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# Ethno-medicinal value of some anticancer medicinal plants from north-east India: an *in vivo* screening in murine tumor model

**Gabriel Rosangkima, Thengtom Rongpi and Surya Bali Prasad***

*Cell & Tumor Laboratory, Department of Zoology, North Eastern Hill University, Shillong 793 022, India*

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## ABSTRACT

Considering the importance of natural products in cancer therapy, a preliminary investigation on some anticancer medicinal plants of north-eastern states of India was conducted in murine tumor model. Nine different plants such as *Ageratum conizoides* Linn. (Asteraceae), *Blumea lanceolaria* Linn. (Asteraceae), *Dillenia pentagyna* Roxb. (Dilleniaceae), *Potentilla fulgens* Wall. (Rosaceae), *Taxus baccata* Linn. (Taxaceae), *Mirabilis jalapa* Linn. (Nyctaginaceae), *Xanthium strumarium* Linn. (Asteraceae), *Dillenia indica* Linn. (Dilleniaceae) and *Gynura conyza* Cass. (Compositae) were studied. Out of these, the ethanol extract of *D. Pentagyna* showed the most potent antitumor activity, i.e. % ILS ~ 55% and % ILS ~ 48% at a dose of 50 and 100 mg/kg/day, respectively; followed by aqueous extract of *P. fulgens* showing % ILS ~ 37% at a dose of 50 mg/kg/day. Out of different fraction extracts of *D. pentagyna* and *P. fulgens*, better antitumor activity was observed with chloroform extract of *D. pentagyna* (% ILS ~ 89%) and hexane fraction of *P. fulgens* (% ILS ~ 37%) at a dose of 50 mg/kg/day. A significantly higher antitumor activity of *D. pentagyna* and *P. fulgens* seems to be due to the presence of alkaloids and flavonoids. Further detailed studies on its toxicity as well as isolation and structural elucidation of biologically active principle(s) are required.

**Key words**: Antitumor activity; Cancer; Dalton's lymphoma; medicinal plants; phytochemicals.

## INTRODUCTION

Chemotherapy is the most effective method in cancer treatment in which drugs like cisplatin, carboplatin, cyclophosphamide, doxorubicin, melphalan, mitomycin-C, and gemcitabine are used.[1,2] However, therapeutic efficacy of most of them is limited due to the development of various side effects in the host and/or the acquired drug resistance by the cancer cells.[3] In an attempt to decrease these side effects and better remedy for various malignancies, many plant derivatives have been used with varying success.[4] Higher plants, a source of medicinal compounds, are well known to play a dominant role in the health care of human beings.[5] More than 50% of all modern drugs in clinical use are of natu-

*Corresponding author*: S. B. Prasad
Phone. +91 0364 2722318
E-mail: sbpnehu@hotmail.com

 

ral product origin. A variety of plant extracts has been reported to have potential antitumor and/or anti-carcinogenic activities.[4,6,7] Currently, the chemotherapeutic management of tumors involves a variety of different plant-based chemicals that are either currently in use or in clinical trials and include such drug classes as the vinca alkaloids, lignans, taxanes, stilbenes, flavones, cephalotaxanes, camptothecins, and taxanes.

North-east India is one of the 25 global biodiversity hotspots. It lies between 22-30°N latitude and 89-97°E longitude. The region is endowed with varied flora to its diversified topography and climatic conditions marked by high rainfall, moderate temperature and high humidity and abound with dense forests, marshes, swamps, etc. with their characteristic and diversified species where a wide spectrum of vegetation ranging from the tropical to the alpine forests types occurs. Different tribes living in this area mostly rely on traditional herbal medicine for their primary healthcare practices. Majority of these tribes settle in rural areas where there are no good modern medical facilities. They are depending mostly on surrounding plant resources for their food, shelter, medicare, and other cultural purposes.[8-11] They believe in traditional system of medicines prepared from plants and animals. Medicinal plants are used either alone or in combination with another. All these information generated interest for the evaluation of traditional anticancer medicinal plants from this region to ascertain their anticancer activity against a murine experimental tumour system as well as screening of phytochemical constituents from the potent plant (s).

## MATERIALS AND METHODS

### *Animals and tumor maintenance*

Inbred Swiss albino mice (male, 10-12 weeks old) were maintained in the laboratory at room temperature of 20 ± 2°C with free access to food pellets and water *ad libitum*. Approximately $1x10^7$ viable ascites Dalton's lymphoma cells (in 0.25 ml phosphate buffered saline, PBS) were intraperitoneally (i.p.) transplanted per animal. Tumor transplanted hosts usually survived for 20 days. The use of animals in the present study was approved by ethical committee of the institution, North Eastern Hill University, Shillong, India.

### *Plant materials and preparation of extracts*

Survey of anticancer medicinal plants was carried out through literature search as well as consultation of local herbal practitioners and elders in some part of the north-eastern states. The plant materials were authenticated by Dr. P.B. Gurung, Department of Botany, NEHU, Shillong, India, and the voucher specimens were deposited in the Department of Zoology, North Eastern Hill University, Shillong, India.

Aqueous and ethanol extracts were prepared following the method described by Alasbahi *et al.*[12] Briefly, the collected plant tissues were washed in distilled water followed by 70% alcohol and shade-dried in a sterilized container which were then grounded into powder with a sterile mortar and pestle, and processed further for aqueous and ethanol extraction. Aqueous extract was prepared by boiling 250 g of ground plant tissue in two litres of double distilled water for two hours. Ethanol extract was also prepared by mixing 250 g of ground plant tissue in one litre of ethanol and incubated at room temperature for 48 hours. The tissue-solvent mixtures were filtered using Whatman No. 1 filter paper and the filtrates were evaporated to dryness in a rotary evaporator at 40 to 45°C. The dry mass extracts were collected and stored under 0°C until used.

The potent plants were also further fractionated into different components based on the solubility and polarity using solvents such as hexane, chloroform and *n*-butanol.[13] Differ-

ent fractions were processed for further *in vivo* antitumor activity studies to achieve the most potent fraction extract.

### In vivo *antitumor activity study*

Antitumor activity of the plant extracts was determined following the method of Sakagami *et al.*[14] Tumor-bearing control received extract vehicle alone. Animals in different groups (consisting of 10 mice each) were treated with different doses (50, 100 and 200 mg/kg b. wt./day) of the plant extracts by intraperitoneal (i.p) injection beginning day one of tumor transplantation, once daily for five days. The antitumor efficacy was expressed in percentage of average increase in life span (% ILS), and was calculated using the formula:

$$(T/C \times 100)-100$$

where, T and C are the mean survival days of treated and control group of mice, respectively.

The patterns of changes in body weight and food consumption of tumor-bearing hosts treated with potent plant extracts were also monitored.

### *Phytochemical screening*

The freshly prepared extracts of *Dillenia pentagyna* Roxb. (Dilleniaceae) and *Potentilla fulgens* Wall. (Rosaceae) were chemically tested for the presence of chemical constitu-

Table 1. Some notable anticancer medicinal plants selected from different parts of north-east India.

| Local name | Botanical name | Family | Part used | Therapeutic use |
|---|---|---|---|---|
| Vailenhlo (Mz) | *Ageratum conizoides* Linn. | Asteraceae | Root | Treatment of tumor and in cuts and wounds as haemostatic. |
| Buarze (Mz) | *Blumea lanceolaria* Linn. | Asteraceae | Leaves | Treatment of tumor, asthma, stomachache, wounds and scabies. |
| Kaihzawl (Mz) | *Dillenia pentagyna* Roxb. | Dilleniaceae | Stem bark | Treatment of tumor, stomachache and diarrhoea. |
| Langniang (Kh) | *Potentilla fulgens* Wall. | Rosaceae | Root | Treatment of colic pain, spasmodic trouble, pyorrhea and tumor. |
| Soh blei (Kh) | *Taxus baccata* Linn. | Taxaceae | Leaves | Treatment of aphrodisiac, epilepsies, irregular menstruation and tumor. |
| Godhuli gopal (As), Mugalei (Mn) | *Mirabilis jalapa* L. | Nyctaginaceae | Leaves | Treatment of tumor, boils, abscesses and urticaria. |
| Ban agara (As) | *Xanthium strumarium* L. | Asteraceae | Root | Treatment of tumor and strumous diseases. |
| Kawrthindeng (Mz) | *Dillenia indica* Linn. | Dilleniaceae | Stem bark | Treatment of tumor and diarrhoea. |
| Buarzo (Mz) | *Gynura conyza* sp. | Compositae | Leaves | Treatment of tumor, tuberculosis, dysentery and stomach ulcer. |

Mz = Mizo, Kh = Khasi, Mn = Manipur, As = Assam.

Table 2. Antitumor activity of aqueous extract of plants against murine ascites Dalton's lymphoma.

| Plant | Test part | Dose (mg/kg/day) | Life span (days) (mean ± SD) | ILS (%) |
|---|---|---|---|---|
| *A. conizoides* Linn. | Root | TB control | 19.8 ± 0.42 | - |
| | | 50 | 22.4 ± 0.60 | 13 |
| | | 100 | 25.3 ± 0.59 | 27* |
| | | 200 | 19.3 ± 0.57 | -2 |
| *B. lanceolaria* Linn. | Leaves | TB control | 19.8 ± 0.42 | - |
| | | 50 | 19.0 ± 0.48 | -4 |
| | | 100 | 17.0 ± 0.65 | -14 |
| | | 200 | 15.2 ± 1.13 | -23 |
| *D. pentagyna* Roxb. | Stem bark | TB control | 19.8 ± 0.42 | - |
| | | 50 | 18.2 ± 0.57 | -8 |
| | | 100 | 18.0 ± 0.48 | -9 |
| | | 200 | 18.6 ± 1.01 | -6 |
| *P. fulgens* Wall. | Root | TB control | 19.8 ± 0.42 | - |
| | | 50 | 27.2 ± 0.67 | 37* |
| | | 100 | 27.0 ± 0.33 | 36* |
| | | 200 | 22.8 ± 1.29 | 15 |
| *T. baccata* Linn. | Leaves | TB control | 19.8 ± 0.42 | - |
| | | 50 | 20.4 ± 0.79 | 3 |
| | | 100 | 19.8 ± 0.36 | 0 |
| | | 200 | 20.0 ± 0.72 | 1 |
| *M. jalapa* Linn. | Leaves | TB control | 19.8 ± 0.42 | - |
| | | 50 | 22.3 ± 0.64 | 12 |
| | | 100 | 19.5 ± 0.52 | -1 |
| | | 200 | 23.1 ± 0.47 | 16 |
| *X. strumarium* Linn. | Root | TB control | 19.8 ± 0.42 | - |
| | | 50 | 16.5 ± 0.70 | -16 |
| | | 100 | 15.3 ± 0.46 | -22 |
| | | 200 | 19.2 ± 0.58 | -3 |
| *D. indica* Linn. | Stem bark | TB control | 19.8 ± 0.42 | - |
| | | 50 | 22.6 ± 0.62 | 14 |
| | | 100 | 25.3 ± 0.44 | 27* |
| | | 200 | 23.6 ± 0.36 | 19 |
| *G. conyza* sp. | Leaves | TB control | 19.8 ± 0.42 | - |
| | | 50 | 14.7 ± 0.39 | -25 |
| | | 100 | 18.2 ± 0.55 | -8 |
| | | 200 | 19.4 ± 0.72 | -2 |

[a] 0.25 ml volume of the extract solution was administered daily on day 1-5.
[b] Control animals received the same volume of the extract vehicle.
* % ILS ≥ 20% were considered to possess antitumor potential.

Table 3. Antitumor activity of ethanol extract of plants against murine ascites Dalton's lymphoma.

| Plant | Test part | Dose (mg/kg/day) | Life span (days) (mean ± SD) | ILS (%) |
|---|---|---|---|---|
| *A. conizoides* Linn. | Root | TB control | 19.2 ± 0.47 | - |
| | | 50 | 19.6 ± 0.66 | 2 |
| | | 100 | 17.6 ± 0.58 | -8 |
| | | 200 | 14.8 ± 1.21 | -22 |
| *B. lanceolaria* Linn. | Leaves | TB control | 19.2 ± 0.47 | - |
| | | 50 | 19.5 ± 0.98 | 1 |
| | | 100 | 18.4 ± 0.74 | -4 |
| | | 200 | 20.0 ± 0.66 | 4 |
| *D. pentagyna* Roxb. | Stem bark | TB control | 19.2 ± 0.47 | - |
| | | 50 | 29.8 ± 0.62 | 55* |
| | | 100 | 28.6 ± 1.34 | 48* |
| | | 200 | 13.5 ± 0.66 | -29 |
| *P. fulgens* Wall. | Root | TB control | 19.2 ± 0.47 | - |
| | | 50 | 18.0 ± 0.92 | -6 |
| | | 100 | 16.6 ± 0.40 | -13 |
| | | 200 | 14.4 ± 0.91 | -25 |
| *T. baccata* Linn. | Leaves | TB control | 19.2 ± 0.47 | - |
| | | 50 | 21.0 ± 0.63 | 9 |
| | | 100 | 20.4 ± 0.46 | 6 |
| | | 200 | 18.8 ± 0.57 | -2 |
| *M. jalapa* Linn. | Leaves | TB control | 19.2 ± 0.47 | - |
| | | 50 | 18.7 ± 0.85 | -2 |
| | | 100 | 20.4 ± 0.44 | 6 |
| | | 200 | 18.6 ± 0.63 | -3 |
| *X. strumarium* Linn. | Root | TB control | 19.2 ± 0.47 | - |
| | | 50 | 22.5 ± 0.62 | 17 |
| | | 100 | 20.5 ± 0.51 | 6 |
| | | 200 | 16.8 ± 0.65 | -12 |
| *D. indica* Linn. | Stem bark | TB control | 19.2 ± 0.47 | - |
| | | 50 | 14.8 ± 0.45 | -22 |
| | | 100 | 18.8 ± 0.77 | -2 |
| | | 200 | 19.3 ± 0.49 | 0 |
| *G. conyza* sp. | Leaves | TB control | 19.2 ± 0.47 | - |
| | | 50 | 22.3 ± 0.41 | 16 |
| | | 100 | 19.7 ± 0.37 | 2 |
| | | 200 | 20.2 ± 0.56 | 5 |

[a] 0.25 ml volume of the extract solution was administered daily on day 1-5.
[b] Control animals received the same volume of the extract vehicle.
[*] % ILS ≥ 20% were considered to possess antitumor potential.

Table 4. Qualitative analysis of phytochemicals of stem bark of *D. Pentagyna* (DP) and root of *P.*

| Chemical group | | Observation (DP) | Observation (PF) |
|---|---|---|---|
| | Mayers Reagent | + | + |
| Alkaloids | Wagners Reagent | + | ++ |
| | Dangendroff Reagent | + | + |
| Flavonoids | | + | + |
| Tannins | | +++ | ++ |
| Saponins | | + | ++ |
| Iridoids | | ++ | ++ |
| Proanthocyanidins | | - | - |

- = Negative (absent); + = Positive (slightly present);

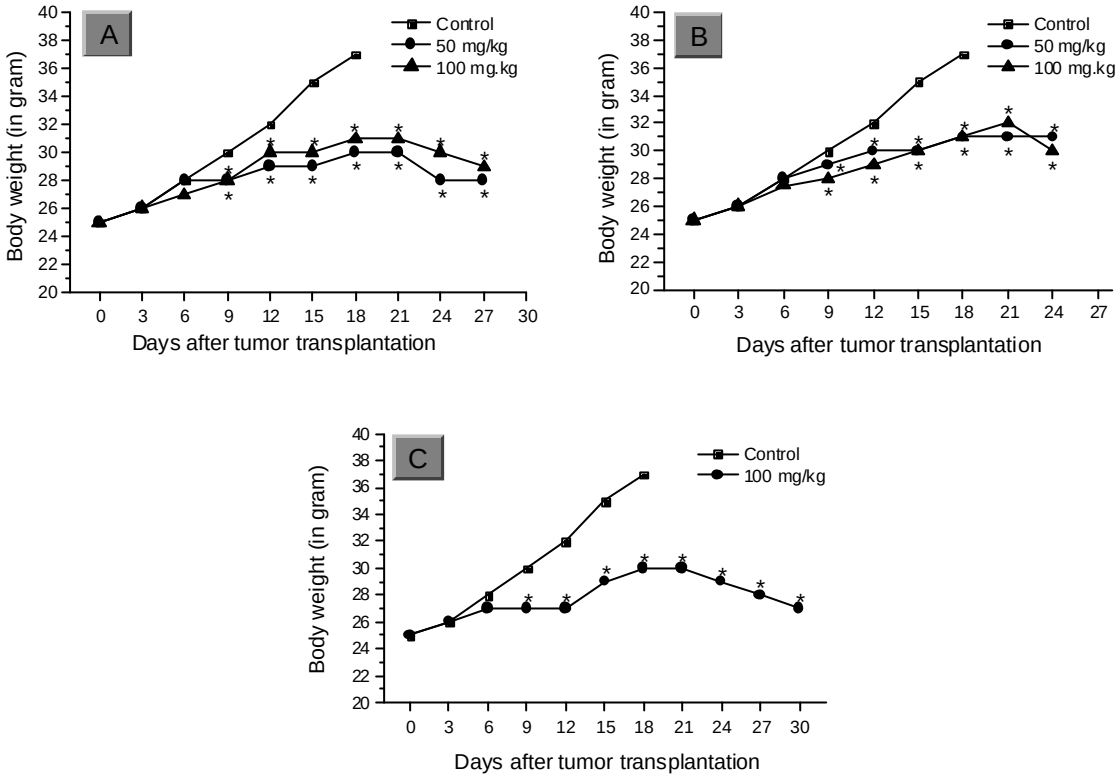


Figure 1. Graph showing the pattern of changes in the body weight of tumor-bearing control and after treatment with the extract of *D. pentagyna* (A), *P. fulgens* (B) and *D. indica* (C).

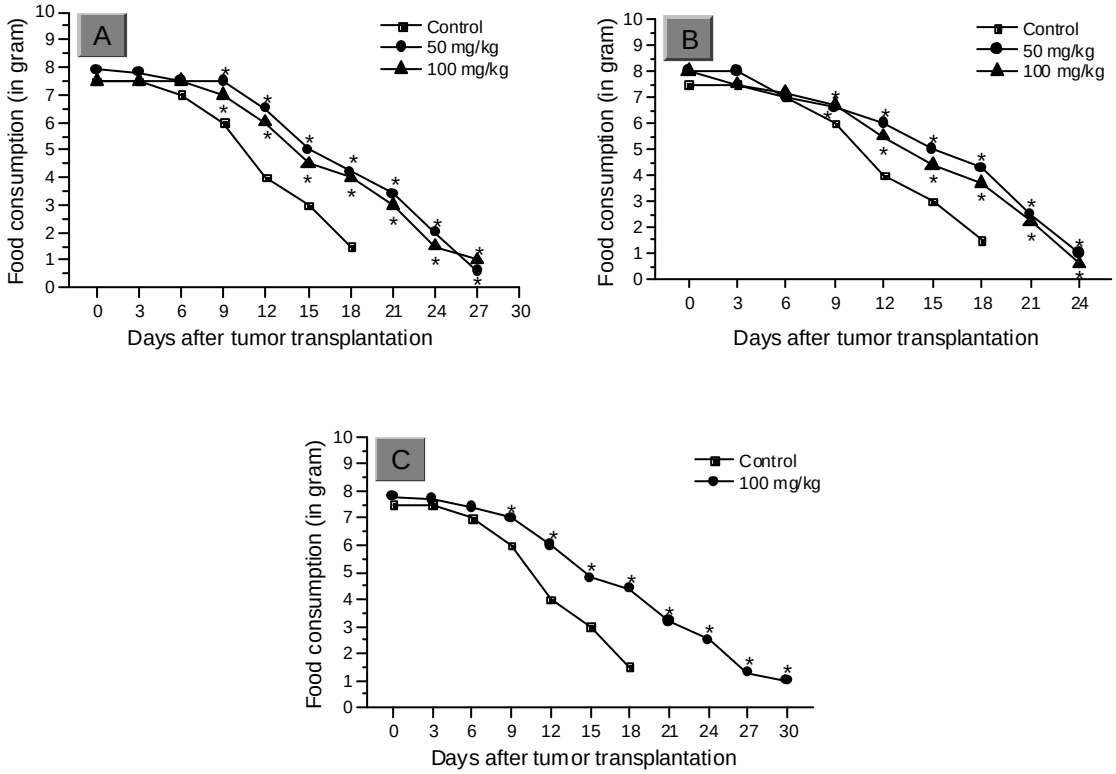


Figure 2. Graph showing the pattern of changes in the food consumption of tumor-bearing control and after treatment with the extract of *D. pentagyna* (A), *P. fulgens* (B) and *D. indica* (C). Results were expressed as mean ± S.D. Student's *t*-test, N = 6. $p \leq 0.05$.

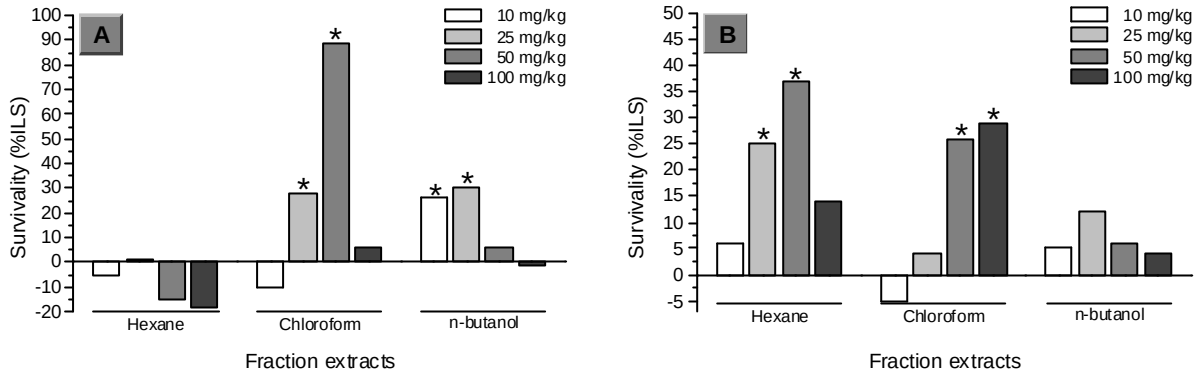


Figure 3. Histogram showing antitumor activity of fraction extracts of *D. pentagyna* (A) and *P. Fulgens* (B) against murine ascites Dalton's lymphoma. * % ILS ≥ 20% were considered to possess antitumor potential.

 

ents such as alkaloids, tannins, saponins, flavonoids, proanthrocyanidins and iridoids.[15-18]

*Statistical analysis*

The results are presented as means ± S.D. Significant differences between control and treatment groups were calculated using Student's *t*-test, number of replicates (N) = 6. *p*-values of ≤ 0.05 were considered significant.

## RESULTS

In vivo *antitumor activity*

Ethnobotanical information of the selected anticancer medicinal plants were presented in Table 1. The various test parts of the plants, doses of extracts and their effects on the survivability of the hosts in different experimental groups have been described in Table 2 and 3. Out of eighteen extracts from nine different plants used in the present study, five plant extracts from five plant species such as aqueous extract of *Dillenia indica* Linn. (Dilleniaceae), *Ageratum conizoides* Linn. (Asteraceae), *P. fulgens* and ethanol extract of *D. pentagyna* showed antitumor activity against ascites Dalton's lymphoma. The comparison of the antitumor effects of these plants depicted in the form of survivability of mice showed that antitumor activity was highest with the ethanol extract of *D. pentagyna* (ILS ~ 55%) at a dose of 50mg/kg/day.

*Changes in body weight and food consumption*

The pattern of changes in body weight and food consumption of the mice after treatment with the most potent plant extracts such as ethanol extract of *D. pentagyna* (A), aqueous extract of *P. fulgens* (B) and *D. indica* (C) were as shown in the Figure 1 and 2. As compared to the tumor-bearing control, a significant decrease in body weight and increase in food consumption were noted after 9$^{th}$ day of plant extract treatment.

*Phytochemical screening*

Some of the most potent plants such as *D. Pentagyna* and *P. fulgens* were processed for phytochemical screening and the results were presented in Table 4. This reveals moderate concentration of iridoids and high concentration of tannins in *D. Pentagyna* and moderate concentration of alkaloids, tannins, saponins and iridoids in *P. Fulgens*.

In vivo *antitumor activity of fractions of* D. pentagyna *and* P. fulgens

Results of antitumor activity study of different fraction extracts showed that chloroform and *n*-butanol fraction extracts of *D. pentagyna* and hexane and chloroform fraction extracts of *P. fulgens* exhibited antitumor activity (Figure 3A, 3B). Among different fraction extracts of the plants studied chloroform fraction extract of *D. pentagyna* showed highest antitumor activity (% ILS ~ 89%) at a dose of 50 mg/kg/day (Figure 3A) followed by hexane fraction extract (% ILS ~ 37%) at a dose of 50 mg/kg/day (Figure 3B).

## DISCUSSION

In the antitumor studies, ascites Dalton's lymphoma has been commonly used as an important murine experimental tumor model.[19,20] Out of nine plants used in the present study, four test plants (four extracts) showed comparatively better antitumor activity against ascites Dalton's lymphoma. The comparison of the antitumor effects of these plants depicted in the form of survivability showed that antitumor activity was highest with ethanol extract of *D. pentagyna* (ILS ~ 55%) at a dose of 50 mg/kg/day, while its ethanol extract did not show antitumor activity. It appears that the active component of this plant was extracted with ethanol while it

might have been destroyed by heat during hot water extraction. The active principle(s) of both *D. pentagyna* and *P. fulgens* were extracted with chloroform while hexane also extracted the active principle(s) of *P. fulgens*.

Alkaloids, such as ellipticine, camptothecin and several of its semisynthetic analogues, e.g., 9-Nitro-CPT, 10-hydroxy-9-dimethylaminomethyl-CPT, 7-Ethyl-10-hydroxy-camptothecin (SN-38), are applied as clinical anticancer drugs in the USA, Europe and Japan.[21,22] They are effective against ovarian, brain, breast, lung cancer etc.[21,23-26] Other alkaloids with anticancer activity include indicine, indicine N-oxide, thalicarpine and tetrandrine.[27] Flavonoids are also reported to have inhibitory action on the growth and proliferation of different types of tumors.[28] In the result of present study also, the presence of alkaloids and flavonoids may play an important role in the antitumor activity of *P. fulgens* and *D. pentagyna* extracts.

In conclusion, among nine different plants studied, ethanol extract of *D. pentagyna* showed the most potent antitumor activity against murine ascites Dalton's lymphoma. The antitumor activity study of different fraction extracts of *P. fulgens* and *D. pentagyna* also showed that most of the active fractions were extracted with chloroform and *n*-butanol. Antitumor activity of *P. fulgens* and *D. pentagyna* may be due to the presence of alkaloids and flavonoids. However, further biochemical studies, isolation and structural elucidation of biologically active principle(s) needs to be conducted.

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