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Antitumor activity of *Pachycereus marginatus* (DC.) Britton & Rose extracts against murine lymphoma L5178Y-R and skin melanoma B16F10 cells

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***Pachycereus marginatus* (DC.) Britton & Rose is a species belonging to the family Cactaceae. In traditional medicine, it is recommended to treat diabetes and gastrointestinal infections; however, there are no studies related to its use in cancer treatment. The *in vitro* antitumor effect of *P. marginatus* hexane, chloroform, methanol, and methanol-aqueous partition stem extracts, against murine lymphoma L5178Y-R and skin melanoma B16F10 cells, was evaluated in liquid medium by the colorimetric 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) reduction assay. The extracts resulted in up to 84, 85, 84, and 82% cytotoxicity ($p < 0.05$) to L5178Y-R cells, respectively, and up to 39, 51, 48, and 42% cytotoxicity ($p < 0.05$) to B16F10 cells, respectively. Vehicle controls were not cytotoxic for tumor cells, and along with the extracts they did not affect viability of resident murine thymus and spleen lymphocytes. Taken together, the present results showed that *P. marginatus* extracts possess antitumor potential against L5178Y-R lymphoma and B16F10 skin melanoma cells.**

Key words: Cancer, cacti, *Pachycereus marginatus*, lymphoma, melanoma, medicinal plants.

INTRODUCTION

In the search for alternatives to treat diseases, researchers worldwide have taken the task of finding native plants with potential health benefit. Among them, numerous cacti species have been reported to possess

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antitumor properties (Shetty et al., 2012; Harlev et al., 2013; Lema-Rumińska and Kulus, 2014). *Pachycereus marginatus* (DC.) Britton & Rose (Caryophyllales: Cactaceae), also known as *Stenocereus marginatus,Cereus marginata*, Central Mexico organ pipe, organo, Jarritos, Chilayo, and Mexican fencepost cactus, belongs to the Pachycereeae tribe. It has columnar trunks that can reach 20 m high and is commonly used as fodder, living fences, fuel wood, and as an alternative medicine. The species is endemic to Mexico, where it grows wild in states that have a dry and hot climate such as Nuevo León, Guanajuato, Aguascalientes, Oaxaca, Puebla, San Luis Potosí, Zacatecas, Ciudad de México, Tamaulipas, Guerrero, Michoacán, Hidalgo, Jalisco, Morelos, Veracruz, Tlaxcala, and Querétaro (Hernández et al., 2004), and in Texas, New Mexico, Arizona, and Southern California (Paredes-Flores et al., 2007; Arias and Terrazas, 2009). *P. marginatus* is traditionally used to treat gastrointestinal infections (Hernández et al., 2003); its antimicrobial potential in plants, animals, and humans has been reported, as well as its activity to improve wound healing, and promote plant growth (Jordan-Hernandez, 2012). However, the antitumor potential of *P. marginatus* has not yet been reported.

Cancer results from the interaction of internal (as genetic predisposition) and external factors that lead to cell degeneration, resulting in precancerous lesions and ultimately malignant tumors. If it is not promptly treated, cancer cells can spread to other organs (metastasis).

Cancer is one of the main causes of morbidity and mortality worldwide, with about 14 million new cases and 8.2 million deaths in 2012 and new cases are expected to increase 22 million in the next 20 years (Stewart and Wild, 2014). In men, most cancers affect prostate, lungs, and gastrointestinal tissues; in women, cancers in the breast, lung, cervix, and stomach are common (Stewart and Wild, 2014). In Mexico, according to the International Union Against Cancer, cancer is the third leading cause of death and estimated that each year 128,000 new cases are reported (Stewart and Wild, 2014).

The aim of the present study was to evaluate the *in vitro* cytotoxic activity of the hexane, chloroform, methanol, and aqueous methanol partition extracts of *P. marginatus* against murine lymphoma L5178Y-R and skin melanoma B16F10 cells.

MATERIALS AND METHODS

Reagents and culture media

Penicillin-streptomycin solution, L-glutamine, and RPMI 1640 and AIM-V media were obtained from Life Technologies (Grand Island, NY). Fetal bovine serum (FBS), concanavalin A (Con A), sodium dodecyl sulfate (SDS), N, N-dimethylformamide (DMF), and 3-[4,5-dimethylthiazol-2-yl]-2,5- diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich (St. Louis, MO). Vincristine sulfate was obtained from Laboratorios PiSA (Mexico City, Mexico). The tumor cell lines L5178Y-R (mouse DBA/2 lymphoma R, clone CRL-1722) and B16F10 (mouse skin melanoma) were purchased from The American Type Culture Collection (Rockville, MD), and were maintained in culture flasks with RPMI 1640 medium, supplemented with 10% FBS, 1% L-glutamine, and 0.5% penicillin streptomycin solution (referred as complete RPMI 1640 medium) at 37°C, in a humidified atmosphere of 5% CO_2 in air; cellular density was kept between 10^5 and 10^6 cells·ml^{-1}. Extraction buffer was prepared by dissolving 20% (w:v) SDS at 37°C in a solution of 50% each DMF and demineralized water, and the pH was adjusted to 4.7.

Preparation of plant extracts

Pachycereus marginatus used in the present study was identified with voucher number 025588. Stems were rinsed with tap water to eliminate dust and other contaminating material, dried at 37°C for 36 h, and pulverized. Sixty grams of the powdered stems were sequentially extracted with 600 ml of hexane, chloroform, and methanol by Soxhlet system during 40 h each. The extracts were concentrated to dryness using a rotary evaporator Büchi (Brinkmann Instruments Inc., Switzerland) and stored at 6°C until use and dissolved in distilled water for biological activity testing. The methanol-aqueous partition of the extract was prepared by using 11 g of methanol extract and dissolving it in methanol, then in hexane, and shaking for 10 min. The resulting solution was separated with a funnel and washed with ethyl acetate. This solution was washed with water and then dried (referred as aqueous partition). Stock solutions were then prepared at 1 mg ml^{-1} in complete RPMI 1640 (for L5178Y-R cells), AIM-V medium (for lymphocyte cultures) or DMEM medium (for B16F10 cells), and sterilized by filtering through a 0.22-microns membrane (Millipore, Bedford, MA). *P. marginatus* hexane, chloroform, methanol, and methanol-aqueous partition stem extracts were tested at concentrations ranging from 0.03 to 500 µg ml^{-1}.

L5178Y-R and B16F10 cells preparation and culture

In order to determine the direct *in vitro* effect of the extracts on tumor cell growth, L5178Y-R cell and B16F10 cultures were collected and the cellular suspensions obtained were washed three times in RPMI 1640 (for L5178Y-R cells) or DMEM medium (for B16F10 cells), and suspended and adjusted to 5×10^4 cells ml^{-1} in those culture media. One hundred microliters of the cell suspensions were then added to flat-bottomed 96-well plates (Becton Dickinson, Cockeysville, MD), containing 100 µl triplicate cultures of complete RPMI 1640 or DMEM media (unstimulated controls), the extracts at various concentrations (extracts were dissolved in complete RPMI 1640 (for L5178Y-R cells) or DMEM medium (for B16F10 cells), extract-free vehicles (vehicles were similarly processed as with *P. marginatus* extracts, but without plant material), and vincristine as a positive control. After incubation for 44 h at 37°C with 5% CO_2, MTT (0.5 mg ml^{-1}, final concentration) was added, and cultures were additionally incubated for 4 h. Next, cell cultures were incubated for 16 h with extraction buffer (100 µl well^{-1}) and optical densities, resulting from dissolved formazan crystals, were then read in a microplate reader (DTX 880 Multimode detector, Becton Dickinson, Austria) at 570 nm (Gomez-Flores et al., 2009). The percentage of cytotoxicity was calculated as follows:

% Cytotoxicity = 100-[(A570 in extract treated cells/ A570 in untreated cells) × (100)]

Table 1. Effect of *P. marginatus* extracts on L5178Y-R cells toxicity [%].

Concentration [µg·ml^{-1}]	Hexane	Chloroform	Methanol	Methanol-aqueous partition
0.03	1	0	14.2±1.9	0
0.06	0	0	16.4±1.4	0
0.121	0	0	8.0±0.6	0
0.243	0	0	15.3±2.0	0
0.487	0	0	17.3±2.4	3.0±0.3
0.975	7.8±0.6	0	22.2±4.7	18.1±1.7
1.95	20.0±1.8*	31.7±1.5*	31.9±6.3*	22.1±3.4*
3.9	19.5±2.9*	81.3±6.5**	36.9±6.8*	65.3±9.4**
7.81	21.7±2.0**	83.8±5.6**	69.4±19**	80.2±2.6**
15.62	29.8±4.5**	84.4±4.7**	83.7±9.9**	82.1±5.2**
31.25	74.5±3.8**	84.9±4.4**	83.6±7.8**	82.0±4.9**
62.5	84.2±6.6**	84.9±4.3**	82.9±7.5**	80.0±5.7**
125	84.2±8.6**	84.4±3.3**	82.1±9.6**	77.7±6.3**
250	84.8±9.9**	84.6±2.9**	79.0±11**	71.5±4.8**
500	84.5±9.9**	84.1±4.3**	72.4±11**	59.4±4.4**

[1]% Cytotoxicity, as compared with untreated control (culture medium). Optical density for untreated control was 0.83 ± 0.006. Data represent mean ± SE of three replicate determinations from three independent experiments. Vehicle controls for hexane, methanol, chloroform, and methanol-aqueous partition were not cytotoxic for L5178Y-R cells; vincristine caused about 75% cytotoxicity to L5178Y-R cells at concentrations ranging from 0.24 to 125 µg·ml^{-1}. *p < 0.05, **p < 0.01 , compared with untreated control.

Animals

Six-week-old female BALB/c mice (22 to 28 g) were purchased from Harlan Sprague-Dawley Inc. (Indianapolis, IN, USA). They were kept in a pathogen- and stress-free environment at 24°C, under a light-dark cycle (light phase, 06:00 to 18:00 h), and given water and food ad libitum.

Cell preparation and culture

Thymus and spleen were removed immediately after mouse death, and a single cell-suspension was prepared by disrupting the organs in RPMI 1640 medium as previously reported (Gomez-Flores et al., 2009). The cell suspensions were washed three times in this medium, suspended, and adjusted to 1 × 10^7 cells ml^{-1} in complete RPMI 1640 medium.

T cell proliferation assay

T cell proliferation was determined by a colorimetric technique using MTT (Gomez-Flores et al., 2009). Thymus and spleen cell suspensions (100 µl of 1 × 10^7 cells ml^{-1}) were added to flat-bottomed 96-well plates (Becton Dickinson) containing triplicate cultures (100 µl) of RPMI 1640 medium supplemented with 5% fetal bovine serum (unstimulated control), Con A (2.5 µg ml^{-1}), and plant extracts at various concentrations for 48 h at 37°C in 95% air-5% CO_2 atmosphere. After incubation for 44 h, MTT (0.5 mg/ml, final concentration) was added, and cultures were additionally incubated for 4 h. Cell cultures were then incubated for 16 h with extraction buffer (100 µl), and optical densities, resulting from dissolved formazan crystals, were then read in a microplate reader (Becton Dickinson) at 570 nm. The lymphocyte proliferation index (LPI) was calculated as follows:

LPI = A_{570} in extract-treated cells/ A_{570} in untreated cells

Statistical analysis

The results were expressed as mean ± SE of three replicate determinations from three independent experiments. Statistical significance was assessed by the analysis of variance (ANOVA), p < 0.05, and pos-hoc Tukey, using statistical package for social sciences (SPSS) 21.

RESULTS

In vitro cytotoxic activity of *P. marginatus* extracts

The hexane, chloroform, and methanol extracts, respectively caused significant (p < 0.05) 20 to 85%, 32 to 84%, and 32 to 72% cytotoxicity to L5178Y-R cells at concentrations ranging from 1.9 to 500 µg ml^{-1}, respectively, and the methanol-aqueous partition caused significant (p < 0.01) 65 to 78% cytotoxicity at concentrations ranging from 3.9 to 125 µg ml^{-}1, respectively, and 72 and 59% cytotoxicity at 250 and 500 µg ml^{-1}, respectively, as compared with untreated control (Table 1). There was no statistical significance between extract treatment groups, as determined by ANOVA, p <

Table 2. Effect of *P. marginatus* extracts on B16F10 cells toxicity [%].

Concentration [µg ml^{-1}]	Hexane/vehicle	Chloroform/vehicle	Methanol/vehicle	Methanol-aqueous partition/vehicle
1.5	1	11.3±0.8	8.5±0.6	0
3.1	0	7.3±0.7	12.0±0.7	0
6.2	0	3.9±0.4	7.0±0.5	0
12.5	0	1.3±0.1	0	0
25	0	42.7±3.1**	0	39.6±3.9**
50	0	51.7±5.7**	44.4±5.2**	44.1±5.6**
100	39 ± 1.5**	50.7±4.9**	48.0±5.8**	41.9±5.9**

[1]% Cytotoxicity, as compared with untreated control (culture medium). Optical density for untreated control was 0.29 ± 0.01. Data represent mean ± SE of three replicate determinations from three independent experiments. Vehicle controls for hexane, methanol, chloroform, and methanol-aqueous partition were not cytotoxic for B16F10 cells; vincristine caused about 75% cytotoxicity to B16F10 cells at concentrations ranging from 0.24 to 125 µg·ml^{-1}. *p < 0.05, **p < 0.01 , compared with untreated control.

Table 3. Effect of *P. marginatus* extracts on resident thymus/spleen cells proliferation [LPI].

Concentration [µg·ml^{-1}]	Hexane	Chloroform	Methanol	Methanol-aqueous partition
3.9	0.93/ND	0.85/ND	0.97/ND	0.9/ND
7.81	0.92[1]/1.08	0.8/1	0.94/0.95	0.8/0.98
15.62	0.90/1.07	0.8/1	0.91/0.96	0.7/1
31.25	0.96/1	0.8/1	0.9/0.96	0.9/1
62.5	0.94/1	0.81/0.95	0.9/0.95	0.7/1
125	0.89/0.5	0.81/0.84	0.92/0.98	0.6*/0.82

[1]LPI, as compared with untreated control (culture medium). Optical density for untreated control was 0.34 ± 0.002. Data represent mean ± SE of three replicate determinations from three independent experiments. Vehicle controls for hexane, methanol, chloroform, and methanol-aqueous partition were not cytotoxic for thymus and spleen cells (data not shown). *p < 0.05, compared with untreated control. ND, Not done.

0.05, and pos-hoc Tukey. With regards to B16F10 cells, the hexane, chloroform, methanol, and methanol-aqueous partition extracts, respectively caused significant (p < 0.01) 39% cytotoxicity at 100 µg ml^{-1}, 43 to 51% cytotoxicity at concentrations of 25 to 100 µg ml^{-1}, respectively, 44 to 48% cytotoxicity at concentrations of 25 to 100 µg ml^{-1} respectively, and 40 to 42% cytotoxicity at concentrations of 25 to 100 µg ml^{-1}, respectively (Table 2), as compared with untreated control. The hexane extract treatment caused the lowest cytotoxicity, whereas the other extract treatments were not significantly different from each other (ANOVA, p < 0.05, and pos-hoc Tukey). Vehicle controls for the extracts were not cytotoxic for L5178Y-R or B16F10 cells (data not shown). In addition, extracts were not cytotoxic for murine resident thymus and spleen cells (Table 3), except for the methanol-aqueous partition that caused significant (p < 0.05) 40% cytotoxicity to thymic cells at the concentration of 125 µg ml^{-1} (Table 3).

DISCUSSION

The pharmaceutical study and application of useful compounds from medicinal plants is very promising, particularly as an alternative to conventional cancer therapy (Tsuda et al., 2004). There are many reports on compounds with anticancer properties (Plaeger, 2003), including taxol, vincristine, vinblastine, tepocan, irinotecan, and etoposide-teniposide, which are commonly used in cancer therapy (Lu et al., 2003). The Cactaceae family is reported to contain about 1,500 species, which are distributed worldwide (Harlev et al., 2013). Medicinal uses of cacti include antitumor (Loro et al., 1999; Sreekanth et al., 2007; Franco-Molina et al., 2003; Harlev et al., 2013;), anti-inflammatory (Park et al., 1998; Loro et al., 1999), neuroprotective (Kim et al., 2006; Shetty et al., 2012), hepatoprotective (Ncibi et al., 2008), and anti-diabetes (Hassan et al., 2011) activities.

An important goal in medicinal plant research is to

avoid extensive and repetitive studies on known plants with limited anticancer potential, and focus on promising plants that have not been investigated; the present study was performed following these basic principles. We evaluated antitumor activity of *P. marginatus* crude extracts against murine lymphoma L5178Y-R and skin melanoma B16F10 cells, and demonstrated cytotoxicity with hexane, chloroform, methanol, and methanol-aqueous partition extracts. Cacti with antitumor potential include *Lophophora williamsii* (Lem. ex Salm-Dyck) Coult., also known as peyote, which was found to be cytotoxic to murine L5178Y-R and fibroblastoma L929, and human myeloid U937 and mammary gland MCF7 tumor cells (Franco-Molina et al., 2003); *Lophocereus schottii* (Engelm.) Britton & Rose has antitumor activity against murine lymphoma (Orozco-Barocio et al., 2013), and *Opuntia spp.* has been reported to have anti-tumor activity (Supino et al., 1996; Veronesi et al., 1999; De Palo et al., 2002; Zou et al., 2005).

The increasing resistance of mammalian tumor cells to chemotherapy, which causes adverse side effects, reduces its clinical efficacy. Thus, it is critical to discover and to develop novel anticancer agents from natural sources, such as plants, to overcome such resistance and side-effects. Cacti-based chemotherapy is a potential alternative to current cancer treatment. After applying *in vitro* bioreactor systems, valuable cacti metabolites could be produced for a large scale at limited costs and time (Lema-Rumińska and Kulus, 2014).

Conflict of Interests

The authors have not declared any conflict of interestS.

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