, abdominal pain, excessive thirst, and vomiting, and even liver disorders like hepatitis [1-46, 47-175]. This pharmacological activities of the plant is due to its chemical constituents like diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds, essential oils, a mixture of fatty acids, and polysaccharides and is present in a different part of the plant body, including root, stem, and whole part [1-46, 47-175-208].

6. *Tinospora cordifolia*: Anticancer activity

Cancer is a growing economic burden worldwide [177-208]. Cancer is a disorder that rigorously affects the human population worldwide. Cancer is a disease of dysregulated and uncontrolled cell division and cell proliferation. Successful malignization requires mutations in multiple genes. Current therapeutic modalities in cancer, including surgery, chemotherapy, and radiotherapy have shown to be associated with significant morbidity [177-208]. The cancer treatment options include surgical interventions, chemotherapy and/or radiotherapy either alone or in combination, stem cell therapy, gene therapy, immunotherapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy and vaccination [1, 175-177-208]. However, they present several limitations including side effects or ineffectiveness. Even though these conventional treatment modalities have shown promise, the unwanted short and long terms side effects are vast[1, 175-177-208]. There is a steady demand for new remedies to both treat and prevent this life-threatening sickness due to toxicities, drug resistance and therapeutic failures in current conventional therapies [1-46, 47-175-208]. Researchers around the world are drawing their attention towards compounds of natural origin. Thus, there is much interest shown in the advent of alternative therapeutics including medicinal plants [1-46, 47-175-208]. Although several studies have explored the therapeutic benefits of natural plant-based products, there is a relative deficit in the number of systematic reviews available, especially with respect to plants present in remote areas such as the *Tinospora* genus [1, 175-177-208]. Among the *Tinospora* genus, only *Tinospora cordifolia*, has shown to exhibit anti-carcinogenic properties genus [1, 175-177-206]. *Tinospora cordifolia* has been shown to contain several phytochemicals with significant anti-carcinogenic properties as elicited by the included in vitro and in vivo studies genus [1, 175-177-208]. Despite promising results in laboratory settings, the future scope of *Tinospora cordifolia* application in cancer therapy depends primarily on the success of translating the in vitro and in vivo results on to the clinical trials [1, 175-177-206]. Thus,

large-scale multicenter prospective studies are required to elicit the potential application of *Tinospora cordifolia* in cancer therapy [1, 175-177-208]. *Tinospora cordifolia* is one such plant and has shown to exhibit anti-carcinogenic properties [1, 175-177-208]. Significant anti-carcinogenic properties were exhibited by *Tinospora cordifolia*-derived phytocompounds including palmatine, berberine, new clerodane furanoditerene glycoside, arabinogalactan, phenolic compounds and epoxy cleodane diterpene [1, 175-177-208]. No significant side effects have been elicited with its use. Based on the data from the included studies, *Tinospora cordifolia* could be a natural therapeutic agent for cancer, provided its anti-carcinogenic properties can be elicited consistently at a large scale in clinical trials [1, 175-177-208]. The oral cavity is one of the most common sites to be affected with cancer. Globally, oral squamous cell carcinoma (OSCC) accounts for 10.4% of all malignancies and is the eighth most common neoplasm of all cancers [1-46, 47-175-208]. Aqueous extract of *Tinospora cordifolia* was found to induce apoptosis inducer in AW13516 cells in a concentration-dependent manner and was potent even at a low concentration of 5 lg/ml[1]. The apoptosis induction was confirmed with the caspase activity assay. Treatment of the cells with the extract for 24 h exhibited a significant decrease in the expression of EMT genes in a dose-dependent manner without an effect on the metastatic genes[1]. Aqueous extract of *Tinospora cordifolia* extracts induces apoptosis-mediated cell death in the oral cancer cell line AW13516 while attenuating its potential for epithelial mesenchymal transition[1]. The MTT assay revealed induction of cell death by *Tinospora cordifolia* extract in a concentration-dependent manner [1]. *T. cordifolia* extract induced apoptosis in AW13516 cells in a concentration dependent manner [1]. Even at a low concentration of 5 lg/ml, apoptosis was induced, a 24 h treatment with Giloy induced a significant reduction in the expression of EMT genes in a dose-dependent manner, although no effect was noted on the metastatic genes [1]. Further studies could be carried out to explore the in-vivo anticancer effects of *T. cordifolia* and **berberine** on oral cancer [1, 175-177-208]. The extract could also be explored for the cancer-preventive activity and management of potentially malignant disorders [1]. The extract exhibited anticancer by effects by induction of apoptosis depicted by Annexin V stain and confirmed by Caspase activity assays[1]. The apoptosis induction was via alteration of mitochondrial membrane potential in a concentration-dependent manner[1]. One of the study reported the anticancer activity of *T. cordifolia* palmatine extract in animal models, alkaloid using response surface methodology (RSM) [1]. The extract indicates the anticancer potential in 7,12-dimethylbenz(a)anthracene DMBA induced skin cancer model in mice[1]. Furthermore, another study prepared the extract of 200, 400, 600 mg/kg dry weight in a dose depend upon manners. 50% methanolic extract of cordifolia to C57 Bl mice for 30 days at a dose of 750 mg/kg body weight the tumor size reduced life span[1]. Mishra et al., showed the anti-brain cancer potential, 50% ethanolic extract of *T. cordifolia* (TCE) using C6 glioma cells significantly induced differentiation in C6 glioma cells, and reduced cell proliferation [1, 175-177-208].

The methanolic, aqueous, and ethanolic *T. cordifolia* extracts of stems caused programmed cell death inhibiting apoptosis[1, 175-177-206]. The in vitro cytotoxic effect of DMSO and ethanolic extract from *T. cordifolia* stems against murine monocyte/-macrophages (J-774-A-1), human melanoma (A-375) and human breast cancer (MCF-7) cell lines was determined by the colorimetric MTT assay and TBE method [1, 175-177-208].

Berberine (BBR) is a natural active principle with potential antitumor activity. The compound targets multiple cell signaling pathways, including proliferation, differentiation, and epithelial-mesenchymal transition [176]. The expression levels of a panel of 44 selected genes in human colon adenocarcinoma (HCA-7) cell line were quantified by real-time polymerase chain reaction (PCR). **Berberine (BBR)** treatment resulted in a time- and dose-dependent down regulation of 33 genes differently involved in cell cycle, differentiation, and epithelial-mesenchymal transition[176-208]. The trend was confirmed across the two types of treatment, the two time points, and the different absolute dosage of **Berberine (BBR)**. These findings suggest that the presence of BBR in *T. cordifolia* extract significantly contributes to its antiproliferative activity [176-208]. One of the study demonstrated that extract of *T. cordifolia* is able to inhibit the expression of several genes involved in colon cancer development and progression[176-208]. The effects of *T. cordifolia* treatment were well resembled by pure **Berberine (BBR)**. This evidence suggested that the main effects of *T. cordifolia* were mediated by **Berberine (BBR)** [176]. The ability to strongly reduce expression of genes involved in proliferation, differentiation, cell motility, and EMT suggests further research efforts to explore the use of these substances as chemotherapeutic agent in colorectal cancer [1, 175-177-208].

7. Conclusion

Amruthballi or Giloy or Guduchi, or *Tinospora cordifolia*, belongs to the *Menispermaceae* family of universal drugs used to treat various diseases in traditional Indian literature. It has received attention in recent decades because of its utilization in folklore medicine for treating several disorders. *Tinospora cordifolia* has been shown to contain several phytocomponents with significant anti-carcinogenic properties as elicited by the included in vitro and in vivo studies. Despite promising results in laboratory settings, the future scope of *Tinospora cordifolia* application in cancer therapy depends primarily on the success of translating the in vitro and in vivo results on to the clinical trials. Thus, large-scale multicenter prospective studies are required to elicit the potential application of *Tinospora cordifolia* in cancer therapy.

Total 34 species of *Tinospora* genus are found in Africa, Australia, Asia, Madagascar and Pacific regions of the World. Nine species of *Tinospora* are naturalized in the different states of India. In traditional medicine, different parts of *Tinospora* are used in the treatment of syphilis, ulcers, bronchitis, jaundice, urinary disease, piles, skin and liver diseases. Indian *Tinospora* species possess various pharmacological attributes such as antioxidant, hepatoprotective, radioprotective, neuroprotective, antidiabetic, anthelmintic, antimicrobial, analgesic, anti-fertility, antiarthritic, antitumor, antistress, anti-inflammatory, immunomodulatory, wound healing, and antiulcer activities. These biological activities of Indian *Tinospora* species can be attributed to the presence of a wide range of phytoconstituents including alkaloids (tinoscorsides A-B, palmatine, tembetarine, jatrorrhizine, magnoflorine, berberine, isocolumbin), clerodane furano diterpene glucosides (amritosides A-D, tinoscorside C, borapetoside B and F, and cordifolide C), flavonoids (diosmetin, genkwanin, genkwanin 7-glucoside, and rutin), lignans (Secoisolariciresinol, syringaresinol, makisterone C), and sterols (campesterol, b-sitosterol, stigmasterol).

The *Menispermaceae* family plant *Tinospora cordifolia* (Amruthballi, Giloy, Guduchi) has components that may be used to investigate nutraceuticals using a range of bioactive principles. The most crucial portions for medical use are the leaves, stem, and roots, even if practically every other part is utilized in traditional medicine. *Tinospora cordifolia* extracts from the bark, stem, and root have the potential to be chemopreventive and anti-tumor agents against various malignant cells. More scientific studies are to be conducted on therapeutic and toxicological properties of *Tinospora* that will help in the development of new therapeutic drug products in the future.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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