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Original Article

Phytochemical profile and biological activities of *Bromelia antiacantha* extracts

Perfil fitoquímico e atividades biológicas de extratos de *Bromelia antiacantha*

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Abstract

Reports from popular medicine usually act as a basis for the development of new drugs from natural compounds with therapeutic actions for serious diseases and prevalence such as cancer. *Bromelia antiacantha* Bertol. is a species of the Bromeliaceae family, considered an unconventional food plant, found in the south and midwest regions of Brazil. Despite the high nutritional content and pharmacological potential of its fruits, few scientific studies report its biological actions. Thus, this study evaluates the phytochemical profile of aqueous and ethanol extracts obtained from *B. antiacantha* fruits, as well as their possible antioxidant, antitumor, and cytotoxic activities. The aqueous extract exhibited phenolic compounds and flavonoids, while ethanol extracts indicated the presence of flavonoids and coumarin in their composition, regardless of the region of collection. The ethanolic extract demonstrated a more promising antioxidant effect than the aqueous extract and also induced a significant inhibition in the viability of human cervical cancer cells of the SiHa strain. In addition, treatment with both extracts did not alter the viability of non-tumor cells of the immortalized human keratinocyte lineage (HaCaT). These results bring new data about extracts obtained from a native plant, edible and traditionally used in popular medicine, opening new perspectives for its possible therapeutic application.

Keywords: *Bromelia Antiacantha*, cervical câncer cells, phytochemical profile, SiHa lineage, HaCaT cells.

Resumo

Relatos da medicina popular costumam atuar como referencial para o desenvolvimento de novos fármacos a partir de moléculas naturais com ações terapêuticas para doenças de alta gravidade e prevalência como o câncer. *Bromelia antiacantha* Bertol. é uma espécie da família Bromeliaceae, considerada uma planta alimentícia não convencional (PANC), encontrada nas regiões sul e centro-oeste do Brasil. Apesar do alto teor nutritivo e potencial farmacológico de seus frutos, poucos estudos científicos relatam suas ações biológicas. Desta forma, este estudo avalia o perfil fitoquímico de extratos aquoso e etanólico obtidos de frutos de *B. antiacantha*, bem como a sua possível ação antioxidante, antitumoral e citotóxica. O extrato aquoso apresentou compostos fenólicos e flavonoides, enquanto os extratos etanólicos apontam a presença de flavonóides e cumarina em sua composição, independente da região de coleta. O extrato etanólico demonstrou efeito antioxidante mais promissor do que o extrato aquoso e também induziu uma inibição significativa na viabilidade de células humanas de câncer cervical da linhagem SiHa. Além disso, o tratamento com ambos extratos não alterou a viabilidade de células não tumorais da linhagem de queratinócitos humanos imortalizados (HaCaT). Estes dados trazem novas informações sobre extratos obtidos de uma espécie vegetal nativa, comestível e já utilizada tradicionalmente, mas abrindo novas perspectivas quanto a possíveis aplicações terapêuticas.

Palavras-chave: *Bromelia Antiacantha*, células do câncer cervical, perfil fitoquímico, Linhagem SiHa, Células HaCaT.

1. Introduction

Natural products, especially those of plant origin, represent the main sources of active substances with potential therapeutic use and the oldest source of medicines ever used by humans (Moga et al., 2016; Cordeiro et al., 2021). Knowledge of the nutritional and medicinal properties of a country's biodiversity species, especially plants, has been the basis for the development of society and human survival, as they bring benefits to science and to the national bioeconomy (Rodrigues and De Simoni, 2010).

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According to Ferro et al (2006), the vast Brazilian biodiversity opens up a wide range of economic benefits from products of plant species, arousing the interest of the academic and industrial sectors. Vegetable species constitute the raw material for the pharmaceutical, food, chemical sectors, as well as for agriculture and horticulture (Ferro et al., 2006). Most plant species also have proven nutritional value and some of them fall into a category that includes unconventional food plants (Kinupp and Lorenzi, 2014). Reports of popular medicine usually act as a reference for the investigation of species with therapeutic potential (Balunas and Kinghorn, 2005). Such bioactive potential is already reported for pathologies such as cancer, for which a series of important drugs, currently marketed, were obtained from natural sources (Newman et al., 2003).

Among the most prevalent and highly serious types of tumors that affect the female population is cervical cancer, occupying a prominent place in the morbidity and mortality rates among the female population worldwide, being the fourth most common type of cancer in women, and the seventh in the general classification (INCA, 2019). In Brazil, this pathology maintains high rates, with an increase of 29% comparing the last two decades, being the fourth leading cause of cancer death in women (INCA, 2019). Despite being preventable, collective efforts to implement screening programs have not yet effectively reduced mortality from cervical cancer, especially in the Americas region (Fonseca et al., 2012).

The non-selective action of the most commonly used conventional treatments leads to side effects in normal cells with a high rate of proliferation, such as intestinal epithelium cells, hair follicles and leukocytes (Nussbaumer et al., 2011). In addition, these therapeutic approaches do not rule out the possibility of tumor recurrence and most patients with recurrence do not respond significantly to chemotherapy (Waggoner, 2003).

All of these data justify the relevance of the search for new therapies, with less adverse effects and that may be economically viable for a large part of the population. With more than 56 thousand species of plants, Brazilian biodiversity reveals a wide range of phytochemical compounds that can be used in agronomic, food, pharmacological and medicinal applications (Coradin et al., 2011). However, many plant species are used in Brazil for different therapeutic purposes without any scientific evidence. In this sense, different studies have stood out for generating relevant information about the efficacy and safety of plants of traditional use, enabling the development of new drugs with new therapeutic actions based on natural molecules.

Bromelia antiacantha Bertol., also known as caraguatá, carauatá, gravatá, bananinha-do-mato, among others, is a species of unconventional food plant of the family Bromeliaceae, found in the south and midwest regions of Brazil (Lorenzi and Matos, 2008; Kinupp and Lorenzi, 2014; Krumreich et al., 2015). *B. antiacantha* occurs in areas of fields, savannahs, and forest edges, normally used for the construction of live fences due to the thorns in the leaves and the possibility of reaching two meters in height (Lorenzi and Matos, 2008).

The fruits of *B. antiacantha* have a yellow to orange color when they are ripe (Vallés et al., 2007) and have an oval shape, small seeds, and edible pulp (Lorenzi and Matos, 2008). They are used in the preparation of jellies, juices, and liquors, and in folk medicine as anthelmintic, diuretic, vermifuge, expectorant and in the treatment of kidney stones (Kinupp, 2007; Lorenzi and Matos, 2008; Manetti et al., 2010). In addition, the fruits are rich in bromelain, a proteinase used by the food industry to tenderize meat, stabilize beer, and provide crispness in roasted foods (Kinupp, 2007). It also has high levels of vitamin C (Krumreich et al., 2015) and relevant levels of manganese, calcium, potassium and magnesium (Kinupp and Barros, 2008). However, despite the high nutritional content and pharmacological potential of the fruits, few studies scientifically report their biological actions.

Thus, this study aims to evaluate the phytochemical profile of extracts obtained from *B. antiacantha* fruits, as well as their possible antioxidant, antitumor, and cytotoxic action.

2. Materials and Methods

2.1. Plant material and preparation of extracts

Fruits of *Bromelia antiacantha* were collected from four cities of Rio Grande do Sul: São Francisco de Assis (29°28'06.33"S 55°07'18.87"W), Guaporé (28°51'54.36"S 51°53'57.36"W), Paverama (29°33'24.91"S 51°44'30.65"W) and Taquari (29°45'35.57"S 51°52'23.06"W). However, in the present study, we considered the fruits from the cities of Paverama and Taquari as a sample from the Taquari Valley, which is composed of a pool between the fruits collected in both regions.

To obtain the water and ethanolic extracts, the fruits were brought to the Botanic Laboratory of the Universidade do Vale do Taquari, Univates, washed in running water to remove the impurities and cut in half to remove the seeds. After the fruits' cleaning, they were stored in ultrafreezer (-80 °C) until the moment of preparation of the extracts. The water extract was obtained through the infusion method, from the immersion of the ground fruits in distilled water and heated to 90°C (initial temperature) for an hour, in the proportion of 1:10 (w:v). Next, the extracts were stored in amber flasks and kept in ambient temperature until cooled down, corresponding to an hour, followed by filtration with a vacuum pump, kitasato, and Büchner funnel, later being stored in ultrafreezer until lyophilization. The obtaining of the ethanolic extract was done through static maceration, with the immersion of the ground fruits for seven days in absolute ethanolic alcohol in the proportion of 1:10 (w:v). After seven days, vacuum filtration and rotation evaporation were performed for alcohol removal, followed by rotation for obtaining the powdered extract. The extracts were stored in ultrafreezer (-80 °C) until the beginning of the tests. The extracts' lyophilization was performed in the Food Chemical Laboratory (CTTPA) of the Technological and Scientific Park of Univates.

2.2. Phytochemical profile

The qualitative tests' methodologies for the presence of phenolic compounds, tannins, flavonoids, cumarines, saponins, quinones, and glycosidic quinones were adapted from Simões et al. (2004).

Saponins: a few milligrams of the extracts were dissolved in test tubes containing 15 mL of distilled water and vigorously agitated. The formation and maintenance of the foam layer equal or superior to 10 mm, for more than one minute, even after the addition of drops of chloridric acid solution (HCl) at 10% represents a positive result;

Phenolic compounds and tannins: a few milligrams of the extracts were dissolved in 10 mL of the appropriate solvent (deionized water or ethanol), filtrated, and added ten drops of ferric chloride alcoholic solution ($FeCl_3$) at 1%. Any change in coloration or precipitate formation is indicative of a positive reaction, in comparison to the blank test (solvent and solution of $FeCl_3$). Initial coloration between blue and red is indicative of phenol presence when the blank test is negative. Dark precipitate with a blue tone indicates the presence of pyrogallic tannins (water-soluble tannins) and green is the presence of catechin tannins;

Flavonoids: a few milligrams of the extracts were dissolved in 10 mL in methanol and filtered. Drops of concentrated HCl and magnesium scraps were added. The formation of pink, red, or orange coloration indicates a positive result;

Coumarins: a few milligrams of the extracts were put in test tubes, capped with 0,22 µm filter paper previously impregnated and dried with a potassium hydroxide methanolic solution at 5%. The test tubes were boiled in a water bath for 10 minutes, and the filter papers were exposed to UV light at 365 nm. The presence of fluorescent blue or yellow points under UV light indicates a positive result;

Alkaloids: a few milligrams of the extracts were dissolved in HCl solution at 5% and filtered. There were four test tubes in which were added the reagents Mayer, Bertrand, Draggendorf, and Bouchardat. The formation of precipitation indicates a positive result;

Quinones: a few milligrams of the extracts were dissolved in 10 mL of ethyl ether and filtered. There was added 4 mL of ammonium hydroxide water solution (NH_4OH) 6M, it was agitated, and observed the appearance of pink or red coloration in the water phase.

2.3. Evaluation of the antioxidant activity

The evaluation of the antioxidant activity was performed based on the potential of the extract to reduce the radical 2,2-Diphenyl-1-picrylhydrazyl (DPPH), according to described by Yao et al. (2012), with some modifications. There were used 96-well flat-bottom microplates (Costar, Corning Incorporated). The extracts, the positive control, and the butylhydroxytoluene (BHT) were used in different concentrations (78-2500 µg/mL), diluted in methanol in serial form in the proportion of 1:1. After 30 minutes with DPPH (0.1 mM) in contact with various extracts' concentrations, the reading of the observance in a was performed in a plate reader (SpectraMax i3x Multimode Microplate Reader, Molecular Devices, USA) (λ =517 nm).

After, the percentage of inhibition of the radical DPPH was calculated according to the equation: % CA. = Abs. D – (abs. A– abs. B) / abs. D, where: % CA= percentage of antioxidant activity; Abs. D= control absorbance of DPPH, Abs A= absorbance of the sample, Abs B= absorbance of the blank.

After, the concentration that inhibited 50% of the radical DPPH (IC50) was measured using linear regression impregnating the values of the concentration and the percentage of inhibition. The results were expressed using the mean ± standard deviation of the three experiments independently and statistically analysed by the one-way analysis of variance (ANOVA) followed by the Tukey test, considering $p < 0.05$.

2.4. Cell culture

The cell line of squamous neoplastic origin of the human uterine cervix (SiHa) and the non-tumor cell line of immortalized human keratinocytes (HaCaT) were obtained from the "American Type Culture Collection" (ATCC, USA). Both strains were maintained in Eagle-modified Dulbecco culture medium (DMEM), supplemented with 10% of fetal bovine serum (SFB), and added with 1% penicillin / gentamicin and amphotericin B antimicrobials (Gibco BRL, Grand Island, NY). The cells were kept in 25 cm^2 sterile culture flasks in a controlled atmosphere with 5% of CO_2 and 37 ºC. Through 80% confluence, cell ringing was performed using Trypsin / EDTA 0.25% solution.

2.5. Cell viability assay

Cell viability was verified using MTT assay - [3-(4,5-dimethylthiazole-2-yl) -2-5- diphenylthetrazolium bromide]. Aqueous and ethanolic extracts from the lyophilized *B. antiacantha* fruits, collected from the Taquari Valley, were solubilized in DMEM culture medium, filtered through a 0.22 µm membrane for sterilization and stored under refrigeration (4 ºC). SiHa and HaCaT cells were seeded at a density of 3.000 cells / well in 96-well culture plates and after adhesion, the cells were treated with crude aqueous and ethanolic extracts individually for 24 hours in concentrations of 200 to 3000 µg/mL. Controls were prepared using only DMEM medium and cells. This control was considered 100% cell viability. After treatment time, the supernatant was discarded and the cells were incubated with MTT (0.5 mg/mL) for 3.5 hours at 37 ºC. The formazan crystals formed were dissolved in DMSO and quantified at 545 and 630 nm using a SpectraMax plate reader. All values were expressed as averages and standard deviation (SD) from at least three independent experiments. Data were analyzed using one-way analysis of variance (ANOVA) followed by the Tukey test using GraphPad Prism 5. Statistical differences were considered significant when the value was $p < 0.05$.

3. Results

3.1. Phytochemical profile

The aqueous and ethanol extracts, prepared from fruits harvested in different locations of Rio Grande do Sul

were qualitatively analyzed and indicated the presence of several groups of compounds (Table 1). The aqueous extract obtained from the fruits of this plant species presented phenolic and flavonoid compounds, regardless of the collection location meanwhile ethanol extracts indicated the presence of flavonoids and coumarins in their composition, regardless of the region of collection.

3.2. Antioxidant activity

The antioxidant activity was evaluated in order to measure the ability of the extracts to sequester the free radical DPPH. The aqueous and ethanolic extracts showed an IC50 of 370.00 µg/mL ± 17.32 and 313.33 µg/mL ± 20.82, respectively, while the IC50 of the BHT positive control was 6.91 ± 0.16 µg / ml. For these samples, the ethanolic extract showed a superior antioxidant potential, but not significantly different from the aqueous extract.

3.3. Effects on cell viability

The different concentrations tested (200 to 3000 µg/mL) of both extracts did not show accentuated inhibition in the studied cell lines, SiHa and HaCaT. In addition, it was not possible to observe a dose-dependency effect in the tested concentration range, which made it impossible to calculate the IC50 for both cell lines. Particularly, the ethanolic extract of this plant species showed a greater reduction in the viability of SiHa tumor cells, by 20 to 30% of inhibition in concentrations greater than 1000 µg/mL (Figure 1). However, our results indicated that both extracts (aqueous and ethanolic) of *B. antiacantha*'s fruits do not have a cytotoxic effect on the studied non-tumoral cell line, HaCaT, in the range of concentrations tested in this study (Figure 2).

Table 1. Phytochemical profile of the aqueous and ethanolic extracts from *B. antiacantha* fruits collected from different cities of Rio Grande do Sul, Brazil.

Location	Solvent	Phenolic compounds	Tannins	Flavonoids	Coumarins	Saponins	Alkaloids	Quinones	Glycosidic quinones
Vale do Taquari	Aqueous	+	-	+	-	-	-	-	-
	Ethanolic	-	-	+	+	-	-	-	-
São Francisco de Assis	Aqueous	+	-	+	-	-	-	-	-
	Ethanolic	-	-	+	+	-	-	-	-
Guaporé	Aqueous	+	-	+	-	-	-	-	-
	Ethanolic	-	-	+	+	-	-	-	-

+ Presence of the compound in the extract. - Absence of the compound in the extract.

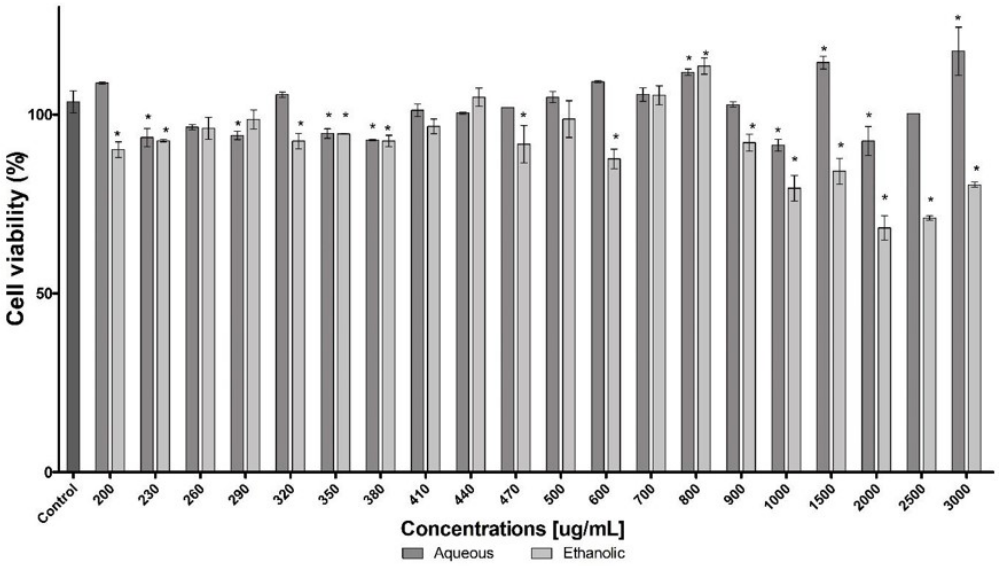

Figure 1. Effect of different concentrations of the aqueous and ethanolic extracts of *B. antiacantha*'s fruits on the viability of the tumor cell line SiHa after 24 h of treatment. The data show the mean and standard deviation of 3 independent experiments, performed in duplicate. * $p < 0.05$ (one-way ANOVA, followed by the Tukey test).

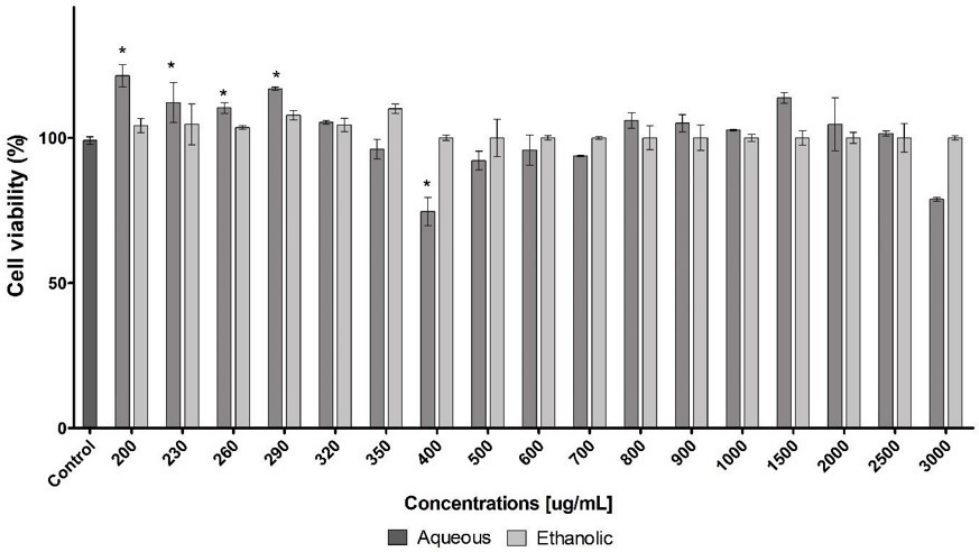

Figure 2. Effect of different concentrations of the aqueous and ethanolic extracts of *B. antiacantha*'s fruits on the viability of the non-tumoral cell line HaCaT after 24h of treatment. The data show the mean and standard deviation of 3 independent experiments, performed in duplicate. * p <0.05 (one-way ANOVA, followed by the Tukey test).

4. Discussion

Considering that *B. antiacantha* species is an edible plant, with high nutritional quality and is already used in popular medicine, studies that bring information regarding its biological potential and/or cytotoxic effects are of great relevance. In this study we bring phytochemical data related to the composition of aqueous and ethanolic extracts obtained from the fruits of *B.antiacantha*, as well as its antioxidant potential and its effect on the viability of tumor and non-tumor cells.

The data of phytochemical analysis point to the presence of phenolic and flavonoid compounds in the aqueous extract of the fruits of *B. antiacantha*, and flavonoids and coumarin in the composition of the ethanolic extract obtained from the fruits of this plant species.

It is known that among the research with natural products involving extracts and essential oils of plants, the presence of polyphenolic, phenolic and terpenic compounds stands out, as potential responsible for different biological effects (Bakkali et al., 2008; Victoria, 2013; Formagio et al.,2015). In addition, phytochemical tests performed from extracts of *B. antiacantha* obtained from other locations, have demonstrated the presence of flavonoids, tannins and saponins (Manetti et al., 2010). However, the used part of the plant, as well asthe way in which the solutions are obtained, are differential factors for the extraction of the molecules of interest. Ethanol solutions are widely used for their effectiveness in the ability to extract the target product and obtain different fractions rich in molecules such as phenols and flavonoids, described by their significant biological activity (Ismail et al., 2004). In our results, the significant effects observed for the ethanol solution and not for the aqueous solution, may be due to the distinct chemical composition resulting from the way these solutions were extracted.

Coumarins are heterocyclic compounds of natural origin, present in several parts of plants, such as roots, flowers and fruits, resulting from the secondary metabolism of some plant species and with medicinal activity already reported in the literature (Ribeiro and Kaplan, 2002). In addition to the medicinal activities presented, coumarins have antiviral, anti-inflammatory, antibacterial and antineoplastic properties, demonstrating to be an interesting target for the development of new drugs with biotechnological application (Bisi et al., 2017; Ibrar et al., 2018).

The presence of phenolic compounds and flavonoids in the extracts of *B. antiacantha*, may be related to the antioxidant action, due to the ability to donate hydrogen, electrons or to present stable intermediate radicals (Silva et al., 2010). It can also confer antitumor property, since such compounds are widely described in the literature for conferring inhibitory actions on different types of tumors (Pimentel et al., 2005).

Thus, the chemical composition of the extracts of *B. antiacantha* can be related to the antioxidant activity exhibited by them, despite the fact that, in general, this was not as marked as that presented by the positive control BHT (Table 2). However, our results demonstrated that the ethanolic extract exhibited an inhibition of oxidizing activity statistically equal to the BHT standard in the highest concentrations (1250 µg/mL and 2500 µg/mL), while the aqueous extract remained with inhibition of oxidative activity below the control in these same concentrations.

From the data obtained it was possible to calculate the IC50 for both studied extracts, revealing a lower value for the ethanolic extract and therefore, more promising than the aqueous extract. However, the purification or isolation of some constituents of these extracts and the performance of bioguided tests, could reveal potentially interesting antioxidant compounds.

Table 2. Percentage of inhibition of DPPH and IC50 of the ethanolic and aqueous extracts of *B. antiacantha* in different concentrations (µg/mL), and comparison with the positive control butylated hydroxytoluene (BHT). Results expressed as mean ± standard deviation.

Concentration (µg/mL)	% Inhibition by extracts		% BHT inhibition
	Aqueous	Ethanol	
2500	84.32 ± 0.13*A	94.51 ± 0.70*A	93.00 ± 0.31
1250	79.76 ± 2.08*A	91.99 ± 2.52A	93.33 ± 0.24
625	70.64 ± 4.82*	71.46 ± 1.84*	93.06 ± 0.18
312	43.87 ± 1.21*A	49.78 ± 1.76*A	92.97 ± 0.62
156	30.24 ± 1.58*	34.06 ± 1.77*	91.81 ± 2.62
78	22.57 ± 0.42*	26.41 ± 1.41*	92.19 ± 0.51
IC50 (µg/mL)	370.00 ± 17.32*A	313.33 ± 20.82*A	6.91 ± 0.16

*Significant difference of the extracts in relation to the BHT control (between same concentrations). ASignificant difference between extracts (between same concentrations) ($p < 0.05$).

We also analyzed, for the first time, the effects of the treatment of a cervical cancer cell line with different concentrations of aqueous and ethanolic extracts obtained from the fruits of *B. antiacantha*. Our data demonstrated an 20 and 30% inhibition in the viability of tumor cells after treatment with the ethanolic extract from the concentration of 1000 µg/mL. This effect may be associated with the presence of coumarins in the composition of this extract, since previous works have reported antineoplastic activity of these compounds through the induction of cell death via apoptosis (Duan et al., 2013).

In addition, the absence of effects of both extracts analyzed on non-tumor cells is an encouraging fact, especially when the plant species under study is an edible species and has already been used traditionally for some purposes.

Cytotoxicity is defined as the set of changes in cellular homeostasis, which leads to a series of changes that interfere with the adaptive capacity of cells, as well as their survival, reproduction and performance of their metabolic functions (Nardone, 1977) and, therefore, the study of this parameter is of great importance to indicate the safety of natural products. In addition, the main problem generated by conventional treatments is their indiscriminate toxicity, as they affect both tumor and non-tumor cells. Data like these justify the increase in the number of research involving natural products and are motivated by the medicinal characteristics observed in different plant species.

The scientific study of plant species used in popular medicine is of great importance, since the absence of technical information about many species can lead to cases of overdosage, allergic reaction and intoxication (Veiga Junior, 2008). In addition, some patients use to replace their allopathic medication for medicinal plants, or use both without the knowledge of possible interactions between them.

Nevertheless, it is important to highlight that data on new possible therapeutic applications and cytotoxicity of PANC's are relevant as they are available species, known to the population, and that can act with the much-needed link between popular and scientific knowledge.

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