



**International Journal of Biology, Pharmacy  
and Allied Sciences (IJBPAS)**

*'A Bridge Between Laboratory and Reader'*

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## A SYSTEMATIC REVIEW ON ANTICANCER STUDIES OF *TINOSPORA CORDIFOLIA* IN RECENT YEARS

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Received 10<sup>th</sup> Feb. 2023; Revised 25<sup>th</sup> April 2023; Accepted 14<sup>th</sup> July 2023; Available online 1<sup>st</sup> March 2024

<https://doi.org/10.31032/IJBPAS/2024/13.3.7842>

### ABSTRACT

Surgery, chemotherapy, and radiotherapy are the main types of cancer treatment. The accompanying morbidity of these treatment regimens lowers overall quality of life even if they have been quite efficient in suppressing malignancy. Researchers are therefore working to find any alternative therapeutic strategy that can prevent cancer without causing further morbidity. The usage of plants is one of the alternative cancer therapies that is receiving a lot of attention since they contain a wide range of anti-carcinogenic chemicals.

The objective of collecting all these research reviews was to thoroughly examine information that has been published about the anti-cancer activity of phytochemicals derived from *Tinospora cordifolia*. *Tinospora cordifolia*, anticancer, anti-neoplastic, carcinoma and phytochemicals in cancer key words were used as search terms for PubMed, Scopus, Web of Science, and Research Gate library search engines.

**Keywords:** *Tinospora cordifolia*, Anticancer, Giloy, Cytotoxicity

### INTRODUCTION:

The Menispermaceae family includes the herbaceous vine known as *T. cordifolia* Wild. It is a glabrous climbing shrub with many different names, such as giloe, guduchi, and amrita, among others. The

word "giloy" is a Hindu mythological term. It has anti-allergic, antidiabetic, antiperiodic, antipyretic, and antispasmodic effects [1, 2]. Only *T. cordifolia* has been found to have anti-carcinogenic qualities

within the *Tinospora* genus [3]. This plant's various parts, including the leaves, roots, and stem have been employed for their numerous therapeutic benefits [4]. However, using stem has received a numerous experimental models, in anti-inflammatory and anti-cancer activities [5, 6].

*T. cordifolia* extracts have shown antitumor effects against prostate cancer, glioblastoma, liver cancer, neuroblastoma, cervical cancer and a variety of other cancer cell lines. Mechanistically extracts from *T. cordifolia* have shown to induce radio sensitization, DNA damage, differentiation, senescence, inhibit side population of cancer stem-like cells as well as chemo-preventive effects on cancer cells [7]. This herb is referred to as Tridosha Shamaka, a Rasayana plant, and is also known as an adaptogen since it boosts general vitality, raises energy levels, and increases the body's resistance to biological, chemical, and physical stress [8].

About 70–80% of people are still using herbal medicines for their primary health because of the less side effects and better compatibility with the human body [9, 10]. One of the most popular and indisputable spices in Ayurvedic medicine is guduchi [11]. In this study, however, we have found the presence of Quercetin [12], Rutin [13] and other active compounds in *T. cordifolia*

that might be responsible for its anti-tumour property.

This review suggests that *T. cordifolia* extract with pharmacologically active phytochemicals might have the potential to be developed as a chemotherapeutic agent for the management of cancer.

Recent research has demonstrated that berberine has anti-tumor properties against leukaemia, lung cancer, cervical cancer, and other malignancies [14]. Through a number of ways, berberine reduces the proliferation of cancer cells. Numerous medicinal herbs suggest a potential involvement in the suppression of cancer cell proliferation [15]. Consequently, this review gives a summary of the studies conducted on *T. cordifolia* in the treatment of various type of cancers.

#### **TAXONOMIC POSITION :**

*T. cordifolia* is a member of the Menispermaceae family. There are 450 species and 70 genera of this family [16,17]. Due to the fact that its leaves are simple, alternating, cordate, whole, glabrous, and 7-9 nerved, this herb is also known as heart leaf moonseed [18]. Unisexual, greenish flowers that bloom throughout the summer. The surface skin is longitudinally fissured and the stem is covered in warty tubercles. Its roots, stems and leaves have all been used medicinally for thousands of years in Ayurveda tradition [19,20].

**The taxonomic classification of *T. cordifolia* is as follows [21,22]**

Kingdom:	Plantae	Order:	Ranunculales
Subkingdom:	Tracheobionta	Family:	Menispermaceae
Division:	Magnoliophyta	Genus:	Tinospora
Class:	Magnoliopsida	Species:	Cordifolia
Subclass:	Ranunculidae	<b>PHYTOCHEMISTRY:</b>	

Table 1: The different active constituents isolated from Giloy (*T. cordifolia*) are listed below

Sr. No	Phytochemical	Name of phytochemicals	Reference no
1	Alkaloids	Choline, Berberine, Magnoflorine, Tinosporin, Palmetine, Isocolumbin, Jatrorrhizine, Tetrahydropalmatine, Tinocordiside (B,C,D) Tetrahydropalmatine	[23,24]
2	Glycosides	Cordifolioside A, Tinocordiside, Syrigin, 18-norclerodane glycoside	[25,26]
3	Steroids	Ecdysterone, Makisterone A Giloinsterol. Sitosterol, stigmasterol	[27,28]
4	Diterpine lactone	Furonlactone, Columbin, Tinosporon	[29,30]
5	Polysaccharide	Arabinogalactan, Tinosporacelerodanol, Tinosporafurandiol, Diflurozene	[31]
6	Miscellaneous	Phenol, 2,4-bis(1,1-dimethylethyl), E-15-Hepta-decenal, Trifluoro-acetoxy hexadecane, 9-Eicosene	[32]

## LITERATURE REVIEW

From the literature review it was observed that there are few review articles based on anticancer potential of *T. Cordifolia*. This review paper has included the research papers published in last seven years from 2015 to 2022. Recently Babji Deepa (2019) published a review article on *T. cordifolia* and its phytocomponents effect on cancer. This article includes collection of information of up till year 2019. Authors have included 11 research articles from the duration 2015-2019. In our search we have found few more studies missed by the authors. Also, we have updated the research papers published till 2022. *Tinospora cordifolia*, anticancer, anti-neoplastic, carcinoma and phytocomponents in cancer,

key-words were used as search terms for PubMed, Scopus, Web of Science, and Research Gate library search engines. Duplicate and already reviewed articles were omitted from the study.

Following are the anticancer studies carried out on *T. cordifolia* from 2015 till 2022.

1. **Ahmad R et al (2015)** Have carried out the in-vitro cytotoxic activity of 50% methanolic extract of the stem of *T. cordifolia* against the normal Vero epithelial cell line and the human breast cancer cell line (MDA-MB-231). *T. cordifolia* methanolic extract inhibited the growth of a human breast cancer cell line significantly (MDA-MB-231) with IC50 values of 59.4 g/ml in 0.25% DMSO and 50.01 g/ml

in 0.5% DMSO. Authors suggested for lead optimization studies, the methanolic extract would be further investigated to isolate and characterise the active components. They concluded the cytotoxic effect of *T. Cordifolia* stem extract against human breast cancer cell line [33].

**2. R. Jayaprakash *et al* (2015)**

Evaluated antioxidant activity of ethanolic extract of *T. Cordifolia* whole plant on N-nitrosodiethylamine (diethylnitrosamine) induced liver cancer in male Wister albino rats. N-nitrosodiethylamine causes cytotoxicity, mutation and carcinogenicity through metabolic activation by Cyt P450 enzymes to generate reactive electrophiles causing oxidative stress. Authors reported that, the lipid peroxidation level has been reversed and enzymatic, nonenzymic antioxidants were restored to levels that were close to normal in cancer-bearing rats after the administration of an ethanolic extract of *T. cordifolia* [34].

**3. Sharma A *et al* [2019]** Investigated anti-cancer activity of *T. cordifolia* chloroform and hexane stem extracts against brain cancer. They claimed *T. cordifolia* extracts retard the proliferation rate and cytotoxicity determined by MTT assay. Induce cell

differentiations and inhibit cell migration of U87MG glioblastomas and IMR32 neuroblastoma. They reported extracts were non-toxic to normal cells [35].

**4. Thongchai Taechowisan *et al* [2019]**

Investigated antibacterial and cytotoxicity activities of major constituents isolated from ethanolic stem extract of *T. Cordifolia* Willd growing on *Mangifera indica* L. They isolated the main components from the *T. cordifolia* using silica gel 60 column chromatography, thin layer chromatography, and medium pressure liquid chromatography. Spectroscopic techniques were used to identify pure substances. Using accepted practices, the purified components and crude extract were examined for their cytotoxicity and antibacterial activities. Magnoflorin and tembetarine, two pure alkaloids, were identified. Both the isolated alkaloids showed antibacterial activity with minimum inhibitory concentration (MIC) of 32–64 µg/ml and minimum bactericidal concentration (MBC) of 128–256 µg/ml against *Bacillus cereus* and *Staphylococcus aureus*. Using the MTT colorimetric assay on the murine fibroblast (L929) and human embryonic kidney (HEK293) cell lines, the cytotoxicity activity of the

isolated compounds and crude extract was determined. IC<sub>50</sub> values of 1162.24 to 2290.00 µg/ml and 1376.67 to 2585.06 µg/ml, respectively, for the L929 and HEK293 cell lines demonstrated modest cytotoxicity activity. According to this study, these compounds have a strong potential for antibacterial action and just moderate cytotoxicity [36].

5. **Palmieri A et al [2019]** Demonstrated a potential anticancer effect of Berberine and *T cordifolia* on colon cancer cells by acting on specific pathways. Authors proposed that the Berberine targets a variety of cell signalling pathways, including differentiation, proliferation, and the transition between epithelial and mesenchymal tissue by using Real-time polymerase chain reaction (RTPCR). They evaluated the expression levels of a panel of 44 chosen genes in the human colon adenocarcinoma (HCA-7) cell line. 33 distinct genes with varying roles in cell cycle, differentiation, and the epithelial-mesenchymal transition were down regulated by berberine administration in a time- and dose-dependent manner. The tendency was supported by the two treatment modalities, the two time periods, and the various absolute berberine dosages.
6. **Noopur H et al [2019]** Evaluated of anti-cancer activity of *T. cordifolia* on experimentally induced spontaneous fibrosarcoma in swiss albino mice. The current data strongly suggested that the *T. cordifolia* stem extract has antitumor potential. When combination therapy of hydroethanolic stem extract of *T. cordifolia* 400mg/kg and paclitaxel drug of 5mg/kg was given, it showed better effects than paclitaxel alone. Therefore, combination therapy can be a good strategy to combat fibrosarcoma [38].
7. **Ludas A et al [2019]** Have tested Anti-cancer potential of polysaccharide isolated from methanolic extract of *T. cordifolia* stem bark against breast cancer. The polysaccharide isolated from methanolic stem bark extract of *T. cordifolia* was investigated using haematological parameters like Red blood cell (RBC), White blood cell (WBC) and platelet counts, platelet level, tumor markers like Carcino Embryonic Antigen (CEA), Cancer Antigen 15.3 (CA 15.3) in the serum of female albino Wistar rats induced with breast cancer using DMBA (7,12-

These results imply that the antiproliferative properties of *T. cordifolia* extract are greatly contributed by the presence of berberine [37].

Dimethylbenz [a] anthracene). Animals treated with polysaccharide were able to restore the decreased RBC, WBC, and platelet levels that were caused by DMBA to normal levels. Tumour markers CEA and CA 15.3 were found to be increased in serum level of DMBA- induced breast cancer group when compared with the level of normal group and polysaccharide treatment group shows no rise in tumour markers [39].

8. **Barua A et al [2020]** Studied phytochemicals, antimicrobial and cytotoxic potential of methanolic extract of *T. Cordifolia*. Brine shrimp lethality assay method was used to test cytotoxic potential. Standard gallic acid and methanolic extract showed approximately 100% and 96.67% mortality of brine shrimp at 800µg/ml, respectively. The mortality rate was increased with increasing concentration. The LC50 values were found, at 292.37µg/ml and 174.16µg/ml for methanolic extract and standard respectively [40].
9. **Mittal J et al [2020]** Unveiled the cytotoxicity of phytosynthesised silver nanoparticles using *T. cordifolia* leaves against human lung adenocarcinoma A549 cell line. Authors have biosynthesised and characterized of AgNPs of aqueous extract of *T.*

*cordifolia* leaves. Prepared AgNPs were evaluated against human respiratory organ adenocarcinoma cell lines A549 by MTT and trypan blue assay, apoptotic morphological changes using Annexin V-FITC and Propidium Iodide (PI), nuclear morphological changes by DAPI (4, 6-diamidino-2-phenylindole dihydrochloride) staining, reactive oxygen species generation, and mitochondrial membrane potential determination. After being exposed to AgNPs for 12, 24, and 48 hours, it was observed that the relative proportion of A549 cells decreased in a dose-dependent manner. Significant cell death was seen when the concentration of AgNPs was greater. Results showed that the human lung cancer cell line A549 was extremely sensitive to the prepared AgNPs [41].

10. **Sreedevi A et al [2021]** Studied antioxidant and breast cancer activity (MCF-7 cell line) of isolated magnoflorine from ethanolic extract of *T. cordifolia* aerial. The anti-oxidant activity was determined by using DPPH reagent, while MTT assay was used to determine anticancer activity. At a concentration of 500 µg/ml magnoflorine showed 64% of antioxidant activity. Cell viability was

found to be 1.9 % at a concentration of 100 µg/ml [42].

11. **Patil S *et al* [2021]** Reported that an aqueous extract of *T. cordifolia* was effective even at a low concentration of 5µg/ml in inducing apoptosis and attenuating epithelial-mesenchymal transition in AW13516 oral cancer cell line in a concentration dependent manner. The caspase activity assay was used to validate the induction of apoptosis [43].
12. **Shrestha T *et al* [2021]** Assessed methanolic extract of *T. cordifolia* (Gurjo) for phytochemicals, antimicrobial, antioxidant and cytotoxicity activity. It was found that as the extract concentration was increased, DPPH radical scavenging activity was also increased. The extract exhibits a lesser scavenging profile when compared to ascorbic acid at a similar concentration. Lethal Concentration (LC50) was used to assess cytotoxicity. The analysis revealed that the extract of *T. cordifolia* had an LC50 value of 232.64 µg/ml determined by Brine shrimp lethality assay method, indicating that it was toxic [44].
13. **Puri A *et al* [2022]** In this work, researchers prepared and evaluated selenium nanoparticles to assess in-vitro tests for antioxidant and anticancer activities. Selenium nanoparticles were prepared by combining *T. cordifolia* stem extract with selenium acid. These particles were then used to assess in-vitro antioxidant and anticancer activity by DPPH and MTT assay. The prepared nanoparticles were tested on human breast cancer MCF-7 cell line and showed moderate cytotoxic activity and inhibit cell proliferation. From the lower IC50 and EC50 values, significant antioxidant capacity of prepared nanoparticles was confirmed [45].
14. **Vichare V *et al* [2022]** Have carried out the cytotoxicity Testing of *T. cordifolia* Extracts against Human Kidney Cancer Cell Line. The SRB assay method was used to assess the cytotoxicity of *T.cordifolia* leaf and stem extracts against the 786-O human renal cell carcinoma cell lines. At maximum concentration, 80 µg/ml, *T.cordifolia* leaf extract exhibited 82.3% control growth and 17.7% control inhibition, *T. cordifolia* stem extract shows 34.07% control inhibition and 65.93% control growth. The drug berberine was considered as good positive control. At higher concentration, it shows 43.13% control growth and 56.87% control inhibition. Unpaired T-tests were used

to compare the control and test groups, and two-way (ANOVA) calculations were followed by the Bonferroni's post hoc test. Thus, to treat human kidney cancer, methanolic leaf and stem extracts of *T. cordifolia* can be considered as potential anticancer drug [46].

#### CONCLUSION:

It has been observed that lot of research is going on anticancer potential of *T. cordifolia* extracts. Anticancer activities were carried out on whole plant extract as well as in most of the cases on stem extract. Organic solvents like methanol, hexane, chloroform were preferred for extract. From the literature it has been clear that *T. cordifolia* exerts anti cancer activity against variety of cancers including breast, liver, brain, oral cancer etc. Researchers are now developing novel drug delivery systems like nano particles of *T. cordifolia* extract for improvement in the anticancer potential. A variety of cell signalling pathways, including differentiation, proliferation, and the transition between epithelial and mesenchymal tissue are major targets proposed by authors for anticancer activity.

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