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Review

Effect of *Tinospora cordifolia*-Derived Phytocomponents on Cancer: A Systematic Review

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Abstract: The major cancer therapeutic modalities include surgery, chemotherapy and radiotherapy. Although these treatment regimens have played a significant role in effectively inhibiting cancer, their associated morbidity reduces the overall quality of life. Thus, researchers are striving to identify any alternate therapeutic approach capable of inhibiting cancer without eliciting the added morbidity. Among the alternate cancer therapeutics being researched, much importance is being given to the use of plants due to the presence of a wide variety of anti-carcinogenic compounds. *Tinospora cordifolia (Tc)* is one such plant and has shown to exhibit anti-carcinogenic properties. The present review aimed to systematically analyze published data on the effect of *Tinospora cordifolia*-derived phytocomponents on cancer. PubMed, Scopus, Web of Science, Embase and Cochrane library were searched using the keywords *Tinospora cordifolia*; anticancer; phytocomponents until March 20, 2019. In vivo and in vitro original studies in the English language were included. Of the 342 articles identified, only 25 articles met the selection criteria and were included in the review. Significant anti-carcinogenic properties were exhibited by *Tinospora cordifolia*-derived phytocompounds including palmative, berberine, new clerodane furanoditerene glycoside, arabinogalactan, phenolic compounds and epoxy cleodane diterpene. 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.

Keywords: cancer; phytocomponents; *Tiospora cardifolia*

1. Introduction

Cancer is a growing economic burden worldwide. The Globocan 2018 database estimates 18.1 million new cancer cases and 9.6 million cancer-related deaths [1]. This frightening and dreadful statistic has motivated the hunt for efficacious anticancer agents. Current therapeutic modalities

in cancer, including surgery, chemotherapy, and radiotherapy have shown to be associated with significant morbidity [2]. Thus, there is much interest shown in the advent of alternative therapeutics including 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. In the *Tinospora genus*, only *Tinospora cordifolia (Tc)*, has shown to exhibit anti-carcinogenic properties. Thus, *Tc* was selected as the subject of the review. *Tc* belongs to Menispermaceae family (universally named as "Guduchi"/ Giloy in Sanskrit). It is a deciduous climbing shrub with typical greenish-yellow flowers, found at higher altitudes like India, Myanmar and Sri Lanka. *Tc* has shown to exhibit several unique features, distinguishing them from other closely related species in the *Tinospora* genus, including *Tinospora malabarica* (*Tm*). *Tc* has an ash-colored cork, higher lenticels, nodes and internode, and a lower mucilage content than *Tm*. A variety of active components are derived from *Tc* including alkaloids, steroids, diterpenoid lactones, aliphatics, and glycoside. Apart from the anti-neoplastic properties, *Tc* is also shown to exhibit anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective and immunomodulatory properties [3,4]. The present review systematically analyzes the published data assessing the effects of *Tc*-derived phytocomponents on cancer.

2. Methods

2.1. Inclusion Criteria

In vitro cell line and in vivo animal model studies in the English language assessing the effect of the *Tc*-derived phytocomponents on cancer.

2.2. Exclusion Criteria

Narrative reviews, systematic reviews, meta-analysis, letters, editorials, conference abstracts, articles in languages other than English.

2.3. Information Sources and Search Strategies

PubMed, Scopus, Web of Science, Embase and Cochrane library were searched using the keywords *Tinospora cordifolia*; anticancer; and phytocomponents until March, 2019.

2.4. Study Selection

The review was conducted in two steps. In the first step, the titles and abstracts of the articles identified from the databases were screened to remove any duplicates and irrelevant articles. The full texts of the articles selected from the first step were assessed in the second step using the inclusion criteria. Both steps one and two were conducted by two reviewers (B.D and H.V.B) independently. The kappa coefficient was assessed to determine the inter-observer reliability between the two reviewers for steps one and two.

3. Results

Selected Studies: A total of 342 articles (PubMed—14, Scopus—36, Web of Science—20, Embase—203, Cochrane—69) were identified using the keywords. Titles and the abstract of the identified articles were screened to remove any duplicates or irrelevant articles in step one. Only 50 articles were included in step two. Based on the full-text assessment of these 50 articles, only 25 articles were found to satisfy the inclusion criteria and were included in the systematic review. Figure 1 illustrates the search strategy employed. The kappa coefficient for steps one and two was found to be 0.9 and 1, respectively. Table 1; Table 2 respectively summarize the overall in vitro and in vivo effect of *Tc*-derived phytocomponents on cancer. The various phytocomponents present in the different parts of

Tc, along with their anti-carcinogenic effects on cancer (both in vitro and in vivo), are elaborated in detail in the discussion.

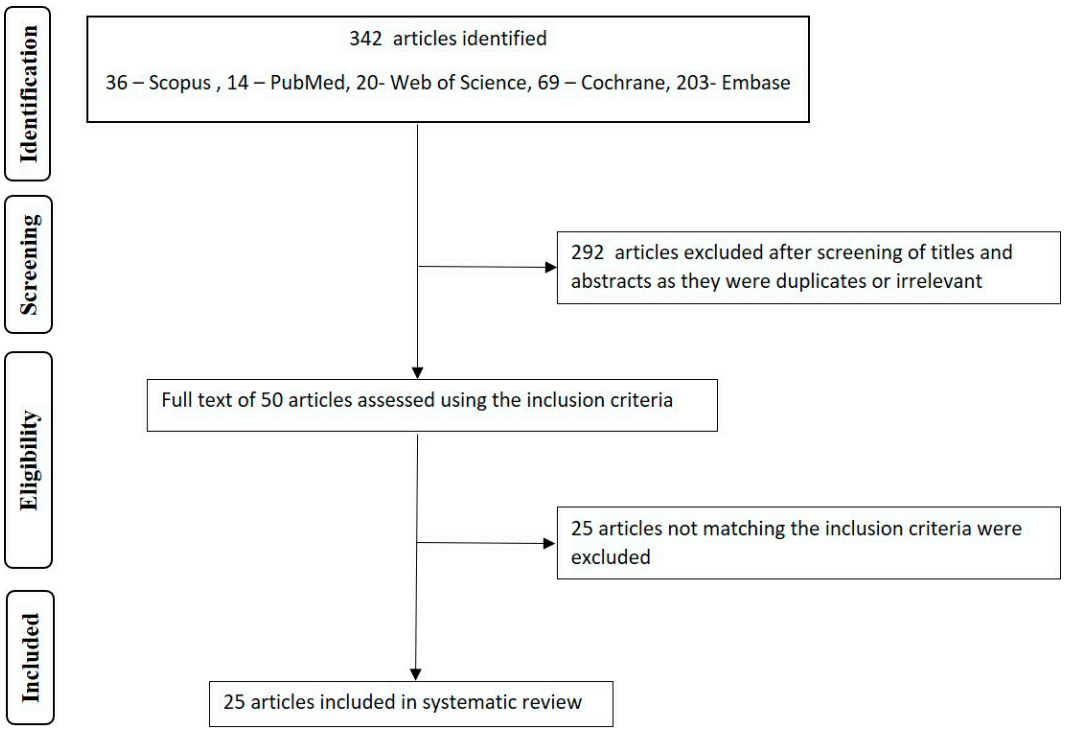

Figure 1. Summary of the search strategy.

Table 1. Summary of the data extracted from in vitro studies.

S. No.	Phytocomponents	Part in Use	Cancer Cell Lines	Anticancer Drugs Used with *Tc*	Effect on the Cancer Cells
1	Berberine and isoquinolone [5]	Information not provided	HEP2 human laryngeal cancer cell line (in vitro)	5-fluorouracil and cisplatin	Decreased gene expression of cell cycle, differentiation, and epithelial–mesenchymal transition
2	A new clerodane furano diterpene glycoside [6]	Fresh stems aqueous alcoholic extract	(in vitro) Human lung carcinoma cell line (A549), Prostate (PC-3), SF-269 (CNS), MDA-MB-435 (Melanoma), HCT-116 (Colon) and Breast (MCF-7)	Paclitaxel	Induction of mitochondria-mediated apoptosis and autophagy in HCT-116 cells
5	Information was not provided [7]	stem part aqueous and hydroalcohol extracts	Human breast carcinoma cell line MCF-7	Doxorubicin	Induction of apoptosis
6	Phenol (ellagic acid and kaempferol) [8]	Leaf and stem Phenolic extract	CHO (Chinese Hamster Ovary) cell line	Doxorubicin	Mild cytotoxic effect noted at a high concentration of the extract

Table 1. *Cont.*

S. No.	Phytocomponents	Part in Use	Cancer Cell Lines	Anticancer Drugs Used with *Tc*	Effect on the Cancer Cells
7	N-formylannonain, magnoflorine, jatrorrhizine palmatine, 11-hydroxymustakone, cordifolioside A, tinocordiside and yangambin [9]	Stem Ethanol extract	Human cancer cell lines, KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT-29 (human colon cancer) and SiHa (human cervical cancer) and murine primary cells	Doxorubicin	Cytotoxicity of cells
8	Ethanol phytofraction [10]	Powdered plant samples hexane, ethanol, and water extract	Human cancer cell lines HeLa-B75, HL-60, HEP-3B, PN-15, and normal liver cell lines	Suramin	Cytotoxicity of cells and induction of apoptosis
9	Phytochemicals of Ethanolic extract [11]	Whole plant and stem ethanolic extracts aqueous extracts	on human breast cancer cells (MCF7 and MDA MB 231)	Doxorubicin	Cytotoxicity of cells, induction of apoptosis, cell cycle arrest in the G2/M phase
11	Anthraquinones, terpenoids, and saponins and phenol [12]	Stem solvents like petroleum, ether, chloroform, ethyl acetate, acetone, and water extract	prostrate (DU-145), ovary (IGROV-1), and breast (MCF-7) cell lines	mitomycin-C (DU-145), paclitaxel against breast (MCF-7), and adriamycin (against ovary (IGR-OV-1)	Cell growth inhibition
15	Pyrrole-based small molecule [13]	Leaves ethyl acetate and aqueous extract	MDA-MB-231 breast cancer cells	Doxorubicin	Induction of apoptosis
17	Information was not provided [14]	Stem alcohol extract	human IMR-32 cell line	None	Upregulation of senescence and apoptosis
18	Phenolics contents quercetin and rutin [15]	Stems methanol extract	human breast cancer MDA-MB-231 cells	None	Anti-proliferative activity
19	Information was not provided [16]	ethanolic extract	Rat C6 glioma, U87MG human glioma, PC3 prostate cancer cell line, and HeLa cell line	None	Anti-proliferative, anti-migratory/ anti-metastatic potential activity, and induction of apoptosis.
20	Ready product from standard ayurvedic pharmacy [17]	Information was not provided	KB cancer cell lines	Methotrexate	Cell cycle arrest at G0/G1 phase

Table 2. Summary of the data extracted from in vivo studies.

S. No.	Phytocomponents	Part in Use	Animals	Outcome
3	Arabinogalactan a polysaccharide [18]	Stem Aqueous extract	Male BALB/c mice (25–30 g) benzo(a) pyrene-induced pulmonary tumor	Reduced tumor incidence and multiplicity, induction of apoptosis
4	Phenolic component [19]	Plant semiautomated capsule	DABA-induced mammary carcinogenesis in female Sprague-Dawley rats (breast cancer)	Tumor inhibition

Table 2. *Cont.*

S. No.	Phytocomponents	Part in Use	Animals	Outcome
6	Phenol (ellagic acid and kaempferol) [8]	Stem phenolic extract	Freshwater air-breathing fish *Channa punctatus* with DNA damage induction by nonionic surfactant nonylphenol	Non-cytotoxic, non-mutagenic, significant antioxidant activity, genoprotective effect
10	Alkaloid palmatine [20]	Stems methanol and aqueous extracts	Swiss albino mice injected with DMBA	Tumor inhibition
12	alkaloids including berberine [21]	stems dichloromethane alcoholic Extract	Swiss albino mice injected with Ehrlich ascites carcinoma (EAC)	Cytotoxicity of the cells
13	Antarth [22]	Plants aqueous extract	male Swiss albino mice injected with Ehrlich ascites carcinoma (EAC).	Reduces the cardiotoxicity associated with doxorubicin, but independently has no anti-carcinogenic effect
14	Triterpenoids and alkaloids [23]	stem methanolic extract	BALB RC and Swiss albino mice injected with Ehrlich ascites tumor cells	Tumor inhibition
15	Pyrrole-based small molecule [13]	Leaves methanolic extract	female Swiss albino mice injected with Ehrlich ascites tumor cells	Reduced tumor burden and two-fold increase in survival
16	Hexane fraction [24]	Stems solvents like hexane, benzene and chloroform	Swiss albino female mice injected intraperitoneally with Ehrlich ascites tumor (EAT) cells	Cell growth inhibition and induction of apoptosis
20	Polysaccharide [25]	Stem methanolic extract	C57BL/6 MICE injected by B16F-10 melanoma cell lines	Tumor inhibition
21	Clerodane-derived diterpenoids [26]	Stems alcoholic extraction	Male Wistar albino strain rats with diethylnitrosamine-induced hepatocellular carcinoma	Inhibiting tumor growth by blocking carcinogen metabolic activation and enhancing carcinogen detoxification.
22	Crude powder [27]	hydroethanolic (1:1) extract	Dalton lymphoma ascites (DLA) tumor model in Swiss albino mice	Reduced clonogenicity
23	Information was not provided [28]	Plant alcoholic extract	Inbred BALB/c mice tumor-associated macrophage (TAM)-derived dendritic cell to Dalton's lymphoma-bearing mice	Enhances the differentiation of dendritic cells

4. Discussion

Phytocomponents are natural components capable of exerting a therapeutic effect on disease entities, including cancer. Unlike conventional cytotoxic chemotherapeutic agents, phytocomponents have shown to inhibit cancer cells without eliciting systemic toxicity. *Tc* is one such plant, whose phytocomponents have shown therapeutic value against several diseases, including cancer [3]. Thus, the present manuscript systematically reviewed the published literature to provide comprehensive data on the effect of *Tc* on cancer based on both in vitro and in vivo experimental models. Assessment of the in vitro studies has shown *Tc* to have a potent anti-carcinogenic property based on induction of apoptosis, cell cycle arrest, anti-migratory, anti-metastatic effect, upregulation of cellular senescence and cell

growth inhibition in cancer cells (Table 1). Assessment of in vivo studies has shown anti-carcinogenic properties in the form of apoptosis induction, decrease in the expression of proliferative markers, an overall reduction in disease burden, and recurrence rate, with a significant increase in the survival rate (Table 2).

4.1. Parts of the Tc with Anti-Carcinogenic Effect

Phytocompounds have been isolated from all parts of *Tc* including the body of the plant, leaves and stem [4]. The stem of *Tc* has shown to contain most of the high phytocomponents, hence, most of the included studies have preferred the use of the stem. Rashmi KC et al. used *Tc* leaves, due to the presence of bis(2-ethylhexyl)-1H-pyrrole-3,4-dicarboxylate. Some studies have even used the whole plant [13].

4.2. Tc-Based Extracts

The various parts of *Tc* were subjected to different types of extracts for isolating the bioactive phytocomponents, including the alcoholic extract and aqueous extract. For alcoholic extracts, the parts were dried, ground in an electrical grinder and dissolved in either ethanol or methanol. Soxhlet apparatus was used for the extracts. For aqueous extracts, either distilled water or double-distilled water was used. Phytocomponents isolation was also accomplished using solvents like petroleum ether, chloroform, ethyl acetate, and acetone with alcohol [8,10]. Some authors preferred using both aqueous as well as alcoholic extracts [7,10]. Hexane extracts utilized solvents including hexane, benzene, chloroform and ethyl acetate [24] Singh B et al. used phenol to extract the dried leaves and stems of *Tc* [18]. Overall, most of the included studies preferred alcoholic extracts.

4.3. Dose Effect of Phytocomponents

According to the US National Cancer Institute, an IC_{50} value (drug concentration required for 50% inhibition in vitro) of less than 100 µg/mL from a medicinal plant is sufficient to be considered as an anticancer agent [29]. Components of such plants are isolated and characterized to delineate their bioactive molecules. The methanolic extracts of *Tc* have shown to exhibit an IC_{50} value of less than 100 µg/mL [29]. Sharma N used 1.5 kg of dried, crushed *Tc* soaked in 4.5 liters and found an IC_{50} value of less than 100 µg/mL [6]. Priya M S et al. used varying dosage (200, 400 and 600 µg/mL) of *Tc*, revealing dose-dependent inhibition [7]. Bala M et al. used 2 kg of dried stem in 80% ethanol extract. They extracted three phytocomponents and elicited an IC_{50} value of less than 100 µg/ml [9]. Maliakkal et al. used 2 kg of the dried crushed stem through alcohol extract and observed a dose which depended on cytotoxicity, with an ideal IC_{50} value of less than 100 µg/mL. They also showed that combining different phytocomponents resulted in a profound anti-carcinogenic effect [11]. Ansari et al. used 10 kg of 50% methanolic extract of *Tc*. The extract showed the anti-carcinogenic effect, while its rutin concentration was found to be higher than quercetin [15]. Ali H et al. found the phytocomponent palmatine showed anticancer effect against environmentally induced carcinogenesis. Jagetia et al. observed that combining the various alkaloid with berberine increased the antineoplastic effect. Thus, in addition to the dose-dependent effect, the overall anti-carcinogenic effect also depended on the type, number and dosage of the used phytocomponents [7,14,15,22].

4.4. Phytocomponents and Its Mechanism of Action against Cancer Cells

The active phytocomponents of *Tc* include alkaloids, glycosides, steroids, aliphatic compounds, essential oils, a mixture of fatty acid, calcium, phosphorous, protein and polysaccharides [4]. The various phytocomponents identified from the studies analyzed in the systematic review included berberine, new clerodane furanodiptherineglycosidae, elligic acid, kaempferol, N-formylannonain, magnoflorine, jatrorrhizine palmatine, 11-hydroxymustakone, cordifolioside A, tinocordiside, yangambin, anthraquinones, terpenoids, saponins and phenol, pyrrole-based small molecules, quercetin and rutin, arabinogalectian, palmatine, clerodane-derived diterpenoids and hexane fractions. These

phytocomponents induced anticancer effect via mitochondrial-mediated apoptosis, cytotoxic activity, mutagenic activity, reduction in tumor size, triggering reactive oxygen species, decreased gene expression of the cell cycle, effectively inhibiting cancer proliferation [5–23]. The mechanism of action of *Tc* depends on the phytocomponents used. The new clerodane furanodiptherineglycosidae exhibits anticancer activity through induction of mitochondrial-mediated apoptosis by triggering reactive oxygen species and autophagy [6]. Phenolic compounds have genoprotective and antioxidant effects on cancer cells [8]. *Tc* ethanolic extracts induced apoptosis via. increased sub G0 phase without altering cell cycle [11]. Arabinogalactans present in aqueous extracts of *Tc* shown to produce immunological activity and cytotoxic activity. Phenols have shown antimutagenic and anti-malignant effects. Flavanoids have a chemopreventive role in cancer. Pyrrole-based molecules induced apoptosis and cytotoxic effects [13]. Palmatine showed enhanced antioxidant activity by the increase in the level of antioxidant enzymes and also showed inhibition of lipid peroxidation showing role in detoxification pathway [20]. Berberine has shown to inhibit tumor cell growth by a reduction in the secretion of growth factors [5]. Hexane fractions have induced apoptosis via caspase 3-activated DNase [24]. Leyo et al. reported the polysaccharides in *Tc* to show antineoplastic effect by reducing the protein levels [25]. Epoxy-clerodane-diterpene blocks the carcinogen metabolic activation and enhances carcinogen detoxification. Singh N et al. reported *Tc* extracts have shown anticancer effect by direct tumoricidal actions [28]. Thus, *Tc* extracts have shown anti-carcinogenic properties through several mechanisms including induction of DNA damage, apoptosis, inhibiting topoisomerase II, clonogenicity, antioxidant activity, glutathione S transferase activity and increasing lipid peroxidase activity.

4.5. Anti-Carcinogenic Effect of Tc Phytocomponents

In vitro studies: In the included studies, the *Tc*-extracted phytocompounds were used in combination with conventional chemotherapeutics including: fluorouracil, cisplatin, paclitaxel, suramin, doxorubicin, mitomycin, adriamycin, and methotrexate. The *Tc* extract berberine (an alkaloid) has shown to inhibit cell cycle, differentiation, and epithelial–mesenchymal transition on HEP2 human laryngeal cancer cell lines [5]. New clerodane-furano-diterpene-glycoside obtained as an aqueous-alcoholic extract through bioassay-guided fractionation exhibited significant cytotoxic effect and induced apoptosis in human lung carcinoma (A549), prostate (PC-3), SF-269(CNS), melanoma (MDA-MB-435), colon cancer (HCT-116) and breast cancer (MCF-7) cell lines. It was observed the induction of apoptosis was Reactive oxygen species-mediated through mitochondria by activation of the caspase pathway [6]. Singh B et al. identified phenolic compounds from a fungal extract of endophytic fungus *Cladosporium velox* TN-9S isolated from the stem of *Tc*. Total phenol content was 730 µg gallic equivalents/mL as determined by Folin Ciocalteu reagent. The IC_{50} value was less than 100 µg/mL. These phenolic compounds have shown to exhibit a mild genoprotective potential against DNA damage on Chinese hamster ovary cell lines after the treatment with non-ionic surfactant nonylphenol. It was also noted that the endophyte's capability to synthesize phytocomponent was similar to the host plant. Their non-mutagenic and non-cytotoxic nature was suggested to enhance the antioxidant and genoprotective potential [8]. Bala et al. identified the phytocompounds from *Tc* extracts such as N-formylannonain, magnoflorine, jatrorrhizine palmatine, 11-hydroxymustakone, cordifolioside A, tinocordiside and yangambin through spectroscopic analysis. These phytocompounds were shown to exhibit anti-cancer properties on several human cancer cell lines including KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT-29 (human colon cancer) and SiHa (human cervical cancer). Bala et al. compared the anticancer activity for different fractions of the *Tc* extract. It was noted that combining the phytocompounds increased the anti-carcinogenic properties through a synergistic effect [9]. The ethanol phytofraction obtained from plant samples of *Tc* by Mishra R et al. were cytotoxic to IMR- 32 human neuroblastoma cancer cell lines. Analysis of the cellular and nuclear morphology through immunostaining revealed Tc induced apoptosis, increased expression of senescence markers. Anti-metastatic activity in the form of a reduced cell migration capacity was also observed. Protein assays result expressed the arrest of cells in the Go/G1 phase. Mishra R et al. extracted

phytocomponents from Tc plant including anthraquinones, terpenoids, saponins and phenol. This component effectively inhibited the growth of prostate, ovary and breast cancer cell lines. *Tc* extracts were also shown to exhibit antiproliferative, apoptotic-inducing, anti-migratory and antimetastatic potential on glioma cells. [12]. Butanoic fractions (pyrrole-based small molecules) were shown to induce apoptosis on breast cancer cells. Rashmi KC et al. determined apoptotic induction by evaluation by various apoptotic markers, ROS generation, caspase activity, and cell cycle analyzing. They found phytocomponents of *Tc* extract having anticancer activity and also observed inhibition of tumor proliferation. Despite promising results, the major limitation of most of the abovementioned studies is that several key aspects, including the complete mechanism of action, signaling, and pharmacological actions were nor clearly delineated [13]. Quercetin and rutin belong to phenolic phytocomponents extracted from Tc showed antiproliferative activity and was confirmed on human breast cancer MDA-MB-231 cells through induction of apoptosis, expression of altered genes and checking for the levels of intracellular ROS. The pharmacokinetics profiles, pharmacodynamic profiles and preclinical evaluation are some examples of the ongoing research by the authors [15]. Table 1 provides a summary of the overall effects elicited by *Tc* against the various cell lines.

In vivo studies: Animals that are used for the study in this review include male or female Swiss albino mice injected with Ehrlich ascites cells; male BALB/c mice with benzopyrene-induced pulmonary tumor; DABA-induced mammary carcinogenesis female Sprague Dawley rats; freshwater air-breathing fish *C. punctatus*; Swiss albino with DABA-induced carcinoma, C57BL/6 mice injected by B16F-10 melanoma cell lines; and male Wistar albino-strain rats with hepatocellular carcinoma. Arabinogalactan, a polysaccharide, was shown to inhibit cancer in male BALB/c mice. The arabinogalactan and the stem extract of *Tc* were shown to have a higher anticancer effect than only *Tc* [18]. Mishra A et al. conducted a scientific evaluation of phenolic components such as ellagic acid and kaempferol obtained from *Tc* extracts. These components were shown to have a genoprotective effect on fresh-air-breathing fish as elicited by the observations made on the morphology of the nucleus. Injecting the extract of fungus of *Tc* plant and nonylphenol caused a drastic reduction in the nuclear abnormalities. [19] Hall et al. extracted alkaloid phytocomponent palmative from *Tc* and studied anticancer property against DMBA induced skin cancer. Palmative caused a gradual decrease in the bodyweight of tumor size. Palmatine phytocomponent was shown to enhance the antioxidant enzyme levels and also inhibit carcinogenesis when administrated orally. [20] Another alkaloid phytocomponent, berberine, showed tumor remission on Swiss albino mice. The study was conducted by Jagetia G C et al. The anticancer effect was dose dependent. The exact mechanism was unknown, and authors concluded that the combinational effect of the alkaloids caused a higher anticancer effect [21]. Phytocomponents including triterpenoids, alkaloids, pyrrole-based small molecules, hexane fraction and clerodane-derived diterpenoids were also shown to exhibit significant anti-carcinogenic effect in different cancer induced in animals by showing reduction in solid tumor growth [22–24,26–28]. Leyon P V and Kuttan G extracted polysaccharide from *Tc* to observe the metastatic effect on C55BL/6 mice and the highly metastatic melanoma cell line B16F-10. Significant inhibition was noted, and although the exact mechanism of action was not known, an antimitogenic effect through natural killer cell-mediated immune modulation was suggested as a possible pathway [25]. Table 2 provides a summary of the overall effects elicited by *Tc* against the various in vivo animal models.

5. 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. Despite promising results in laboratory settings, the future scope of *Tc* 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 *Tc* in cancer therapy.

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