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Review Article

Tinospora Cordifolia – As An Anticancer Agent: Recent And Advance Study

Arpita R. Pawar*[1], Ashwini T. Chougule[2], Jaya R. Kamble[3], Pritam Salokhe[4], Nilesh B. Chougule[5]

[1-2]*Student Ashokrao Mane Institue of Pharmacy, Ambap-416112.*
[3-4]*Assistant Professor Ashokrao Mane Institute of Pharmacy, Ambap.*
[5]*Principal Ashokrao Mane Institute of Pharmacy, Ambap.*

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ABSTRACT

The woody, succulent, glabrous climbing shrub Tinospora cordifolia, sometimes referred to as Guduchi, is mostly found in tropical regions of the world, including China, India, Myanmar, and Sri Lanka. All conventional medical systems, including Ayurveda, Unani, Siddha, Folk, and others, have detailed the plant's curative qualities. Guduchi or Giloe are popular names for Tinospora cordifolia, a member of the Tinospora genus. The Menispermaceae family plant Tinospora cordifolia (Guduchi) has plant 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. A variety of phytochemical components are involved, including phenolics, diterpenoids, lactones, glycosides (syringin, cordiol), steroids, sesquiterpenoids, aliphatic chemicals, and polysaccharides (α-D glucan). Alkaloids include palmetin, berberine, and its derivatives. The anti-inflammatory properties of berberine, palmetin, G1-4A, and α-D glucan are particularly effective against malignant cell lines. Tinospora cordifolia extracts from the bark, stem, and root have the potential to be chemopreventive and anti-tumor agents against various malignant cells. To investigate and determine T. cordifolia's phytochemistry and pharmacological activities, the present study is being conducted. This study centers on a methodical examination of the body of research about T.cordifolia's anti-cancer

INTRODUCTION

80% of people worldwide utilize plant extracts or their active ingredients in traditional treatment, according to the World Health Organization. Because of its mega-biodiversity and knowledge of extensive historical traditional medicinal systems (including Ayurveda, Siddha, Unani, Amchi, and local health traditions), India offers a

***Corresponding Author:** Arpita R. Pawar
Address: *Student Ashokrao Mane Institue of Pharmacy, Ambap-416112*
Email ✉: arpitapawar04032002@gmail.com
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strong foundation for the use of several plants in general healthcare and the alleviation of common illnesses in people [1]. Because of the significance of medicinal plants in the medical domain, a study was conducted to check for Tinospora cordifolia. The most common cause of dread is cancer, which is defined as the uncontrolled growth of abnormal cells in an organ, tissue, or part of the body that is affected. According to WHO (2012), 32.6 million individuals with cancer survive for five years after being diagnosed, 8.2 million deaths attributable to cancer, and 14.1 million new cases of cancer globally. Breast, cervical, colorectal, oral, and stomach cancers are the five most prevalent malignancies that occur in India; for males, the top five cancers are oral, lung, stomach, colorectal, and pharyngeal. It becomes very challenging to diagnose and cure this lethal condition because all conventional treatment methods, including radiation therapy, chemotherapy, and surgery, are costly, have numerous side effects, and are only effective while the cancer is still in its early stages. Tc, sometimes called Giloy in Sanskrit or "Guduchi" in general, is a member of the Menispermaceae family. The family Menispermaceae, which comprises 450 species and 70 genera, is extensively found in tropical lowland regions. The Tinospora genus, which has about 15 different species, is one of the most common genera in the Menispermaceae family [2]. Growing at higher elevations in regions like India, Myanmar, and Sri Lanka, it is a deciduous climbing shrub with unique greenish-yellow flowers.The active ingredients found in various plant sections include lactones, aliphatics, glycosides, steroids, alkaloids, flavonoids, saponins, phenolics, and diterpenoids. These components are effective against a variety of illnesses [3].

(a)Fruits

(b)Leaves

(c)Steams

(d)Flowers

Common appellations:

Latin	Tinospora cordifolia
English :	Gulancha / Indian Tinospora
Sanskrit:	Guduchi, Madhuparni, Amrita, Chinnaruha, Vatsadaani, Tantrika.
Hindi	Giloya, Guduchi
Bengali:	Gulancha
Telugu :	Thippateega
Tamil	Shindilakodi
Marathi:	Shindilakodi
Gujarathi:	Galo
Kannada:	Amrita balli, Madhupa

Taxonomy classification:

Kingdom :	Plantae – Plants;

Super- division :	Spermatophyta-Seed bearing plants;
Division :	Magnoliophyta-Flowering;
Class	Magnoliopsia-Dicotiledons
Subclass :	Polypeptalae-Petals are free;
Series :	Thalamiflorae-Many stamens and flower hypogynou;
Order :	Ranunculales;
Family :	Menispermaceae-The Moonsee family;
Tribe :	Tinosporeace;
Genus :	Tinospora;
Species :	Cordifolia.

BOTONICAL DESCRIPITION:

MOR The Menispermaceae family, which includes the big deciduous climbing shrub Guduchi, is rich in terpenes and alkaloids. Guduchi's scientific name is Tinospora cordifolia. Its 450 species are distributed throughout 70 genera [4]. Guduchi is originally from Sri Lanka, Myanmar, and India.; it has enormous leaves with papery bark and excellent stalks. It is an alternating, perennial shrubI.e. This native plant grows exclusively in the tropical parts of India, where the maximum temperature ranges from 25 to 450C at 500 meters above sea level[5]. This enormous deciduous climbing plant has many intertwined, long branches.It spreads abundantly. Simple, alternating leaves with long, rounded, pulvinate petioles that can reach a maximum length of 15 cm are characterized by esculent foliage. Compared to the apical leaf, the basal leaf is longer and somewhat bent. Lamina has a profoundly cordate base and seven nerves. It is 10–20 cm long and 8–15 cm broad. Little, greenish yellow, unisexual blooms with axillary and terminal racemes form on various leafless plants. Together, or often alone, are flowers with male and female petals. There are two groups of three sepals in the sixth set, the inner group being larger than the outer. The group is free. Six free, membrane-coated, obovate, smaller-than-sepal-sized petals. Clusters of fruits with one to three ovoid, smooth drupelets grouped together on a sturdy stem with red or orange subterminyle scars can be found. Because of the heart-shaped, distinctive, slimy, simple, alternating, membranous, and cordate leaves of Guduchi, this plant is also known as heart leaf moonseed [6]. Wood is white, pliable, and porous. Greenish-hued unisexual flowers that bloom in summer. Both male and female flowers have six sepals and six petals; male flowers are smaller, clustered together, and have a yellow or green hue [7].Fruits are orange-colored and come in clusters of one to three drupes with a red color. Both aerial and subterranean roots are observed [8**].**

PHOLOGICAL DESCRIPITION:

T. cordifolia is a broad, glabrous, deciduous shrub that grows quickly [9]. It has numerous coiling branches that reach up to 4 feet in height and around 1 foot in length. India is the natural home of the woody, succulent, glabrous climbing shrub Tinospora cordifolia. It frequently soars to tremendous heights, flourishes in tropical climates, and climbs big tree trunks. T. cordifolia has long, filiform, succulent aerial branch roots that give it an extremely enticing appearance [10]. The cylindrical, bitter, somewhat woody, and 25–25 mm in diameter plant stem is described as follows [11]. Several Tinospora areas exhibit the following morphological types [12, 13].

Stem:

This plant has a long, filiform, fleshy, ascending stem that has a hint of succulent flavor. The branches produce roots that are in the air. Deeply left spirally, the bark is a variety of colors from creamy white to gray.

Arial Roots:

Their basic structure is tetra to penta-arch, and they have aerial roots. On the other hand, the cortex of the root is separated into an internal parenchymatous zone and an outside thick-walled zone.

Leaves:

This plant has simple, alternating, heart-shaped, spherical, pulvinate, long petioled, ex-stipulate, and partly or partially twisted leaves. They are around 15 centimeters long. The membrane-covered oval lamina is 10–20 cm in length, has seven nerves, and has a deep cordate base.

Flowers:

Without leaves, the plant produces regressive, unisexual, greenish yellow blooms. Female flowers are alone in an inflorescence, whereas male flowers are in clusters. Three sepals total, divided into two sets. Sepals on the exterior are smaller than those within. Petals are free, membrane-bound, and have six petals—six less than sepals. Flowers appear from March to June.

Seed:

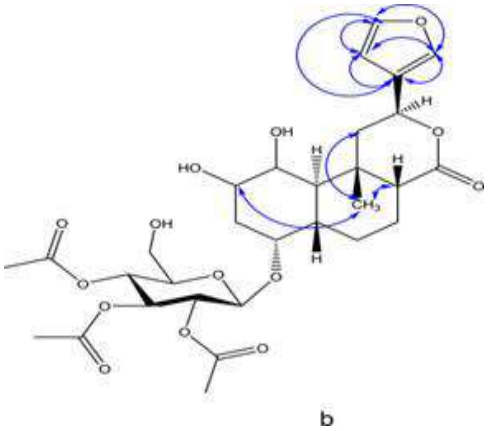
This species' twisted seeds have been reported. For this reason, this family is known as the Moonseed family.

Fruit:

They are drupelets that are smooth, ovoid, and orange-red in color. They are clustered in 13 on a sturdy stalk and with subterminal style scars. Winter is the time when fruits develop. The fruit combination has a crimson hue and is meaty and red in appearance. It has large drupelets arranged on a tall stem [14]. Records exist for the bent seed of this plant. This is the reason this family is often referred to as the Moonseed family. Due of the curved nature of seeds, the embryo naturally gravitated toward a curved form. On the other hand, the endocarp is embellished in a variety of settings and provided with significant taxonomic traits [15].

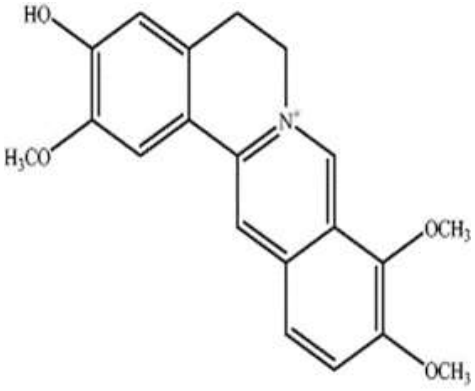
PHYTOCHEMISTRY OF TINOSPORA CORDIFOLIA (TC):

Clerodane furano diterpene glycoside [16], N-formylannonain, 11hydroxymustakone, N-methyl-2-pyrrolidone [17], arabinogalactone polysaccharide (G1-4A) [18], α-Dglucan [19], epoxy clerodane diterpene (ECD) [20], Jatrorrhizine [23], Berberin, Palmatine, Tembetarine, Mangoflorine, choline, Tinosporine, Isocolumbin, tetrahydropalmatine, [24,25,26], and furanoid diterpene glucoside [27]. Syringin [28], cordioside [31], β and δ sitosterol [29,30], and β sitosterol [32,33],which, utilizing a variety of chemical solvents, are mostly extracted from the TC stem. Most of these chemicals are categorized as antioxidants (remaining compounds), immune-suppressive (α-Dglucan, G1-4A, N-formylannonain, etc.) and anticancer (berberine, palmatine, clerodane furano diterpene, etc). These substances fight cancer, inflammatory, and oxidative illnesses directly or indirectly by means of a range of

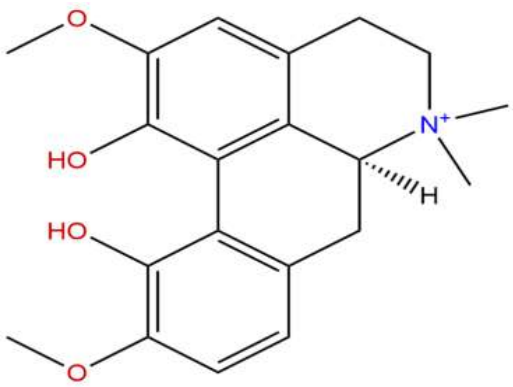


b

a. Jatrorrhizine[35]



b. Clerodane furano diterpene glycoside [34]



c. Mangoflorine[36]

NUTRITIONAL COMPOSITION:

Guduchi's medicinal qualities are mostly attributed to the presence of phytochemicals, macronutrients, and micronutrients. From ancient times, people have used the numerous nutraceuticals found in the plant's leaves, stem, fruits, and roots. A study came to the conclusion that guduchi stems may provide both humans and animals with nourishment and minerals [37]. Guduchi satva is a plant whose stem contains bitter starch that is used to treat a variety of ailments. It is an extremely nutritious and readily absorbed starch. [38].It is also said to have an abundance of nutrients, such as protein, calcium, fat, and dietary fiber [39]. Tables 2 analysis leads to the conclusion that guduchi is a nutrient-dense food that is excellent for immune system stimulation and body building. Phosphorus and calcium are beneficial for the development of teeth and bones. An essential part of erythropoietin and oxygen transport is iron.

Contents of Nutrients Concentration (%)

Table 1: Nutrients in Guduchi leaves [40].

Nutrients	Concentration%
Carbohydrate	65.31
Moisture	7.78
Protein	8.74
Fat	2.80
Fibre	8.25
Ash	7.12
Iron	1.53
Calcium	0.11
Vitamin C	1.24

Clinical method evaluation of anticancer drug Tinospora cordifolia:

The Drugs' origin and Authenticity:

The clinical investigation's guduchi (Tinospora cordifolia) stem came from a reliable supplier in the Dehradun market. It was made out of chopped guduchi stem fragments. The Dravyaguna Postgraduate Department of the Uttaranchal Ayurvedic College in Dehradun, Uttarakhand, affirmed its legality.

Medicine Preparation for Clinical Trials:

Five kilograms of the drug's constituent parts were sent to a respectable pharmaceutical company so that they might produce ghan wati, or guduchi in concentrated tablet form. We have Guduchighan tablets for the pharmaceutical trial (GGT).

Dosage:

After meals, it was advised to take 1 g (2 tablets) of GGT three times a day with lukewarm water.

Patient count and categorization:

Of the 56 volunteers selected for this study, 38 successfully completed the clinical trial and were subsequently enrolled at the Uttaranchal Ayurvedic Hospital located on Rajpur Road in Dehradun. Among the 38 patients were those under contracts from the Gaudham Cancer Treatment and Research Centre in New Delhi.Four groups were randomly assigned to each patient, and they were as follows:

Group A:

Control group: no experimental medication is given; chemotherapy is administered.

Group B:

Patients are given GGT (guduchi ghan tablet) in addition to chemotherapy.

Treatment Duration:

The adjuvant treatment lasted for three months in total.

Follow-up:

In order to ascertain whether adjuvant treatment was beneficial in reducing the side effects of chemotherapy for the full three months, three

follow-ups were carried out after the clinical study began: the first after one month, the second after two months, and the final follow-up after one month.

Patient Selection:

Qualifications for Inclusion:

Patients with cancer who have been diagnosed at stage 1 or stage 2, irrespective of their gender, caste, religion, or socioeconomic status, are undergoing chemotherapy. Those who have short-term, severe adverse effects from chemotherapy. Individuals in the age range of 20 to 60.

Exclusion Standards:

Exclusion from the trial occurred for patients in stages 3 and 4 who had persistent, long-term local side effects.

Patients suffering from serious consequences from several opportunistic infections. Patients in the age category of under 20 and over 60.

Individuals who have accompanying complications, such as mental disorientation, hepatic problems, and chronic renal failure Exclusion from the trial will occur for patients who have long-term side effects from radiation and chemotherapy, such as esophageal stricture, urine, or feces incontinence. To verify different activities, the author of this article conducts a number of tests, including the HRB membrane stabilizer test, total phenolic content, and flavonoid content. Tinospora cordifolia methanolic extract shown notable cytoprotective properties against standards, according to the results presented by author Murlidhar. Furthermore, the findings suggest that plant extract is a noteworthy natural antioxidant source that may aid in delaying the onset of a number of illnesses caused by oxidative stress. For this reason, the extract may be thought of as a natural source of membrane stabilizers and as a potential substitute medication for the control and treatment of inflammatory illnesses.

ANTI-CANCER/ANTI-TUMOR ACTIVITY:

With an IC50 value of 5 µg/ml, the TC methyl chloride extract exhibited the maximum cytotoxicity,was seen in HeLa cells; this was followed by methanolic and aqueous extracts. The cytotoxicity may have been caused by damaged DNA inhibiting cell division [41]. Additionally, it was observed that the circulating antibody titre, enhanced macrophage activation, and rise in splenic plaque-forming cells were all indicative of a considerable increase in humoral immune response caused by the extract of Tinospora cordifolia.Tinospora extract prevented the growth of solid tumors.The anti-neoplastic properties of Tinospora cordifolia extract are outstanding due to its exceptional ability to kill cells in vitro. In a mouse model of skin cancer generated by 7,12-dimethylbenz(a)anthracene (DMBA), the alkaloid palmatine extracted from Tinospora cordifolia using response surface methodology (RSM) shown strong anticancer potential [42]. The alcoholic extract of TC increases the synthesis of NO at 100 and 200 mg/kg body weight in mice with Dolton lymphoma (DL). It also increases the production of IL1, phagocytic activity, antigen-presenting ability, dendritic cells associated with tumor-associated macrophages (TAM), and arginase activity (which is highest at 100 mg/kg body weight). These chemicals are linked to dendritic cells' and macrophages' tumoricidal activity [43], and they also cause a dose-dependent reduction in the tumor cells' capacity to proliferate [44]. In the study by Manju Bala et al., four distinct human cancer cell lines—HT-29 (human colon cancer), SiHa (human cervical cancer), KB (human oral squamous carcinoma), and CHOK-1 (hamster ovary)—were used to assess eight secondary metabolites from Tinospora cordifolia. While pure compounds showed activity against HT-29, KB, and CHOK-1, KB and yangambin,

and KB and tinocordiside, in that order, all fractions and extracts displayed activity against KB and CHOK-1 cells [45]. T1 therapy significantly reduced the proliferation, migration, and invasion of MCF-7 cells in comparison to T2, according to two molecules from the hexane and methanol fractions (T1 and T2) from the plant Tinospora cordifolia. T1 repressed the expression of two genes linked to the epithelial-mesenchymal transition: Twist and Snail[46]. Growth of solid tumors was inhibited by tinospora extract. When used as an anti-neoplastic drug, extract from Tinospora cordifolia successfully destroyed the cells in vitro. To prove that guduchi herbs have anti-cancer properties, several experimental animal models were employed. This plant exemplifies the radioprotective characteristic in that it significantly increases both body weight and the weight of various tissues. It also provides defense against sub-lethal gamma radiation emitted by Swiss Albino mouse testicles. Exposure of the cultivated HeLa cells to varying concentrations of methylene chloride extracts occurs . In a dose-dependent way, Tinospora Cordifolia boosted cell death or killing by 0,5,10,25,50, and 100 µg / ml in comparison to untreated (control) cultured cells.this particular case, [47]. A two-stage skin carcinogenesis mouse model was employed to showcase guduchi's strong anti-tumor properties. This indicates that the weight and incidence of papillary tumors have decreased, while the patient population's phase II enzyme count has increased at the same time [48].

MECHANISM OF ANTI-CANCER ACTIVITY:

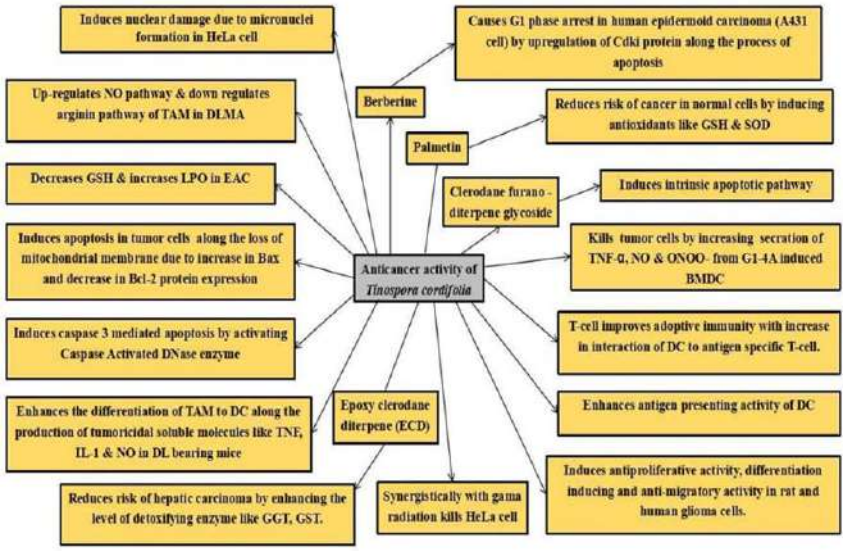


Fig.no. 1 Mechanism of Tinospora cordifolia[49]

FORMULATIONS :

A. GJ Guduchi Capsule

B. ARV Giloy Capsule

CONCLUSION

Understanding the chemical components of plants is beneficial and vital as it will be necessary for the production of other chemicals. It could be a good fit for use in the pharmaceutical sector. By using biotechnological methods, this plant may be preserved and its quality enhanced through the synthesis of secondary metabolites. As a result, it can be utilized as a resource for the creation of novel medications and their commercialization. Numerous plant extracts include chemicals that may be active. The physiological and biological roles of the aforementioned essential components highlight Tinospora cordifolia's many adaptabilities. Development of the crucial routes, particularly the biochemical ones, for Tinospora cordifolia's essential components must proceed. T. cordifolia has been disappearing from its native environment at a rapid rate, despite its immense therapeutic potential. As such, the need for biotechnological progress in the selection, classification, and preservation of planting material is critical.

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