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Antiproliferative activities of the extracts from *Feijoa sellowiana* and *Psidium cattleyanum*

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Abstract

Bladder cancer is a relevant human health problem worldwide. Although a number of chemotherapies are available, many of them present unwanted side effects and are prone to develop resistance to treatment, so they eventually become ineffective, causing low survival rates. The search for selective cytotoxic (antiproliferative) activities on cancer cells from wild plant extracts has markedly increased in recent years. In this work, the antiproliferative effect of total alcoholic extracts of leaf and flowers from *feijoa* or *guayabo del país* (*Feijoa sellowiana*) and *arazá* (*Psidium cattleyanum*) was evaluated. Cytotoxic activity was assessed based on resazurin and sulforhodamine B assays on RT4, HT1197 and EJ138 bladder cancer cell lines. The obtained results indicated that an extract of *arazá* flower (ExAF) showed a strong, concentration-dependent antiproliferative activity. Furthermore, ExAF revealed high selectivity with very low cytotoxic effects on the keratinocyte-derived HaCaT cell line. In this way, ExAF would be a promising candidate for further studying its antitumor activity. These results contribute to the valorization of these native species by expanding their potential use in new technological areas.

Keywords: arazá, bladder cancer, cytotoxic, feijoa, guayabo del país

Actividad antiproliferativa de los extractos de *Feijoa sellowiana* y *Psidium cattleyanum*

Resumen

El cáncer de vejiga es un problema de salud pública relevante a nivel mundial. Si bien existen diversas quimioterapias disponibles, muchas de ellas presentan efectos secundarios indeseables y son propensas a desarrollar resistencia al tratamiento, por lo que eventualmente se vuelven ineficaces, causando bajas tasas de supervivencia. La búsqueda de actividades citotóxicas (antiproliferativas) selectivas sobre células cancerosas a partir de extractos de plantas silvestres ha aumentado notablemente en los últimos años. En este trabajo, se evaluó el efecto antiproliferativo de extractos

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alcohólicos totales de hojas y flores de feijoa o guayabo del país (*Feijoa sellowiana*) y arazá (*Psidium cattleyanum*). La actividad citotóxica se evaluó con base en ensayos de resazurina y sulforodamina B en las líneas celulares de cáncer de vejiga RT4, HT1197 y EJ138. Los resultados obtenidos indicaron que un extracto de flor de arazá (ExAF) mostró una fuerte actividad antiproliferativa dependiente de la concentración. Además, ExAF reveló alta selectividad con efectos citotóxicos muy bajos sobre la línea celular HaCaT derivada de queratinocitos. De esta manera, ExAF sería un candidato prometedor para un estudio más profundo de su actividad antitumoral. Estos resultados contribuyen a la valorización de estas especies nativas, ampliando su potencial de uso en nuevas áreas tecnológicas.

Palabras clave: arazá, cáncer de vejiga, citotóxico, feijoa, guayabo del país

Atividade antiproliferativa em extratos de *Feijoa sellowiana* e *Psidium cattleyanum*

Resumo

O câncer de bexiga é um problema de saúde humana relevante em todo o mundo. Embora existam várias quimioterapias disponíveis, muitas delas apresentam efeitos colaterais indesejados e são propensas a desenvolver resistência ao tratamento, de modo que eventualmente se tornam ineficazes, causando baixas taxas de sobrevivência. A busca por atividades citotóxicas seletivas (antiproliferativas) em células cancerígenas a partir de extratos de plantas selvagens aumentou significativamente nos últimos anos. Neste trabalho, o efeito antiproliferativo de extratos alcoólicos totais de folhas e flores de feijoa (*Feijoa sellowiana*) e araçá (*Psidium cattleyanum*) foi avaliado. A atividade citotóxica foi avaliada com base em ensaios de resazurina e sulforrodamina B em linhagens de células de câncer de bexiga RT4, HT1197 e EJ138. Os resultados obtidos indicaram que um extrato de flor de araçá (ExAF) mostrou uma forte atividade antiproliferativa dependente da concentração. Além disso, ExAF revelou alta seletividade com efeitos citotóxicos muito baixos na linhagem de células HaCaT derivadas de queratinócitos. Dessa forma, o ExAF seria um candidato promissor para estudos mais aprofundados de sua atividade antitumoral. Esses resultados contribuem para a valorização dessas espécies nativas ao expandir seu potencial de uso em novas áreas tecnológicas.

Palavras-chave: araçá, câncer de bexiga, citotóxico, feijoa, goiabeira-serrana

1. Introduction

Bladder cancer is of great importance to human health according to incidence and prevalence metrics. Worldwide, an estimated number of 573,000 new cases and 212,000 deaths per year has been reported, ranking tenth in incidence[(1)]. In Uruguay, malignant neoplasms represent the second cause of death[(2)]. In particular, annual incidence of urological neoplasms, between 2012 and 2016, was 17.68 per 100,000 for men, ranking fourth in incidence, and 3.66 per 100,000 in women, with mortality rates of 4.38% and 1.64%, respectively[(3)]. Average age of onset of bladder cancer is between 60 and 70 years, and its frequency increases with age. Although the incidence is higher in developed countries, mortality is higher in developing countries[(4)].

Conventional cancer therapies, although effective in many cases, are often accompanied by adverse side effects and treatment resistance problems[(5)]. In particular, the unwanted side effects developed by cisplatin-based neoadjuvant chemotherapy have motivated the search and development of alternative treatments. In recent years, a marked increase in research on wild plant extracts that have cytotoxic capacity against cancer cells, that is, that have antiproliferative effects, has been reported[(6)].

The Myrtaceae species *guayabo del país* or *feijoa*, *Feijoa sellowiana* (Berg) Berg, and *arazá* or strawberry guava, *Psidium cattleyanum* Sabine, are woody, evergreen, fruit species, native to southern Brazil and northeastern Uruguay, that, in the case of *feijoa*, further include northeastern Argentina[(7)(8)]. Both species have been

shown to exhibit anti-inflammatory, antibacterial, and antifungal activities, and like other members of the myrtle family, they are highly rich in a diverse array of secondary metabolites such as terpenoids, phenolic acids, flavonoids, and tannins[9][10][11][12][13]. Currently, these groups of plant metabolites are intensively researched as candidates for the treatment of different types of cancer[14][15][16]. Only recently, a reduced number of studies have reported the promising *in vitro* antiproliferative activity from secondary metabolite-enriched extracts of *feijoa* and, to a lesser extent, *arazá*[17][18][19][21][22][23][24][25][26][27][28], highlighting these underutilized, diverse species as valuable and versatile sources of anticancer agents. However, bladder cancer cell lines have not yet been included in these analyses.

The current search for anticancer bioactives in *feijoa* and *arazá* plants has been mainly based on fruit extracts, while leaf and floral tissues have received less attention[10][17][18][19][20][21][22][23][24][25][26][27][28]. Notably, anticancer activities and chemical profiling of leaf extracts from *arazá*[23][26] and *feijoa*[25] have been reported. Conversely, only one report concerning *arazá* floral tissues, restricted to the essential oil components, referred to anticancer activity[26], while for *feijoa* flowers, the search for anticancer agents has not been described yet, although the finding of *feijoa* flowers being a rich source of diverse flavonoids and ellagitannin-related metabolites[17][28] may indicate these tissues as candidate sources of anticancer compounds. Moreover, a recent transcriptome-based study on *feijoa* flowers predicted the activity of 15 different secondary metabolites pathways, including those related to flavonoids and terpenoids[29]. Indeed, floral tissues of a wide range of plant families are being increasingly studied as sources of a wide range of bioactive compounds[30]. Consequently, both leaf and floral tissues from *arazá* and *feijoa* plants naturally growing in Uruguay might be considered candidate sources of novel biomedical compounds.

In this work, the antiproliferative and selective cytotoxic properties of alcoholic extracts from leaves and flowers of *feijoa* and *arazá* on bladder cancer-derived lines were evaluated. First, all extracts were evaluated with RT4 and HT1197 bladder cancer lines. Then, for the most promising extract, showing the highest antiproliferative activity, the IC50 parameter was estimated, including EJ138, as an additional cell line in the experiment.

2. Materials and Methods

2.1 Leaves and Flowers Harvest

Leaves (30) and flowers (30) were collected, in triplicate, from single, 10-year-old plants of *feijoa* (*Feijoa sellowiana)* and *arazá* (*Psidium cattleyanum* f. *cattleyanum;* purple-red fruit morphotype), in full blooming stage, in November 2023, from the garden of Faculty of Agronomy, Universidad de la República, Montevideo, Uruguay. These plants were located in well-illuminated plots, and were not subjected to any agronomical practices. Expanded leaves and complete flowers with open petals at stages 64-65 of BBCH scale[31] were chosen, as described in **Figure 1**. After collection, the samples were washed with distilled water and dried in an oven at 40 ºC for five days, until constant weight.

2.2 Cell Lines

Cell lines derived from bladder cancer tumors RT4 (ECACC 91091914) stage I, EJ138 (ECACC 85061108) stage III, and HT1197 (ECACC 87032403) stage IV[32] were obtained from the European Collection of Authenticated Cell Cultures (ECACC). In addition, the spontaneously immortalized normal human keratinocyte cell line, HaCaT, was used[33]. Cell lines were grown in EMEM medium (M0643, Sigma) supplemented with 10% FBS (FBS-11A, Capricorn).

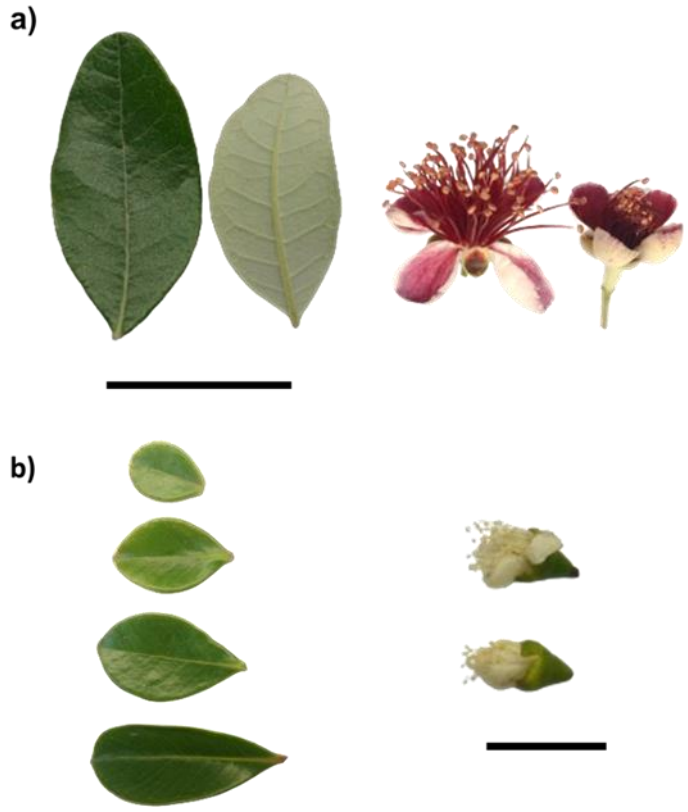

Figure 1. Representative flower and leaf development stages of collected samples. (a) *Feijoa sellowiana* (bar = 3 cm); (b) *Psidium cattleyanum* f. *cattleyanum* (bar = 2 cm)

2.3 Ethanolic Extract

Ten grams of dehydrated tissue (leaf or complete flower) were macerated in 150 mL of 95% ethanol for 48 h at 40 °C. This procedure was performed twice. The total alcoholic extracts were then concentrated in a rotary evaporator at <40 °C. Finally, the dried extracts were weighed and stored at -20 °C in the dark. Prior to inclusion in cell cultures, the extracts were resuspended with Dimethyl sulfoxide (DMSO).

2.4 Antiproliferative Activity Evaluation

RT4 and HT1197 cell lines were grown in 96-well plates, seeding 2500 cells per well in EMEM culture medium with 10% FBS, and cultured at 37 °C and 5% CO_2 for 24 h. They were then treated with different concentrations of the alcoholic extracts (4, 40, and 400 µg/mL), using DMSO as vehicle control. The assay took place for 48 h, under the culture conditions described.

Cell viability was evaluated by resazurin (RZ) and sulforhodamine B (SRB) tandem assays[34]. Briefly, for RZ assay, after 44 h of incubation with the extract, 20 µL of 0.25 mg/mL RZ, prepared in PBS, was added, and the plate was further incubated at 37 °C, 5% CO_2 for 4 h. Fluorescence was measured on a spectrofluorometer plate (BMG Clariostar Plus) using an excitation wavelength of 530-560 nm and an emission wavelength of 590 nm. After that, the same plate was then used for the SRB assay. Cells were fixed by adding 50 µL of 50% trichloroacetic acid (TCA) in distilled water for 1 h at 4 °C. The solution was then discarded, washed with distilled water three times, and dried at 37 °C for 1 h. One hundred microliter of a 0.057% (w/v) solution of SRB in 1% acetic acid was added to each well and incubated at 37 °C for 1 h. After this step, the solution was discarded and the plate was quickly washed three times by adding 200 µL of 1% v/v acetic acid in Milli-Q water and dried for 1 h at 37 °C. Finally, 100 µL of 10 mM Tris-Cl pH 10.5 was added, and the plate was shaken for 10 min on an orbital shaker at room temperature. The absorbance was measured at 510 nm on the aforementioned spectrofluorometer.

The median inhibitory concentration (IC50) of the compounds was determined as the concentration that reduces cell viability by 50% compared to the DMSO-treated control, using the SRB assay. Two additional cell lines were included in this analysis: EJ138 (derived from bladder cancer) and HaCaT (immortalized human keratinocyte line). The plating and culture conditions were the same as those already described. The extracts were assayed in a concentration range from 25 to 400 µg/mL. The IC50 was determined by linear regression analysis. The selectivity index (SI) was calculated as the ratio between the toxic concentration of a sample and its effective bioactive concentration. SI = IC50 HaCaT/ IC50 tumor cells[35]. Three independent experiments were performed, each including technical triplicates.

2.5 Statistical Analysis

All experiments were done in triplicate and at least two biological replicas were performed for every experimental condition. Data analyses and statistical calculations were performed using one-way ANOVA followed by Tukey's multiple comparisons test.

3. Results

3.1 Leaves and Flowers Harvest

The fresh weights of the replicated samples of flowers and leaves from *arazá* were similar. The wet weights of the *feijoa* samples were slightly more variable, especially for flower replicates (**Table 1**). In both species, the dry weight was proportional to the initial fresh weight, with percentages of dry weight/fresh weight of flowers of 19.4 ±1.0% and 24.6 ±1.3%, and of leaves of 51.8 ±2.7% and 31.1 ±0.3%, for *feijoa* and *arazá*, respectively. The yields of the ethanolic extracts (dry weight of the extract/dry weight of the sample) varied between 2.26% and 10.58% (**Table 1**).

Table 1. Sample weight and extract yield (dry weight of the extract/dry weight of the sample) of *Feijoa sellowiana* leaves (ExGL) and flowers (ExGF), and of *Psidium cattleyanum* leaves (ExAL) and flowers (ExAF)

Extract	Fresh weight (g)	Dry weight (g)	Extract weight (g)	Extract yield (%)
ExGF1	19.97	4.10	0.10	2.44
ExGF2	19.43	3.63	0.15	4.13
ExGF3	28.44	5.39	0.57	10.58
ExGL1	12.88	6.49	0.15	2.31
ExGL2	9.70	4.85	0.18	3.71
ExGL3	9.92	5.45	0.27	4.95
ExAF1	4.20	1.07	0.07	6.58
ExAF2	4.24	0.98	0.01	10.22
ExAF3	4.17	1.06	0.09	8.45
ExAL1	11.89	3.74	0.19	5.13
ExAL2	11.82	3.67	0.32	8.58
ExAL3	10.32	3.18	0.21	6.73

3.2 Antiproliferative Activity

To evaluate the antiproliferative activity of leaf and floral extracts of *feijoa* (ExGL and ExGF) and *arazá* (ExAF and ExAL), RZ and SRB tandem assays were performed, using the RT4 and HT1197 lines. Based on RZ assay for HT1197 line, the most active extract was ExAF, obtaining 27% and 53% of viable cells at 400 and 40 µg/mL, respectively, while the rest of the extracts showed activity only at 400 µg/mL or did not show activity at HT1197. For RT4 cell line, none of the extracts showed activity with the RZ assay. On the other hand, for the SRB method, a concentration-dependent antiproliferative effect was observed for floral extracts ExAF and ExGF, although ExAF showed a more significant decrease in cell viability, accounting for 25% of cell viability for 40 µg/mL. In addition, for the SRB assay, all extracts showed cytotoxic activity on HT1197 and RT4, at 400 µg/mL.

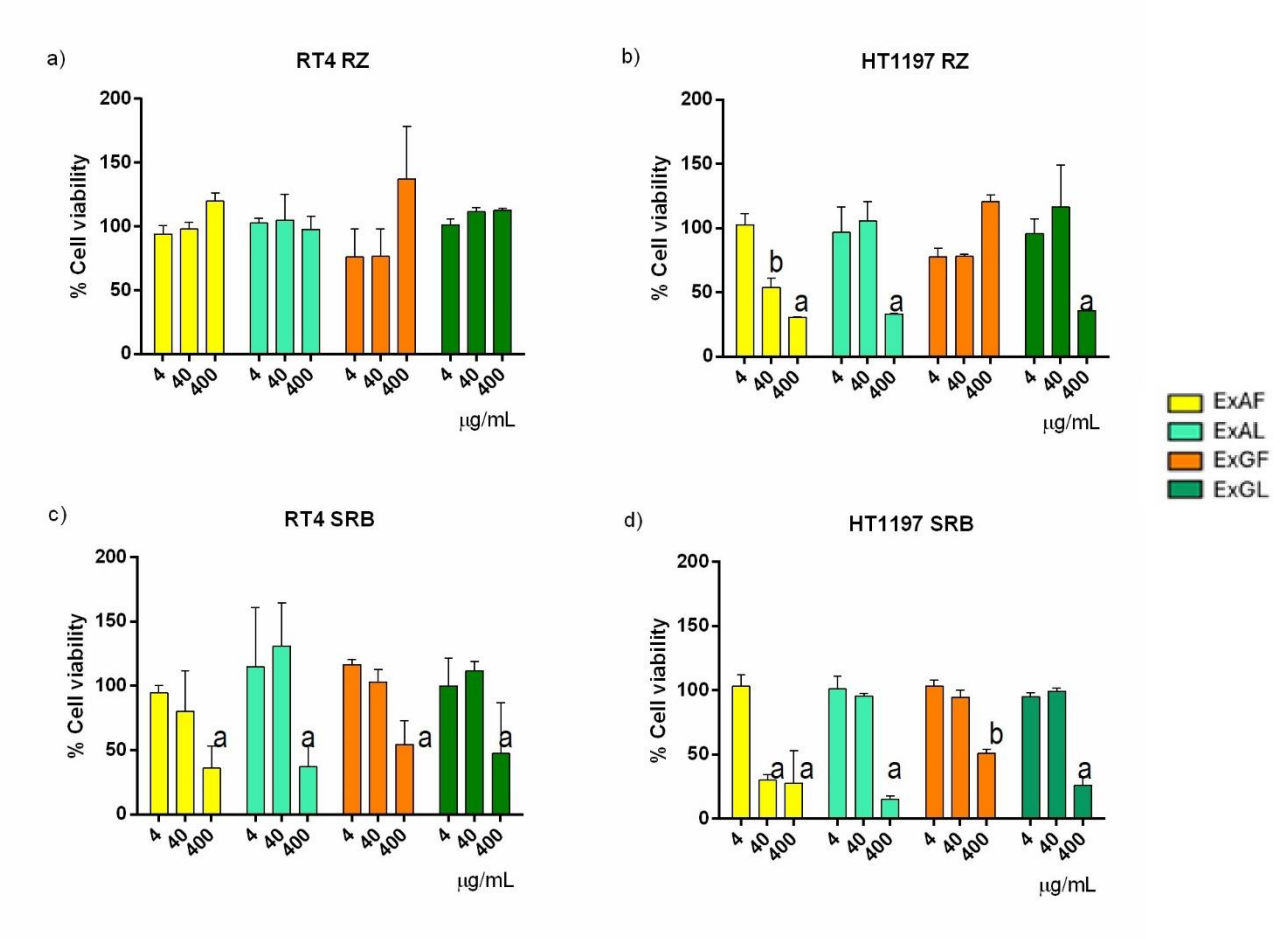

Figure 2. Antiproliferative activity of *feijoa* (*Feijoa sellowiana*) and *arazá* (*Psidium cattleyanum*) leaf and flower extracts, based on resazurin (RZ) and sulforhodamine B (SRB) assays, for 48 h, with RT4 (a and c) and HT1197 (b and d) cell lines

The % of cell viability is shown as a function of the concentration of each extract evaluated. The data are mean ± standard deviation. Bar colors indicate the extract identity: ExAF (*arazá* flower); ExAL (*arazá* leaf); ExGF (*feijoa* flower); ExGL (*feijoa* leaf). [a]p < 0.01, [b]p < 0.1 correspond to significant difference between the untreated (DMSO) and treated cells as calculated by one-way ANOVA and Tukey's test.

3.3 Antiproliferative Activity and Selectivity Index of ExAF

Based on the promising results obtained with ExAF, a further characterization including the estimation of the IC50 value using the SRB method was implemented. In this analysis, in addition to the RT4 and HT1197 lines, the tumor line EJ138 and a line derived from normal keratinocytes HaCaT were also included. At 48 h, ExAF showed an antiproliferative effect on all three tumor lines (**Figure 3**). The calculated IC50 were 127.2 ± 2.2 µg/mL for RT4, 27.9 ± 1.9 µg/mL for EJ138, and 25.37 ± 1.83 µg/mL for HT1197, demonstrating that ExAF showed the largest effects on EJ138 and HT1197 tumor lines. Conversely, ExAF showed a mild cytotoxic effect

(85% cell viability) on the HaCaT cell line at 48 h, evidenced by IC50 higher than 400 µg/mL. Accordingly, the selectivity index (SI) of ExAF, with respect to HaCaT, was 3.1 for RT4, 14.3 for EJ138 and 15.8 for HT1197.

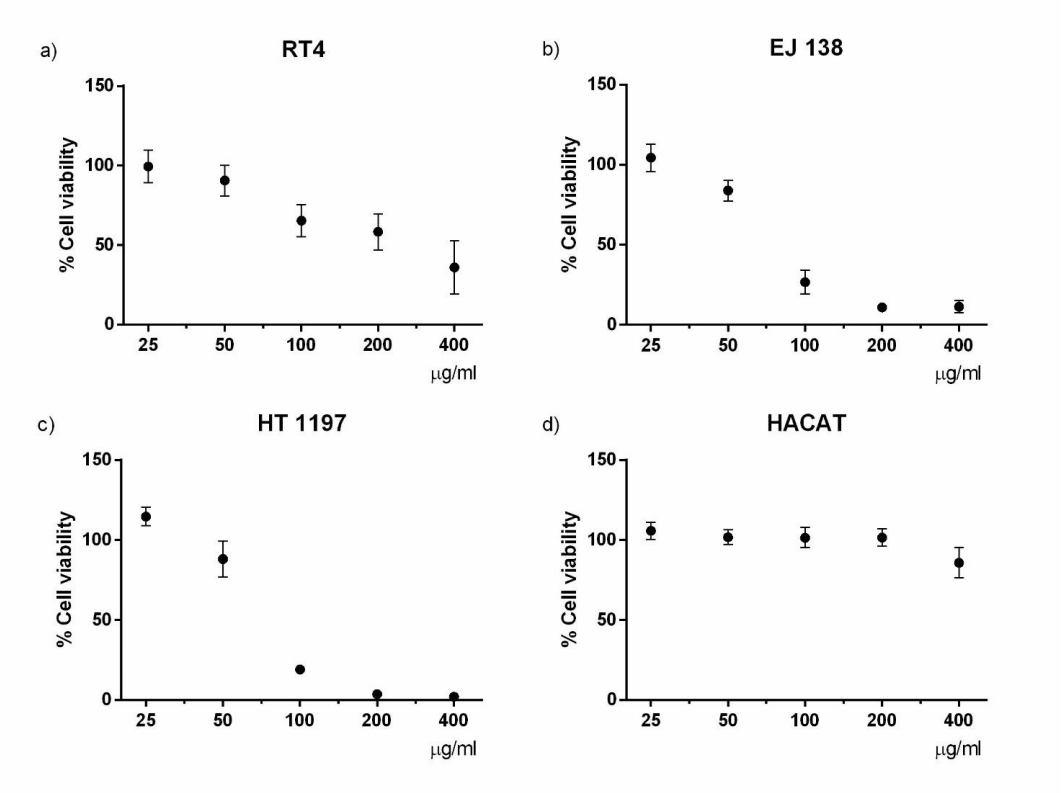

Figure 3. Antiproliferative effect of *arazá* (*Psidium cattleyanum)* flower extract (ExAF) determined at 48 h by the SRB assay in the bladder cancer-derived lines a) RT4, b) EJ138, c) HT1197, and d) the normal keratinocyte-derived line HaCaT

The mean and standard deviation of three independent experiments normalized to the DMSO control are represented.

4. Discussion

Plants have been widely used in traditional medicine. More than 60% of the compounds used in anti-tumor therapies are derived from natural plant products[36]. Plant compounds, such as polyphenols and terpene-rich essential oils, have shown efficacy in inhibiting the growth of bacteria, fungi and cancer cells. The cell growth inhibition properties of these plant compounds have been associated with their ability to induce apoptosis and interfere with critical biological processes, such as DNA synthesis, cell proliferation and cell membrane integrity, making them valuable sources of treatments in modern medicine[10][18]. The antiproliferative activity, i.e. inhibiting the growth of cancer cells, of phytochemicals such as polyphenol, tannins and terpenoids frequently found in species of the myrtle family has been frequently reported[37].

An increased research interest on anticancer activities of *feijoa* and *arazá* extracts has become evident in recent years. Antiproliferative activity against oral squamous cell carcinoma, cutaneous melanoma, and hematological, breast, cervical, colon, gastric, prostate cancer cells lines was found for *feijoa* leaf and fruit extracts[17][18][19][20][21][22][25]. In the case of *arazá*, leaf and fruit extracts showed antiproliferative activity on breast, colon and stomach cancer cell lines[9][23]. Lately, essential oil extracts obtained from *arazá* flowers showed only weak cytotoxic activity with low selectivity rate for hepatic, breast and leukemia cancer cell lines[26]. In our study, we found that, at the highest concentration (400 µg/mL), the ethanolic extracts from *arazá* and *feijoa* leaf and flower tissues exhibited antiproliferative activity on two (*feijoa* extract) and three (*arazá* extract) different bladder cancer lines. Thus, our work expanded the search for anticancer agents in *feijoa* and *arazá* species by

considering, for the first time, the ethanolic floral extracts from both species. Moreover, the inclusion of bladder cancer cell lines in this study widened the range of malignant neoplasms for which *arazá* and *feijoa* extracts were effective.

The most promising extract in this study was the extract of *arazá* flower (ExAF), with high cytotoxicity and selectivity at 40 µg/mL. The highest activity was observed on EJ138 and HT 1197 lines (IC50 25.4-27.9 µg/mL), which are derived from tumors at advanced cancer progression (stages III and IV, respectively) compared to RT (IC50 127.2; µg/mL, stage I). Furthermore, the IC50 values of ExAF are comparable to those obtained by Peng and others[22] for *feijoa* fruit extracts in SRB-based assays (IC50 of 13.7 - 43.0 µg/mL). On the other hand, ExAF cytotoxic activity was high compared to that of aqueous and acetone extracts of *arazá* fruit on breast (MCF 7) and colon (CaCo2) cancer lines[38]. Therefore, the finding of strong cytotoxicity activity with high selectivity on bladder cancer cells for ExAF is a relevant contribution of this study.

Recently, Peng and others[22] described for the first time the association between the phenolic composition of *feijoa* fruit extracts and the extent of pro-apoptosis activity against prostate cancer cells[22], supporting the high anticancer potential of the polyphenolic chemical group against a wide range of cancers, including bladder carcinoma[5][6]. Moreover, a metabolomic study of methanolic leaf and fruit extracts of *arazá*, carried out by Zangh and others[38], described four hundred sixty nine metabolites, including various phenolic subclasses predominantly flavonoids and phenolic acids[38], which gives us an idea of the complexity of the alcoholic *arazá* extracts. Future works should be addressed to fill the gap of information on the chemical composition of ethanolic extracts of *arazá* flowers, as well as to further determine which molecules are responsible from *arazá* antiproliferative action.

The initial studies of the mechanisms underlying the antiproliferative activity of *arazá* and *feijoa* extracts, with varying chemical composition, have been recently undertaken and globally postulated the induction of programmed cell death or apoptosis associated with the caspase pathway[22][26][39] and epigenetic modulation through histone deacetylases[40]. Our finding of a promising extract from *arazá* warrant further research on its chemical composition as well as the underlying mechanisms of its cytotoxic action on bladder cell lines.

5. Conclusions

This study reported the finding of plant-derived products with biomedical potential from two myrtle tree species from the native flora of Uruguay. A description of a methodology for obtaining extracts from leaf and flowers is provided. Floral extracts from *arazá* revealed for the first time high, selective antiproliferative activities against bladder cancer cells.

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Transparency of data

Available data: The entire data set supporting the results of this study was published in the article itself.

Author contribution statement

	I Lavié	L Canclini	C. Pritsch	D Alem
Conceptualization				
Data curation				
Formal analysis				
Investigation				
Methodology				
Writing – original draft				
Writing – review and editing				

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