

Antineoplastic potential of *Trichosanthes dioica* Root: A treatise

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Medicinal plants have duly been implicated in the development of typical antineoplastic agents. Here, the medicinal plant under discourse, *Trichosanthes dioica* Roxb., commonly known as Pointed gourd in English, *Potol* in Bengali, is a climber vine found wild and cultivated all over the plains of India and its neighbouring countries for its fruits, consumed as a favoured vegetable. The present work attempts to assemble and critically assess the literature outcome of the antineoplastic potential of *T. dioica* root. The antineoplastic effects involved cytotoxic, antimetabolic, antitumor and cancer chemopreventive potential of its root - mediated through multifaceted mechanisms. The cytotoxic, antimetabolic and antioxidant effects together may furnish the mechanistic grounds for its reported antitumor and cancer chemopreventive activities. Further studies on *T. dioica* root in this direction, may afford newer effective antitumor leads/drugs from this plant part.

Keywords: Antitumor, Chemoprevention, Mitotic index, Oxidative stress, *Trichosanthes dioica*

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Introduction

Cancer is one of the most critical diseases causing global morbidity and mortality. The typical antineoplastic agents affect the general non-diseased body tissues particularly blood and haematopoietic system, epithelial tissues, reticuloendothelial and reproductive systems thus aggravating the morbidity^{1,2}. Medicinal plants have traditionally been utilized worldwide to cure cancerous disorders. Medicinal plants and their constituents i.e., natural products or phytochemicals, have been duly implicated in the development of current antineoplastic chemotherapy^{3,4}.

Several human cancers are caused by environmental contaminants, mainly chemicals. Different chemicals namely polycyclic aromatic hydrocarbons, nitrosamines, alkylating agents, and certain inorganic elements (heavy metals/metalloids) of the environment are carcinogenic^{5,6}. Chemoprevention is the application of certain natural or synthetic compounds to arrest carcinogenesis and thus prevent cancers⁵⁻⁷. Most of these agents are endowed with additional health-beneficial effects like antioxidant, hepatoprotective, cardioprotective and other health-giving effects^{3,4}.

The medicinal plant on extant review, *Trichosanthes dioica* Roxb. (Cucurbitaceae) generally called Pointed

gourd in English, *Potol* in Bengali, is a climber vine found wild and cultivated widely all over the plains of India and its neighbouring countries (Bangladesh and Myanmar) for its fruits, consumed as a favoured vegetable (Fig. 1). It is a well-reported medicinal plant of the Indian subcontinent. Traditionally, the leaf, fruit and root of this plant are used in India for several medicinal purposes. The root is specifically used as purgative, tonic and febrifuge. All these parts of this plant have been scientifically studied with several encouraging outcomes^{8,9}. However, the literature study reveals that the antineoplastic and analogous effects have only been reported for its root (Fig. 2). The aim of the present article is hence to review the extant literature pertaining to these effects on the root of *T. dioica* and to explicate the underlying mechanisms casting about for newer safe and effective natural antitumor leads/drugs.



Fig. 1 — *Trichosanthes dioica* plant.

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Fig. 2 — Dried roots of *Trichosanthes dioica*.

Review method

An Internet-assisted literature study was performed by searching the online bibliographic databases namely Google, Scholar Google, PubMed, Scopus, Wiley, Science Direct etc. by using keywords and key phrases like - *Trichosanthes dioica* root with antitumor/ anticancer/ chemopreventive/ cytotoxic/ antiproliferative, in different possible combinations. The scientific research articles pertaining to the antineoplastic and related effects (like cytotoxic and antioxidant) of *T. dioica* root published in the English language within the last 12 years i.e., 2010-2022 were appraised. Articles other than the language English were not considered. The non-peer-reviewed pre-prints hosted in certain web portals were excluded. The papers dealing with other pharmacological effects or other parts of *T. dioica* were not within the scope of the present compilation and review.

Reported antineoplastic-related activities

A literature survey through online databases revealed several pharmacological studies on *T. dioica* root. Out of them, there are seven specific studies describing the antineoplastic-related effects of *T. dioica* root. These include cytotoxic, antimetabolic, antitumor, tumour proliferation (at higher doses) and cancer chemopreventive activities. One additional study of *in vitro* antioxidant effect was also included to be pertinent (Table 1). Most of these pre-clinical studies used the water-alcohol extract of mature *T. dioica* root followed by the triterpenoid-enriched extract thereof.

Cytotoxic activity

In vitro, by trypan blue cell viability and MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay against murine Ehrlich ascites carcinoma (EAC) cells were employed to evaluate the cytotoxic effect of hydro-alcohol extract of *T. dioica* root (TDA). In the trypan blue assay, TDA increased non-viable cells when compared to normal control ($n = 3$, $P < 0.001$); the non-viability was highest $48.45\% \pm 1.12$ (SEM), at the TDA concentration of $4 \mu\text{g/mL}$, subsequently declined at the increased TDA concentrations. Similarly, in the MTT assay ($n = 3$, $P < 0.001$), the cytotoxicity was highest $34.58\% \pm 1.20$ (SEM) at the TDA concentration of $2 \mu\text{g/mL}$, then decreased at higher TDA concentrations¹⁰.

Antimetabolic activity

The dichloromethane, methanol and water extracts of *T. dioica* root (denoted as DCTD, METD and AQTd respectively) were assessed for *in vitro* antimetabolic activity by using onion root i.e., *Allium* assay ($n = 12$). All three foregoing extracts markedly demonstrated concentration-wise arrest of root length and number and reduction in mitotic index, indicating an antimetabolic effect. DCTD was the most active, followed by METD and AQTd¹¹.

Similarly, the *in vitro* antimetabolic activity of the triterpenoid-enriched fraction of *T. dioica* root (CETD) was also determined by the *Allium* assay ($n = 12$). The CETD significantly retarded root length, reduced root number and declined mitotic index in a concentration-based way, demonstrating antimetabolic property¹². These outcomes envisage the antimetabolic potential of *T. dioica* root.

Antitumor activity

TDA demonstrated antitumor and oxidative stress-abrogating activity in Ehrlich ascites carcinoma (EAC) bearing Swiss albino mice. TDA was given orally at 5 and 10 mg/kg body weight, one day after intraperitoneal tumour inoculation (EAC) in mice ($n = 12$), daily for 9 consecutive days. On the 10th day, half of the mice ($n = 6$) were sacrificed for the determination of tumour proliferation parameters (Table 1); haematological and hepatic enzymatic and non-enzymatic antioxidant parameters and the remaining mice ($n = 6$) were kept alive for the assessment of survival. TDA exhibited dose-wise and significant ($P < 0.001$) decrease in tumour parameters and extended the life stretch of tumour-bearing mice. Haematological and liver antioxidative profiles were

Table 1 — Digest of antineoplastic-related activities of *T. dioica* root.

S. No.	Effect	Bioassay/Model	Elicitor	Extract	Doses	Activities	Reference
1	<i>In vitro</i> cytotoxic	Trypan blue, MTT	EAC* cells	Hydroalcoholic	1 to 10 µg/mL	↓ viable cells, ↑ non-viable cells	10
2	Antimitotic	<i>Allium cepa</i>	-	Dichloromethane, methanol, aqueous	1-16, 20-320, 100-1600 mg/mL, 4 days	↓ root number, ↓ root length, ↓ mitotic index	11
		<i>Allium cepa</i>	-	Triterpenoid-enriched	0.75-12 mg/mL, 4 days		12
3	Antitumor	Mice	EAC* cells	Hydroalcoholic	5, 10 mg/kg, oral, daily, 9 days	↓ tumour volume, ↓ tumour weight, ↓ viable cell count, ↓ packed cell volume, ↑ life span, restoration of haematological and antioxidant parameters	13
		Mice	EAC* cells	Triterpenoid-enriched	2, 4 mg/kg, oral, daily, 9 days	↑ life span, restoration of haematological and antioxidant parameters	14
4	Tumorigenic and pro-oxidant	Mice	EAC* cells	Hydroalcoholic	25, 50 mg/kg, oral, daily, 8 days	Reversal of exactly above parameters	15
5	Chemopreventive	Mice	3-MC [†] , 200 µg s.c., once	Hydroalcoholic	2, 4 mg/kg, oral, 45 days	↓ tumour incidence, ↑ life span, normalization in haematological and antioxidant parameters	16
6	<i>In vitro</i> antioxidant	DPPH, hydroxyl, nitric oxide, peroxyxynitrite and superoxide radicals	-	Hydroalcoholic	25, 50, 100, 150 µg/mL	Free radical scavenging activity	17

*EAC: Ehrlich ascites carcinoma, †: increase, ‡: decrease, †3-MC: 3-methylcholanthrene.

significantly ($P < 0.001$) restored in TDA-receiving mice when compared with those of the control. Hence, TDA possessed marked antitumor activity in mice, by multimodal attenuation of oxidative stress¹³.

Similarly, the CETD was assessed at 2 and 4 mg/kg doses orally for 9 days in the foregoing EAC suffering mice protocol ($n = 12$) and its antitumor and tissue antioxidant efficacy (same parameters as above, $n = 6$, $P < 0.001$) has also been documented with melioration of tissue oxidative distress¹⁴. These studies affirm the antitumor effect of *T. dioica* root (Table 1).

Conversely, the TDA was found to induce tumour growth in EAC-carrying mice. Here, TDA was administered orally after 24 h of intraperitoneal EAC inoculation in albino mice ($n = 12$), at 25 and 50 mg/kg body weight for 8 successive days. Evaluation of similar tumour growth and survival parameters, haematological and hepatic biomarker estimations demonstrated a marked increase in tumour proliferation parameters and reduced

lifetime of tumour-bearing mice ($n = 6$, $P < 0.001$); aggravated hematological and hepatic antioxidative parameters ($n = 6$, $P < 0.001$) indicating rather pro-oxidant effect¹⁵.

Chemopreventive activity

The TDA was evaluated for cancer chemopreventive potential against chemical carcinogenesis i.e., 3-methylcholanthrene (3-MC) induced fibrosarcoma in Swiss albino mice. 3-MC (200 µg) was once administered subcutaneously in mice ($n = 25$). After 24 h, these mice were treated with TDA on alternative days orally at 2 and 4 mg/kg body weight for 45 consecutive days and observed to notice the occurrence of fibrosarcoma i.e., tumour incidence and survival/death for further 15 weeks. Then, the mice were sacrificed for the assessment of haematological and hepatic enzymatic and non-enzymatic antioxidant parameters. Treatment with TDA lowered tumour incidence and prolonged the life

duration of fibrosarcoma-bearing mice as compared to the 3-MC control (Table 1). TDA therapy considerably ($P < 0.001$) modulated the haematological and hepatic antioxidative status of sarcoma-affected mice¹⁶.

Free radical scavenging activity *in vitro*

The TDA at different concentrations (Table 1) was evaluated *in vitro* against free radicals viz. 1,1-diphenyl-2-picryl-hydrazyl (DPPH), nitric oxide, hydroxyl radical, peroxyxynitrite and superoxide radicals ($n = 3$). TDA exhibited marked and concentration-related free radical scavenging activity in these *in vitro* studies¹⁷. Therefore, *T. dioica* root possessed an antioxidant effect *in vitro*.

Discussion

The cytotoxic effect is one of the essential preconditions of any antitumor agent. The cytotoxic potential of *T. dioica* root extract (TDA) against EAC cells was ascertained *in vitro* via trypan blue and MTT bioassays. Trypan blue is a vital dye that selectively stains dead cells blue. Live or viable cells are not coloured because, in a viable cell, trypan blue is not absorbed through the living intact cell membranes; nonetheless, it traverses the necrotic membrane into dead cells which are observed distinguishingly blue¹⁸. Trypan blue staining is a fast experiment to assess cell viability however, the process is not so sensitive.

MTT assay is quite a sensitive method for assessing cell viability. MTT, a yellow tetrazole compound, is reduced to a purple formazan compound by NADH-dependent mitochondrial reductase of the living cells (Fig. 3). This reduction is directly proportional to the quantity of live cells present¹⁰. It was found that TDA is a moderately active cytotoxic agent *in vitro*, though did not precipitate more than 50% EAC cell death but has a significant effect at the lower concentrations. The trypan blue assay exhibited higher cytotoxicity whereas, the MTT assay demonstrated comparatively lower cytotoxicity. However, at higher concentrations, an inverse relationship was observed in both the assays i.e., an increase in TDA concentration could not affect increased cell death. This biphasic dwindling response may require further studies. Nevertheless, the root extract of *T. dioica* demonstrated notable cytotoxic properties at lower concentrations against EAC cells *in vitro* thus putting forward its prospect as a natural antitumor agent.

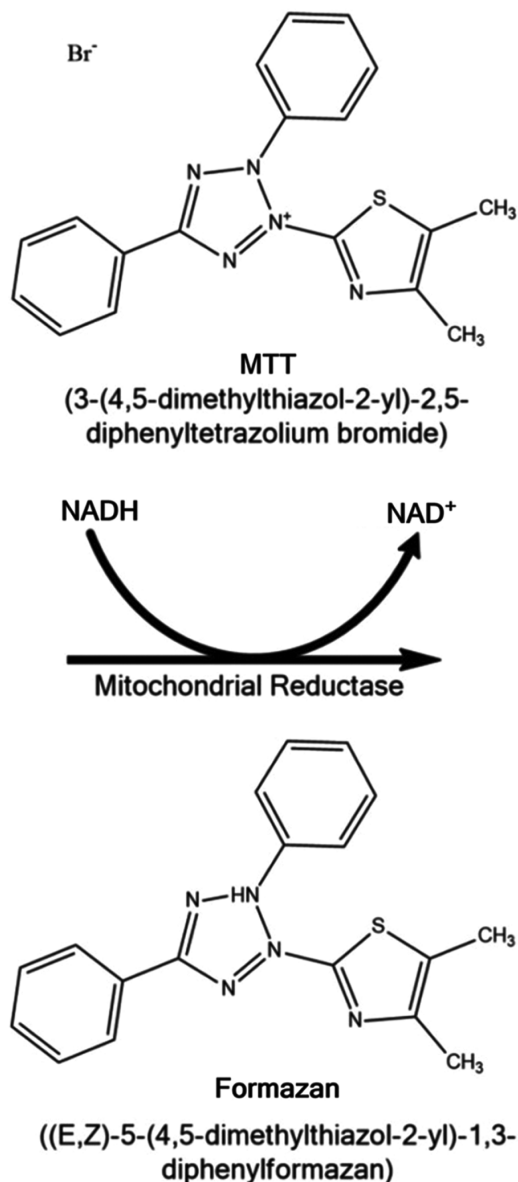


Fig. 3 — MTT assay reaction.

Cell division involving the mitosis process is essential for the proliferation of normal as well as cancer cells. Antimitotic effect i.e., impediment of mitosis brings about cytotoxicity affected by contemporary plant-derived anticancer drugs viz. vinblastine, vincristine, eribulin, paclitaxel, docetaxel etc. The extracts from *T. dioica* root while evaluated by using *Allium cepa* root, the observed antimitotic effects indicated cytotoxicity^{11,12}. The antimitotic activity was affirmed by mitotic indices, the reduction of which implied inhibited cell division thus furnishing considerable evidence on the mode of cytotoxic action. Hence, *T. dioica* root can hamper or cease the cell division process (cell cycle arrest). It

plausibly weakens the microtubule (cytoskeleton) functions or hindered the activity of the cell cycle elements. Therefore, *T. dioica* root had significant *in vitro* antimetabolic properties which further advocates its promise as a natural antitumor candidate.

The Ehrlich ascites carcinoma (EAC), first found as spontaneous murine hyperdiploid mammary adenocarcinoma, is a malignant type of cancer. It may be transplanted and it is high spreading carcinoma which can grow in both solid and ascitic forms in almost all mice¹³.

On the other hand, chemical carcinogenesis is caused by notorious carcinogens. Polynuclear/polycyclic aromatic hydrocarbons (PAH) are generated in the aftermath of pyrolytic activities. These are dangerous air pollutants, as some PAHs are mutagenic, carcinogenic and teratogenic. Amongst the different PAHs, benzo[a]anthracenes are carcinogenic. The alkyl-substituted derivative of benzo[a]anthracene like 3-methylcholanthrene (3-MC, Fig. 4) is a vicious carcinogen and teratogen^{6,16}.

In mice with Ehrlich ascites carcinoma (EAC), the higher ascitic fluid is due to an increase in total cell count¹⁹. In mice, TDA and CETD treatments lowered intraperitoneal tumour burden, thereby reducing tumour volume, packed cell volume, tumour weight and viable cell count with increased non-viable cell count. This implies the cytotoxic potential of *T. dioica* root extracts *in vivo* on the tumour (EAC) carrying mice.

The primary attribute for assessing the efficacy of an antineoplastic agent is the extension of the life period of the cancer affected organisms²⁰. The extracts remarkably prolonged the life span of carcinomatous and sarcomatous mice which is owing to the inhibition of tumor progression.

The common adverse events occurred in typical cancer chemotherapy are myelosuppression and anaemia^{1,2}. The extracts restored the murine erythrocyte count and haemoglobin content considerably with a decline in leucocyte count when

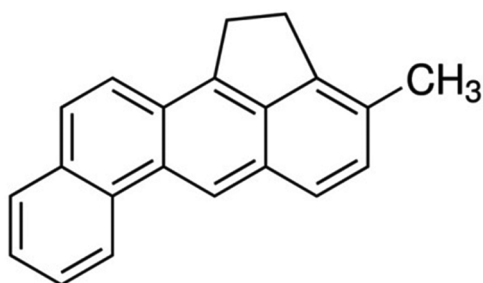


Fig. 4 — 3-methylcholanthrene (3-MC).

compared with EAC and 3-MC control mice. A study of these haematological parameters indicated that TDA and CETD were less noxious to the blood and haematopoietic system and certainly had cytotoxicity towards carcinoma and sarcoma cells and in this way, they could hold the normal haematological status in both the cases.

The cellular redox (oxidation-reduction) profile is related to regulating its growth behaviour²¹. Tissue has endogenous composite non-enzymatic (GSH) and enzymatic (SOD, CAT, GST, GPx etc) antioxidant defence network that becomes compromised during malignancies²². Oxidative stress is imposed through over generation of reactive oxygen species (ROS) which consequently elicit tissue lipid peroxidation and thus increases lipid peroxides i.e., thiobarbituric acid-reactive substances (TBARS) e.g., malondialdehyde (MDA) that cause deformation of cellular biomacromolecules namely, proteins (enzymes), fatty acids (essential fatty acids), nucleic acids (DNA, RNA)^{14,23}. *T. dioica* root extract treatments normalized MDA levels exhibiting inhibition of hepatic lipid peroxidation i.e., the suppression of excess free radical (ROS) production in carcinoma and sarcoma-carrying mice. This suggests that the antitumor and chemopreventive potential of *T. dioica* root are affected by reversing ROS-induced tissue toxicity.

Glutathione is the chief element of the bodily non-enzymatic antioxidative system. In reduced form (GSH), it has a critical function as a reducing agent. It detoxifies hydrogen peroxide (ROS) by the enzyme glutathione peroxidase (GPx) and itself gets oxidized (GSSG) (Fig. 5)¹³. In the studies being discussed, the depleted GSH is due to reduced hepatic synthesis of GSH or a decline in GSH content by oxidative impact in cancer-suffering mice. The treatments considerably normalized the hepatic GSH pool in carcinoma and sarcoma-bearing mice. Therefore, the antitumor and chemopreventive potential of *T. dioica* root was connected to the augmentation of non-enzymatic antioxidative protection.

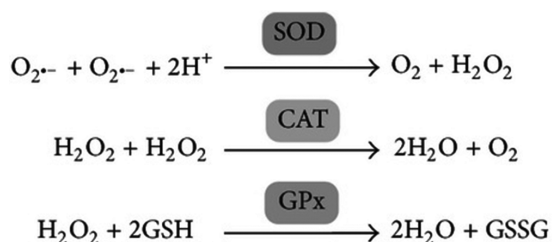


Fig. 5 — Chief tissue enzymatic and non-enzymatic pathways for the disposal of ROS.

Glutathione-*S*-transferases (GST) catalyze the nucleophilic conjugation of the sulfhydryl group of GSH to the electrophilic centre of various carcinogens, mutagens, xenobiotics etc for their disposition/elimination¹⁶. Studies demonstrated, reduced GST activity in EAC and fibrosarcoma control mice. *T. dioica* root extracts recuperated the lower hepatic GST activity in carcinoma and fibrosarcoma-affected mice. Thus, GSH and GSTs played their respective roles in the attenuation of oxidative stress, leading to the retardation of tumour progression in mice.

The enzymes are regarded as the first line of endogenous antioxidant defence. Superoxide dismutase (SOD) and catalase (CAT) are the enzymes responsible for catalyzing the disposal of superoxide and hydrogen peroxide (H₂O₂) radicals (ROS) respectively (Fig. 5)¹⁸. The decline in hepatic SOD and CAT activities was reported in EAC and fibrosarcoma control mice. Treating with TDA and CETD remarkably modulated the SOD and CAT activities in both spheres. Retrieval of endogenous enzymatic activities like GSTs, SOD and CAT; in cancer-affected mice receiving TDA and CETD, showed the fortification of cellular enzymatic antioxidant defence processes through which carcinoma and sarcoma-induced oxidative impact was obviated in rodents.

Different antioxidant natural products have been found to show both pro-oxidant and antioxidant activities^{4,24}. It is fascinating to place on record that, TDA exhibited a pro-oxidant effect *in vivo* at larger doses in EAC-bearing mice leading to tumour growth instigation i.e., a totally reverse effect. In the case of the cytotoxic studies *in vitro* against EAC cells, TDA exhibited an inverse relationship with concentration as already discussed above. The biphasic response of TDA both *in vitro* and *in vivo* against EAC needs rigorous further studies.

The *in vitro* free radical scavenging activity of TDA may furnish a ground for its demonstrated antioxidative activity *in vivo* towards the carcinoma and sarcoma-affected mice. *In vivo* antioxidant and antigenotoxic effects of *T. dioica* root were also reported against arsenic toxicity in rodents²⁵⁻²⁷. The cytotoxic and antimitotic properties may be the cause for its antitumor activity and the cytotoxic and antitumor effects, on the other hand, may be accountable for its chemopreventive potential, the antioxidant role being the general determinant. All these activities may be responsible for the other

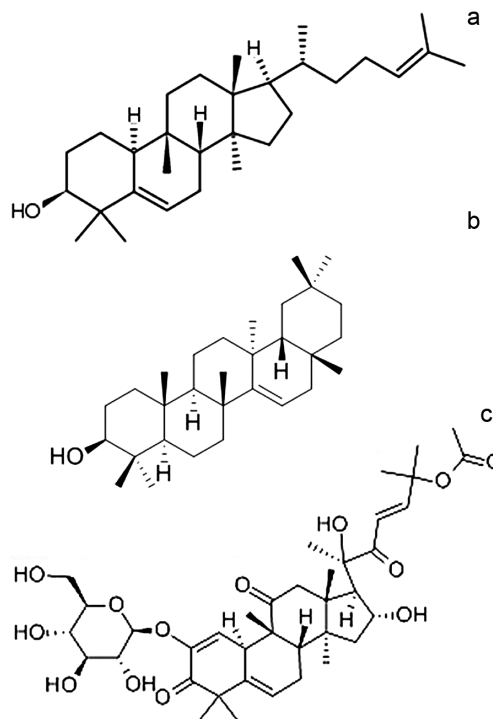


Fig. 6 — a) Cucurbitadienol; b) Taraxerol; and c) Colocynthin.

reported pharmacological activities like laxative, analgesic, anti-inflammatory, and anthelmintic properties of *T. dioica* root^{19,28-31}.

The prevalence of cucurbitacin-type triterpenoid aglycones was ascertained in *T. dioica* root in the research works being discussed by qualitative phytochemical estimation along with high-performance thin layer chromatography (HPTLC)^{13,16}. Cucurbitacins (a class of tetracyclic triterpenoids) are reported to bear several beneficial pharmacological effects embracing anticancer effect³²⁻³⁴. *T. dioica* root has already been reported to possess specific antitumor triterpenes like cucurbitadienol (Fig. 6a), α -amyrin, β -amyrin, euphol, lupeol, taraxerol (Fig. 6b) etc. It also has additional antineoplastic constituents viz. cucurbitacin glycoside – colocynthin (Fig. 6c) and a protein trichosanthin^{8,9,34}. The occurrence of the foregoing putative active principles could furnish the phytochemical basis for the discussed cytotoxic, antitumor and cancer chemopreventive potential of *T. dioica* root.

Conclusion

The plant kingdom yielded several potential clinically useful antineoplastic agents. *Trichosanthes dioica* (pointed gourd) is a well-utilized and explored Indian traditional medicinal plant. From the present

pre-clinical antineoplastic studies reviewed, it can be inferred that *T. dioica* root possessed marked cytotoxic effect *in vitro*, antimutagenic effect *in vitro*, antitumor and cancer chemopreventive actions *in vivo* in mice by means of its inherent antioxidative property mediated by multiple modalities. It may hence be concluded that the *in vitro* cytotoxic, antimutagenic and antioxidant effects of *T. dioica* root together may yield the mechanistic ground for its antitumor and chemopreventive potential *in vivo*. Further chemical and pharmacological investigations on *T. dioica* root in this direction, may furnish newer safe and effective antitumor leads/ drugs from this plant for possible clinical utilization in antineoplastic medication.

Conflict of interest

The author declares no conflicts of interest.

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