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A Therapeutic Evaluation of Anticancer and Pharmacological Abilities on *Tinospora cordifolia*: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Tinospora cordifolia (Tc), commonly called as Giloy, it is a herbaceous vine that is widely used in traditional medicine systems for its alleged anti-cancer effects. The purpose of this systematic study is to assess *Tinospora cordifolia's* (Tc) medicinal potential against cancer. A thorough search of various scientific databases was done for studies looking at *Tinospora cordifolia's* anti-cancer properties. The findings demonstrate a varied variety of *In vitro* and *In vivo* research demonstrating *Tinospora cordifolia's* (Tc) anti-proliferative, apoptotic and anti-metastatic activities against many cancer types, including breast, prostate, colon, and leukaemia. Mechanistic insights into its mode of action, such as modulation of signaling pathways involved in cell cycle regulation, apoptosis and angiogenesis, are presented. However, limitations in study designs, inconsistency in methodology, and differences in reported outcomes highlight the need for more well-designed clinical trials to evaluate *Tinospora cordifolia's* efficacy and safety as a potential supplementary medicine in cancer treatment regimens. Therapeutic plants, such as *T. cordifolia*, can strengthen the body's defences against disease and cure specific areas, displaying more body compatibility and fewer side effects than medications. In conjunction with this, the current study highlights *T. cordifolia's* pharmacological potential against a variety of illnesses.

Keywords: Tinospora cordifolia; anti-cancer properties; apoptosis; leukaemia; signaling pathways.

1. INTRODUCTION

Cancer presents a significant global health challenge, characterized by a rising incidence and limited treatment options often hampered by adverse effects and resistance to conventional therapies [1]. Consequently, there's been a surge in interest in exploring alternative approaches to cancer management, including medicinal plants with potential anti-cancer properties [2]. Among these, *Tinospora cordifolia* (Tc), known as Giloy, has emerged as a subject of interest. Cancer is globally becoming a more expensive disease [1]. 25 million cancer-related deaths and 32 million new cancer cases are estimated by the Globocan 2018 database [3]. The search for effective anticancer medicines has been sparked by this horrifying and terrible fact [4]. Radiation, chemotherapy and surgery are some of the current cancer treatment modalities that have been linked to a high rate of morbidity [3]. As a result, there is a lot of interest in the development of complementary therapies, such as medicinal plants. 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 [4]. In the Tinospora genus, only *Tinospora cordifolia* (Tc), has shown to exhibit anti-carcinogenic properties. Tc was therefore chosen as the topic of the evaluation. Tc is a member of the Menispermaceae family, which is also known as "Guduchi" or "Giloy" in Sanskrit [5]. It is a climbing deciduous shrub that often has greenish-yellow blooms [5]. Higher up in places like Sri Lanka, Myanmar, and India. It has been demonstrated that Tc differs from other closely related species in the Tinospora genus, such as *Tinospora malabarica* (Tm), in a number of distinctive ways [6]. Compared to Tm, Tc has a lesser mucilage content, higher lenticels, nodes, and internodes, and a cork with an ash colour [5,6].

Tc is the source of several active ingredients, including as alkaloids, steroids, glycosides, aliphatics, and diterpenoid lactones [7]. Tc has been demonstrated to have anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, and immunomodulatory qualities in addition to its anti-neoplastic qualities [8]. The current review methodically examines the literature to determine the impact of phytocomponents derived from Tc on cancer [9].

Tinospora cordifolia (Tc) is a climbing shrub native to the tropical regions of India, Sri Lanka, and Myanmar, revered in traditional medicine, especially Ayurveda, for its diverse therapeutic properties [10]. Traditionally, it has been used for its anti-inflammatory, immunomodulatory, and antioxidant effects. However, recent research has increasingly focused on its potential as an anti-cancer agent [11].

The exploration of *Tinospora cordifolia's* (Tc) anti-cancer properties is backed by a growing body of preclinical studies, revealing its mechanisms of action and demonstrating

promising outcomes in hindering tumor growth, prompting apoptosis, and impeding metastasis across various cancer models [12]. These findings have spurred further interest in investigating its therapeutic potential in clinical settings as a complementary or adjunctive cancer therapy [13].

Despite accumulating evidence suggesting *Tinospora cordifolia's* (Tc) anti-cancer properties, challenges persist [12]. Translating preclinical findings into clinical practice demands rigorous evaluation via well-designed clinical trials to establish efficacy, safety and optimal dosing regimens [14]. Additionally, understanding the mechanisms underlying its anti-cancer effects is crucial for optimizing therapeutic use and identifying potential synergies with existing cancer therapies [15].

This review endeavors to provide a thorough evaluation of *Tinospora cordifolia's* (Tc) therapeutic potential in combating cancer [16]. By synthesizing existing evidence from preclinical studies, elucidating its mechanisms of action and pinpointing future research directions, this review aims to contribute to the expanding understanding of *Tinospora cordifolia* as a promising candidate in the fight against cancer.

2. METHODS

2.1 Inclusion Criteria

It has been discovered that the Ayurvedic medicinal plant *Tinospora cordifolia* (Tc) may have anti-cancer properties. Bioactive substances found in it include tinosporide, cordifolide, and berberine, all of which have been linked to anti-cancer properties. These substances have the ability to suppress angiogenesis, induce apoptosis, stop the cell cycle, reduce oxidative stress, and obstruct important signalling pathways. Studies conducted in vitro have demonstrated the effectiveness of phytocomponents derived from Tc against a range of cancer cell lines, including leukaemia, colon cancer, and breast cancer. Research conducted in vivo has demonstrated noteworthy decreases in tumour mass and volume in mice, as well as in lung cancer tumour growth and metastasis, and skin cancer tumour incidence and multiplicity. Preclinical research has shown that Tc-derived phytocomponents have a largely positive safety profile, with no appreciable side effects at therapeutic doses.

2.2 Exclusion Criteria

Reviews that are narrative, methodical, meta-analytic, comprising letters, editorials, conference abstracts, and pieces written in languages other than English.

2.3 Information Sources and Search Strategies

Google scholar, PubMed, Scopus, Web of Science, Embase and Cochrane library were searched using the keywords *Tinospora cordifolia*; anticancer; and phytocomponents until March, 2023.

3. CONCEPTUAL DESCRIPTION OF *Tinospora cordifolia* – TABLE 1 & FIG. 2

T. cordifolia is a swift-growing, wide, deciduous shrub with glabrous leaves. Reaching up to 4 feet in height and about 1 foot in length, it contains many coiled branches. *Tinospora cordifolia* (Tc) is a woody, succulent, glabrous climbing shrub that grows naturally in India [17,18]. It commonly climbs large tree trunks, flies to incredible heights, and thrives in tropical climes [18]. The long, filiform, succulent aerial branch roots of *T. cordifolia* give it a very alluring appearance. The description of the cylindrical, somewhat woody, bitter, and 25–25 mm in diameter plant stem is as follows [18]. These morphological characteristics are present in several Tinospora locations.

3.1 Stem

The long, filiform, fleshy, ascending stem of this plant tastes slightly succulent. Airborne roots are produced by the branches [15]. The bark is colored in a range of tones, from creamy white to grey and is deeply left spirally.

3.2 Arial Roots

They feature aerial roots and a tetra to penta-arch fundamental structure. Conversely, the root cortex is bifurcated into an external thick-walled zone and an internal parenchymatous zone [1].

3.3 Leaves

This plant features simple, alternating, spherical, pulvinate, long petioled, ex-stipulate, slightly twisted, and heart-shaped leaves. About 15

Table 1. Taxonomical position of plant

Taxonomical position of plant		Plant species
Kingdom	❖ Plantae	
Division	❖ Mangnoliophyta	
Class	❖ Magnoliopsida	
Order	❖ Ranunculales	
Family	❖ Menispermaceae	
Genus	❖ Tinospora	
Species	❖ *T. cordifolia*	

Source: Anuradha Sharma et al,.2020

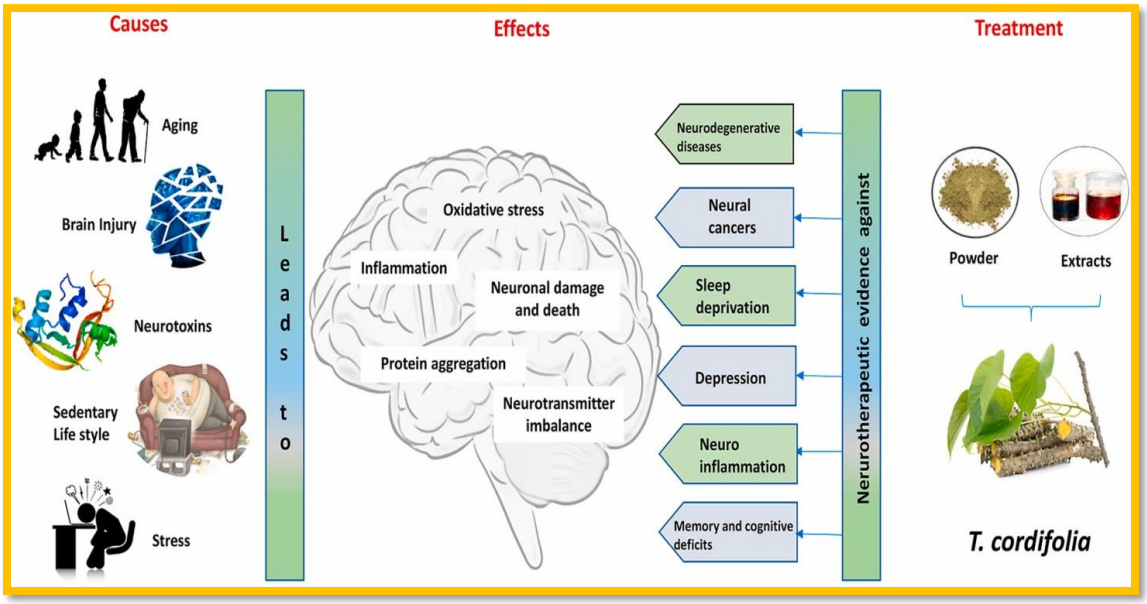

Fig. 1. Causes, effects and treatment for *T. cordifolia*

centimeters is how long they are [2]. With a deep cordate base, seven nerves, and an oval lamina coated in membrane, it measures 10–20 cm in length [3].

3.4 Flowers

The plant produces retrograde, greenish yellow, unisexual blooms without leaves. Male flowers are found in groups, while female blooms are solitary inside an inflorescence [7]. Two sets of three sepals in total. The external sepals are smaller than the inside ones [8]. There are six petals on a free, membrane-bound flower, which is one fewer than on a sepal. From March until June, flowers are in bloom.

3.5 Seed

It has been noted that this species produces twisted seeds. This family is referred to as the Moonseed family as a result [9].

3.6 Fruit

These are smooth, ovoid, orange-red drupelets. They have subterminal style scars and are grouped in thirteen on a robust stalk. Fruits develop in the winter [1,3]. The fruit combination looks red and meaty, with a crimson tint. It has a long stem with big drupelets grouped on it. There are records regarding this plant's crooked seeds [11]. For this reason, this family is frequently called the Moonseed family [10]. The embryo gravitated naturally towards a curved form because seeds are curved. Conversely, the endocarp has important taxonomic features and is decorated in a number of contexts [9].

4. MEDICINAL IMPORTANCE OF *T. cordifolia* AND THEIR CONSTITUENTS

Historically, *T. cordifolia* has been used in folk and Ayurvedic medicine preparations to treat a

wide range of conditions, such as fever, skin disorders, chronic diarrhoea, jaundice, asthma, and bone fractures. The plant's stem has been certified by the Indian Ayurvedic Pharmacopoeia because of its high alkaloidal content. Bitter and more medicinally effective is the plant's starch [3]. Extracts from *T. cordifolia* have demonstrated anticancer biomarkers, decreased neutropenia brought on by cyclophosphamide administrations, and stimulated macrophages by phagocytosis and antigen presentation. Alkaloids, terpenoids, phenols, steroids, essential oils, aliphatic chemicals, and polysaccharides are some of the chemical components [12]. The glucose, arabinose, rhamnose, xylose, mannose, and galactose units make up the polysaccharide found in T. cordifolia stems [16]. Additional T. cordifolia substances have not been well studied chemically or biologically. T. cordifolia leaves are high in calcium, phosphorus, zinc, and protein. Alkaloidal components (choline, palmatine, tetrahydropalmatine, and magnoflorine), (-)-epicatechin, and an aromatic glycoside (secoisolariciresinol) are responsible for the antioxidant activity [16]. In a dose-dependent manner, the alkaloidal fraction (mostly palmatine, jatrorrhizine, and magnoflorine) exhibits superior antioxidant activity compared to columbin. Because of its glycosidic, diterpene, and alkaloids, T. cordifolia is included in the Indian Ayurvedic Pharmacopoeia as an antidiabetic herbal medicine [18]. Research has demonstrated that the alkaloids palmatine, jatrorrhizine, and magnoflorin work together to produce the hyperglycemic effect by a mechanism that inhibits gluconeogenesis, releases insulin, and mimics insulin [19].

5. *Tinospora cordifolia*: ANTICANCER ACTIVITY

Tinospora cordifolia (Tc)s, popularly known as Giloy, has been examined for its anticancer properties. This climbing shrub, native to India, Sri Lanka, and Myanmar, has been found to suppress cancer cell proliferation, induce apoptosis, reduce tumour progression, and boost the immune system [19]. Its mechanisms include regulating cell proliferation, apoptosis, angiogenesis, and metastasis, as well as reducing oxidative stress [19,20]. More research is needed to fully understand its efficacy, safety, and potential interactions with other cancer treatments. A clerodane diterpenoid, (5R,10R)-4R, 8R-dihydroxy-2S,3R:15,16-diepoxycleroda-13(16),17,12S:18, 1S dilactone, was found to prevent chemically- induced hepatocellular carcinoma in rats and inhibit tumor growth through an antioxidant and detoxification mechanism [21]. The dual action of the diterpenoid was transmitted by blocking carcinogen metabolic activation and enhancing carcinogen detoxification.

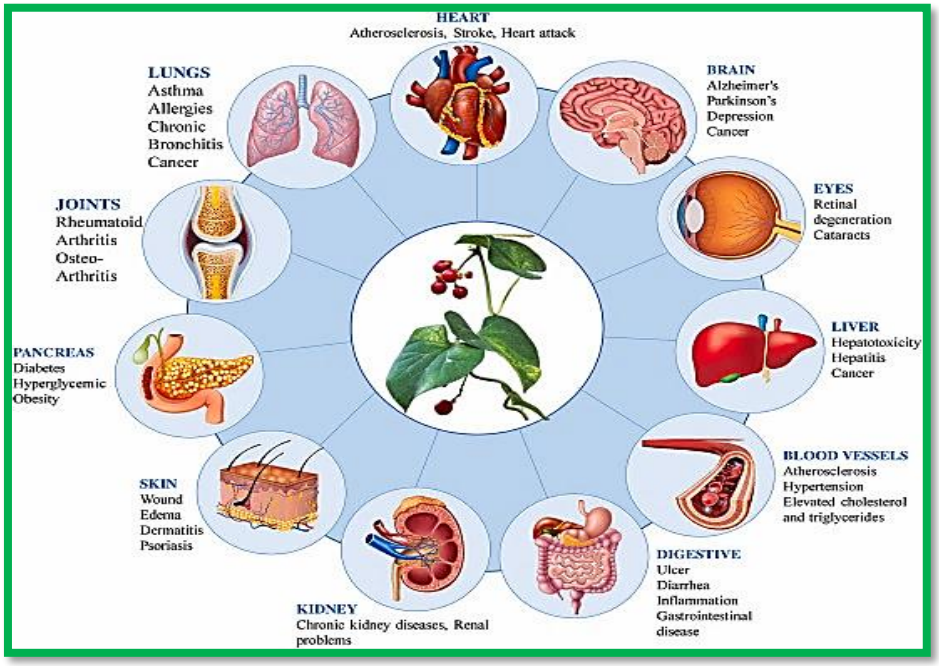

Fig. 2. Various pathological aspects of Tc
Source: Karuppusamy Arunachalam et al,.2022

Cancer is a growing economic burden worldwide [8,6]. 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 [3,6]. Current therapeutic modalities in cancer, including surgery, chemotherapy, and radiotherapy have shown to be associated with significant morbidity [2]. 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 [11,12]. Cancer poses a significant global economic burden, characterized by dysregulated cell division and proliferation due to mutations in multiple genes. While conventional therapies like surgery, chemotherapy, and radiotherapy have limitations and side effects, researchers are exploring natural compounds for alternative treatments [20,21]. Tinospora cordifolia, a plant species, shows promise due to its anti-carcinogenic properties, particularly in oral squamous cell carcinoma (OSCC).

In vitro studies highlight the cytotoxic effects of *Tinospora cordifolia* (Tc), extracts on various cancer cells lines, including murine monocytes/macrophages, human melanoma, and breast cancer cells [22]. Further exploration is needed to understand the in vivo anticancer effects of *Tinospora cordifolia* (Tc), and its components, such as berberine, across different cancer types. Moreover, its potential for cancer prevention and management of precancerous conditions warrants investigation [23]. Overall, *Tinospora cordifolia* (Tc), emerges as a natural therapeutic agent with significant potential in cancer therapy, offering a promising avenue for further research and clinical trials to validate its efficacy and safety [22].

One study investigated the anticancer effect of *T. cordifolia* palmatine extract in animal models, utilising response surface methodology (RSM). The extract has anticancer properties in a 7,12-dimethylbenz(a)anthracene DMBA-induced skin cancer model in mice. Another study generated extracts of 200, 400, and 600 mg/kg dry weight in a dose-dependent manner. When C57 BI mice were given a 50% methanolic extract of cordifolia for 30 days at a concentration of 750 mg/kg body weight, the tumour size decreased and so did their life expectancy. Mishra et al. demonstrated the anti-brain cancer potential of a 50% ethanolic extract of *T. cordifolia* (TCE) using C6 glioma cells, which greatly increased differentiation and reduced cell proliferation. Methanolic, aqueous, and ethanolic *T. cordifolia* stem extracts inhibited apoptosis by inducing programmed cell death. The colorimetric MTT assay and TBE method were used to assess the in vitro cytotoxicity 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 [24].

6. CONCLUSIONS

Tc has been shown to contain several phytocomponents with significant anti-carcinogenic properties as elicited by the included in vitro and in vivo studies. Understanding plant chemical components is critical for chemical production and medicinal applications. Biotechnological approaches can preserve and improve plant quality by producing secondary metabolites, developing innovative treatments, and commercialising them. *Tinospora cordifolia's* versatility is demonstrated by its vital components. Despite its therapeutic potential, the plant's quick disappearance needs biotechnological advancements in the selection, classification, and preservation of planting material.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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