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Original Article

Genotoxic and cytotoxic potential of essential oils from plants of the Cerrado and southern Pantanal of Mato Grosso do Sul, Brazil

Potencial genotóxico e citotóxico de óleos essenciais de plantas do Cerrado e Pantanal Sul-Mato-Grossense, Brasil

J. A. Avanci-Júnior[a]*, M. F. Silva[a], K. F. D. P. Santos[a], N. C. Yoshida[b], É. L. Santos[b], Z. R. Guterres[c], J. G. Gouveia[c] and D. Bogo[a]

[a]Universidade Federal de Mato Grosso do Sul – UFMS, Programa de Pós-graduação em Saúde e Desenvolvimento na Região Centro-Oeste, Instituto de Biologia, Laboratório de Biologia Molecular, Campo Grande, MS, Brasil

[b]Universidade Federal de Mato Grosso do Sul – UFMS, Instituto de Química, Campo Grande, MS, Brasil

[c]Universidade Estadual de Mato Grosso do Sul – UEMS, Instituto de Ciências Biológicas, Ivinhema, MS, Brasil

Abstract

Cancer represents a major public health concern, and the therapeutic potential of medicinal plants has been extensively studied as an alternative approach for its treatment. This study evaluated the genotoxic, cytotoxic properties, and selectivity of essential oils from native plants of the Brazilian Cerrado and Pantanal: *Cymbopogon citratus*, *Endlicheria paniculata*, *Matayba guianensis*, and *Siparuna guianensis*. These species, popular in traditional medicine, were tested for their ability to inhibit the growth of skin (B16-F10), breast (MCF-7), and brain (U251) cancer cells, to assess selective tumor toxicity. The essential oils were analyzed for their cytotoxicity, evaluating their capacity to inhibit cell growth in cancer and normal lines, such as murine fibroblasts (NIH/3T3) and human umbilical vein endothelial cells (HUVEC). Among the oils tested, *Matayba guianensis* exhibited significant activity against all cancer cell lines studied, while *Siparuna. guianensis* showed strong inhibitory action on brain cancer cells. *Endlicheria paniculata* displayed cytotoxicity in both tumor and normal cells, whereas *Cymbopogon citratus* was toxic only to normal cells. This profile was investigated to assess the oils' ability to preferentially target cancer cells, with *Siparuna. guianensis* notably displaying high selectivity for brain and breast cancer cells, suggesting safer potential use. Genotoxicity analysis indicated that *Siparuna guianensis* essential oil lacks mutagenic effects, suggesting an additional safety profile for therapeutic development. Based on these results, *Matayba guianensis* and *Siparuna guianensis* oils show promise as anticancer agents, demonstrating selective activity and potential for future therapeutic strategies aimed at cancer treatment.

Keywords: anticarcinogens, medicinal plants, mutagenicity tests.

Resumo

O câncer representa uma grande preocupação de saúde pública, e o potencial terapêutico de plantas medicinais tem sido amplamente estudado como uma abordagem alternativa para seu tratamento. Este estudo avaliou as propriedades genotóxicas, citotóxicas e a seletividade de óleos essenciais de plantas nativas do Cerrado e Pantanal brasileiro: *Cymbopogon citratus*, *Endlicheria paniculata*, *Matayba guianensis* e *Siparuna guianensis*. Essas espécies, populares na medicina tradicional, foram testadas quanto à sua capacidade de inibir o crescimento de células cancerígenas de pele (B16-F10), mama (MCF-7) e cérebro (U251), a fim de avaliar a toxicidade seletiva para tumores. Os óleos essenciais foram analisados quanto à sua citotoxicidade, avaliando sua capacidade de inibir o crescimento celular em linhagens tumorais e normais, como fibroblastos murinos (NIH/3T3) e células endoteliais da veia umbilical humana (HUVEC). Entre os óleos testados, *Matayba guianensis* exibiu atividade significativa contra todas as linhagens de células cancerígenas estudadas, enquanto *S. guianensis* apresentou forte ação inibitória sobre células de câncer cerebral. *Endlicheria paniculata* mostrou citotoxicidade tanto em células tumorais quanto em células normais, enquanto *Cymbopogon citratus* foi tóxico apenas para células normais. Este perfil foi investigado para avaliar a capacidade dos óleos em direcionar preferencialmente células cancerígenas, com *Siparuna guianensis* apresentando notável seletividade para células de câncer cerebral e de mama, sugerindo um uso potencial mais seguro. A análise de genotoxicidade indicou que o óleo essencial de *Siparuna guianensis* não apresenta efeitos mutagênicos, sugerindo um perfil de segurança adicional para o desenvolvimento terapêutico. Com base nesses resultados, os óleos de *Matayba guianensis* e *Siparuna guianensis* mostram potencial como agentes anticancerígenos, demonstrando atividade seletiva e potencial para futuras estratégias terapêuticas voltadas ao tratamento do câncer.

Palavras-chave: anticarcinógenos, plantas medicinais, testes de mutagenicidade.

*e-mail: amarildo.avanci@gmail.com
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1. Introduction

Natural plant resources have been extensively explored throughout history, providing essential elements for human life and other organisms, serving various purposes such as food, construction, medicine, and ornamentation (Těšitel et al., 2021). Brazil, with its rich biodiversity, holds valuable traditional knowledge and technologies, particularly regarding the management and use of medicinal plants (Cerqueira et al., 2020).

Plants with biological activities, such as anti-inflammatory and antineoplastic effects, are of significant interest due to their potential to combat the damage caused by free radicals, including DNA mutations, protein oxidation, and lipid peroxidation (Vaou et al., 2021). Contemporary research seeks to deepen the understanding of traditional medicine and identify plants with effective therapeutic activities that can complement modern medical practices (Melro et al., 2020; Chaachouay and Zidane, 2024).

The Brazilian Ministry of Health currently promotes the use of 71 medicinal plant species within the Unified Health System (SUS). However, this usage requires caution, as much of the research focuses on the pharmacological potential of these plants rather than their toxicity. In the state of Mato Grosso do Sul, located in the Central-West region of the country, many communities rely exclusively on traditional medicine to treat and manage various symptoms (Mendonça et al., 2020).

To meet their needs, many inhabitants of the Cerrado and Pantanal biomes in Mato Grosso do Sul utilize medicinal plants readily available in their daily lives. Over time, these residents have discovered several culinary and therapeutic applications for these plants. The local population, which is highly diverse and influenced by indigenous culture, provides a significant contribution to medicinal research (Pilnik et al., 2023). In emerging countries like Brazil, diseases are often linked to poor sanitation, malnutrition, and limited access to medications, making ethnomedicinal and phytotherapeutic practices commonplace (Michelin et al., 2005). Nonetheless, few medicinal plants used in these contexts have had their efficacy scientifically proven.

Among the medicinal plants with therapeutic potential are *Cymbopogon citratus* (DC.) Stapf, *Endlicheria paniculata* (Spreng.) J. F. Macbr, *Matayba guianensis* Aubl., and *Siparuna guianensis* Aubl., whose essential oils have garnered scientific interest. These oils, typically extracted via steam distillation, are complex mixtures of volatile compounds exhibiting antimicrobial, antioxidant, and antitumor activities (Dhifi et al., 2016). A notable example is the essential oil of *Cymbopogon citratus*, commonly known as lemongrass, widely used in traditional medicine due to its high citral content, a compound associated with antimicrobial and anti-inflammatory properties (Oliveira and Santos, 2021).

Similarly, *Endlicheria paniculata* is notable for its essential oil with antitumor and antioxidant properties, attributed to the presence of sesquiterpenes and other bioactive compounds, although it remains relatively understudied scientifically (Yamaguchi et al., 2013). *Matayba guianensis*, on the other hand, produces essential oils with antifungal, antibacterial, and potential anticancer effects, increasing its relevance for therapeutic applications (Jesus et al., 2020). Meanwhile, *Siparuna guianensis* is recognized for its essential oils rich in monoterpenes and sesquiterpenes, compounds that exhibit significant cytotoxic potential against tumor cells (Barbosa et al., 2023).

Among the main constituents of these plants are sesquiterpenes such as bicyclogermacrene, germacrene D, and β-caryophyllene, which were identified in high concentrations in the essential oils of *Siparuna guianensis* and *Matayba guianensis*. These compounds have been widely associated with relevant biological properties, including antimicrobial, antioxidant, and cytotoxic activities (Costa et al., 2022). This chemical composition provides a strong theoretical basis for evaluating their potential genotoxic and antiproliferative effects.

This scenario highlights the importance of studying species from the Cerrado and Pantanal biomes as novel sources of bioactive compounds with potential pharmaceutical applications, including cancer treatment. Therefore, this study aims to evaluate the in vitro antiproliferative activity and in vivo genotoxic effects of the essential oils of *Cymbopogon citratus, Endlicheria paniculata*, *Matayba guianensis* and *Siparuna guianensis*.

2. Materials and Methods

The study was experimental, following a standardized methodology established by the Molecular Biology and Cell Culture Laboratory at the Federal University of Mato Grosso do Sul - UFMS (Micheletti et al., 2011; Garcez et al., 2011; Figueiredo et al., 2011).

The chemical composition of the essential oils from *Siparuna guianensis* (OESG) and *Matayba guianensis* (OEMG) was analyzed using gas chromatography coupled with mass spectrometry (GC-MS). This analysis identified 39 distinct compounds across the two oils, as summarized in Table 1. Key components of OESG included sesquiterpenes such as bicyclogermacrene, germacrene D, and β-caryophyllene, all of which are known for their bioactive properties. Similarly, OEMG exhibited high concentrations of germacrene D, β-caryophyllene, and other sesquiterpenes, contributing to its biological activity. The detailed chemical profiles of these oils supported the rationale for investigating their cytotoxic and genotoxic potential in the subsequent assays.

Neoplastic cell lines (B16, MCF7, U251, and 786) and non-tumor cell lines (HUVEC and 3T3) were used to determine cytotoxicity, selectivity index (Houghton et al., 2007), and perform the SMART assay (Zijlstra et al., 1987). The SMART test detects mechanisms that can cause loss of heterozygosity, leading to homozygosity in daughter cells through genetic events. It is, therefore, suitable for a "broad spectrum of genotoxic agents, complex mixtures, and gaseous particles" (Amorim, 2016).

The collection of *Cymbopogon citratus*, *Endlicheria paniculata*, *Matayba guianensis*, and *Siparuna guianensis* was carried out between September and October 2022 in different regions of Mato Grosso do Sul, Brazil, including the municipalities of Campo Grande, Corumbá, and Bonito. For each species, 20 healthy adult individuals were randomly selected,

Table 1. Chemical composition of essential oils from *Siparuna guianensis* (OESG) and *Matayba guianensis* (OEMG) determined by gas chromatography-mass spectrometry (GC-MS).

Peak	Compounds	Peak Area (%)	Peak Area (%)	OESG	OEMG
		OESG	OEMG		
1	bicycloelemene	1.11	-	+	
2	δ-elemene	-	2.73		+
3	α-Cubebene	-	0.14		+
4	α-ylangene	-	0.24		+
5	α-Copaene	0.23	1.34	+	+
6	β-Bourbonene	-	0.21		+
7	β-elemene	0.94	1.95	+	+
8	α-Gurjunene	-	0.21		+
9	β-Caryophyllene	-	15.45		+
10	γ-elemene	2.13	-	+	
11	Aromadendrene	0.24	1.28	+	+
12	α-Humulene	-	2.10		+
13	Alloaromadendrene	0.27	0.81	+	+
14	α-Amorphene	-	1.37		+
15	Germacrene D	5.16	28.39	+	+
16	β-Selinene	0.44	0.33	+	+
17	*cis*-muurolo-4,5-diene	0.48	-	+	
18	(-)-Isoledene	-	0.47		+
19	α-bisabolene	0.66	-	+	
20	Bicyclogermacrene	13.12	31.32	+	+
21	α- Muurolene	-	0.56		+
22	zonarene	0.23	-	+	
23	isogermacrene D	0.88	-	+	
24	δ -Cadinene	2.38	0.76	+	+
25	Germacrene B	4.48	5.19	+	+
26	9-epi-*E*-caryophyllene	3.56	-	+	
27	Spathulenol	-	2.29		+
28	Globulol	1.79	-	+	
29	Unknown ($C_{15}H_{26}O$)	-	4.79	+	
30	Viridiflorol	-	1.83		+
31	Unknown ($C_{15}H_{26}O$)	-	1.42	+	
32	5-epi-7-epi-α-Eudesmol	-	0.67		+
33	10-epi-y-Eudesmol	-	0.36		+
34	epicubenol	0.75	-	+	
35	Unknown ($C_{15}H_{26}O$)	2.05	-	+	
36	τ-muurolol	1.64	-	+	
37	α-muurolol	2.25	-	+	
38	Unknown ($C_{15}H_{26}O$)	0.63	-	+	
39	cadin-4-en-10-ol	2.56	-	+	
	Identified Compounds (%)			96.00	99.98

Identified compounds are listed by peak number and percentage area. Key sesquiterpenes with potential bioactive properties are highlighted. +: present; -: absent.

preferably in reproductive stage, in areas representative of native vegetation, avoiding anthropized sites or those showing signs of recent disturbance. Collections were conducted in the morning (7:00–10:00 a.m.) to ensure tissue integrity, using sterilized pruning shears and disposable gloves to minimize contamination. Leaves were selected based on their developmental stage, prioritizing fully expanded and mature structures, while excluding very young or senescent leaves. To capture morphological variability, leaves from different canopy positions (base, middle, and apex of branches) were sampled.

Immediately after collection, the material was placed in properly labeled kraft paper bags and stored in thermal boxes with ice to ensure temporary preservation during transport. In the laboratory, part of the samples was fixed in FAA 50 solution (formaldehyde, acetic acid, and 50% ethanol in a 1:1:18 ratio) for 24 hours, following the classical method described by Johansen (1940), for subsequent anatomical analysis. The material was then transferred to 70% (v/v) ethanol and stored in tightly sealed amber glass containers.

For taxonomic identification, leaves and fruits were sent to the Botany Laboratory at UFMS, where they were analyzed using specialized literature and compared with herbarium specimens. Voucher specimens were prepared following standard herbarium techniques, including drying in an oven at 40°C for 72 hours, mounting on acid-free cardboard, and labeling with collection and morphological data. The specimens were deposited in the CGMS Herbarium under the accession numbers 53328 (*C. citratus*), 72774 (*E. paniculata*), 74339 (*M. guianensis*), and 74331 (*S. guianensis*), ensuring their availability for future reference. These procedures aimed to ensure not only data reliability but also the reproducibility of the study, in accordance with best practices in systematic botany and plant ecology.

2.1. Essential oil extraction and chemical profile analysis via gas chromatography-mass spectrometry (GC/MS)

The essential oils (EOs) from fresh leaves of *Cymbopogon citratus*, *Endlicheria paniculata*, *Matayba guianensis*, and *Siparuna guianensis* were extracted via hydrodistillation using a Clevenger-type apparatus, following standardized protocols. For each species, 500 g of freshly collected leaves were carefully rinsed with distilled water to remove surface impurities, gently blotted dry with absorbent paper, and manually cut into 2–3 cm pieces to maximize surface area. The plant material was immersed in 1.5 L of distilled water in a 3 L glass flask and distilled for 3 hours post-boiling, with temperature control to prevent thermal degradation of volatile compounds. The EO was collected in the Clevenger arm, separated from the aqueous phase by decantation, dried over anhydrous sodium sulfate, and stored in amber glass vials at 4°C until analysis. The yield was calculated as % (w/w) based on the fresh leaf mass.

For gas chromatography-mass spectrometry (GC-MS) analysis, the EOs were solubilized in DMSO (0.1 g/mL) and diluted in culture medium to a final DMSO concentration of 0.4%. Analyses were performed using a Shimadzu GC/MS QP-2010 PLUS system equipped with an Rtx-MS column (30m×0.2mm×0.25µm; 5%-diphenyl-95%-dimethylpolysiloxane). Operational conditions included: injector temperature at 250°C, carrier gas (helium) flow rate of 1 mL/min, pressure of 87.1 kPa, and oven temperature program starting at 50°C (2 min), with a ramp of 3°C/min to 260°C (5 min). Constituents were identified by comparing mass spectra with Wiley 7 and NIST 08 libraries, and retention indices (RI) calculated via calibration with linear alkanes (C9–C22), as described by Adams (2017).

2.2. Screening for in vitro antiproliferative activity and cytotoxicity/antiproliferative testing

The antiproliferative activity of essential oils was evaluated using the Sulforhodamine B (SRB) cytotoxicity assay according to Skehan et al. (1990) with modifications from the Sigma-Aldrich (USA) commercial kit. SRB, an anionic dye, specifically binds to basic amino groups of cellular proteins, enabling precise quantification of viable biomass.

Cells were initially thawed in a 37°C water bath and transferred to 15 mL tubes containing DMEM or RPMI medium supplemented with gentamicin (50 µg/mL) (Freshney, 2016; ATCC, 2021; Sigma-Aldrich, 2016) and 10% fetal bovine serum (FBS). After centrifugation (1000 rpm, 4 minutes), the pellet was resuspended in 5 mL complete medium and cultured in 25 cm^2 flasks at 37°C with 5% CO_2 until reaching 80% confluency. For subculture, adherent cells were treated with 0.5 mL trypsin-EDTA (0.25% + 1 mM EDTA in PBS pH 7.4) for 3-4 minutes, neutralized with complete medium (1:3 ratio), and centrifuged. The final pellet was resuspended in 2 mL medium for cell counting.

For the assay, cell suspensions were seeded in triplicate in 96-well plates: a T0 plate for baseline reading after 24 hours and a T plate for treatment with four oil concentrations (0.25-250 µg/mL), including blank, negative (untreated cells), and positive (doxorubicin 0.025-25 µg/mL) controls. After 48-hour incubation, medium was aspirated and cells fixed with 100 µL 20% TCA for 1 hour at 4°C. Plates were washed with distilled water, air-dried, and stained with 100 µL 0.4% SRB in 1% acetic acid (30 minutes, light-protected). Excess dye was removed by five 1% acetic acid washes, and SRB-protein complexes solubilized with 200 µL 10 mM Tris base (pH 10.5) for 10 minutes.

The absorbance averages, subtracted from their respective blanks, were calculated: $T > C$ indicated stimulation of cell growth; $T \geq T0 < C$ indicated cytostatic effect; and $T < T0$ indicated cytocidal effect, and the concentration-response curve was established for each cell line using nonlinear regression analysis (sigmoidal fitting), determining three effect levels:

1. GI50: concentration that inhibits 50% of cell growth, calculated using Origin 6.0 Software. Samples with GI50 ≤ 30 µg/mL were classified as highly active (Itharat et al., 2004).
2. TGI: concentration causing total growth inhibition, also calculated in Origin 6.0 Software, considered active when TGI ≤ 50 µg/mL.
3. LC50: concentration causing 50% cell death (Monks et al., 1991).

Absorbance was measured at 540 nm using a microplate reader, and the percentage of cell growth was calculated considering both cytostatic and cytocidal effects.

2.3. Selectivity index

The selectivity index (SI) was calculated as the ratio of the GI50 value of the test sample in normal NIH/3T3 cells to the GI50 value in neoplastic cell lines (SI = GI50 3T3 / GI50 tumor cells). The SI of the EOs was determined as the ratio of CC50 (non-tumor cells) to CI50 (tumor cells), indicating how many times the oil is more selective for a neoplastic lineage than a normal one (Bogo, 2012). According to Suffness and Pezzuto (1991), SI values ≥ 2.0 are significant, but more recent standards consider an oil selective when SI > 10 (Indrayanto et al., 2021).

2.4. Somatic mutation and recombination test (SMART)

Three *Drosophila melanogaster* strains (flr^3, ORR;flr^3, and mwh) carrying specific marker genes on chromosome 3 were used to monitor gene mutations, chromosomal aberrations, and mitotic recombination (Possenti et al., 2005). The genotypes are as follows: flr^3 - flr^3/In(3LR)TM3,ri pp sep l(3)89Aa bx^{34e} e BdS; ORR;flr^3 - (ORR;flr^3/In(3LR)TM3, ri pp sep l(3)89Aa bx^{34e} e BdS); and mwh - mwh/mwh.

Two types of crosses were conducted: Standard Cross (ST) - Virgin females of the flr^3 strain were crossed with mwh males. The progeny from this cross displayed basal levels of enzymatic activity and two types of individuals: MH (marker heterozygotes) and BH (balancer heterozygotes); High Bioactivation Cross (HB) - mwh males were crossed with virgin females of the ORR;flr^3 strain. The ORR strain has a high constitutive level of cytochrome P450 enzymes (CYP6A2), enabling the detection of promutagens requiring bioactivation through cytochrome P450.

Both crosses (ST and HB) produced two types of progeny: MH (marker heterozygotes) - mwh flr^{3+} / mwh$^+$flr^3, with wild-type wing phenotypes; BH (balancer heterozygotes) - mwh flr^{3+} / mwh$^+$ TM3 BdS, with serrated wing phenotypes.

Among the four species analyzed in this study, *Siparuna guianensis* was selected for its high biological potential, identified in previous studies (Ferreira et al., 2019) and preliminary in vitro treatments in this study. Eggs from females of both crosses were collected over 8 hours in glass vials containing a layer of 4% (w/v) agar-agar, covered with live baker's yeast supplemented with sucrose.

After three days, third-instar larvae (72 ± 4 hours) were distributed into vials containing 1.5 g of potato flakes and 5 mL of different concentrations of *Siparuna guianensis* essential oil. Negative controls (ultrapure water, 1% Tween-40, and 3% ethanol) and positive controls (Doxorubicin - DXR at 0.125 mg/mL) were included as follows: Group SG, comprising vials with *Siparuna guianensis* essential oil (OESG) at concentrations of 1.25, 2.5, and 5.0 mg/mL.

The oil was tested in two independent experiments conducted at 25 ± 1°C and approximately 60% humidity. Larvae were allowed to feed until the end of the larval stage (~48 hours). After eclosion, flies were fixed in 70% (v/v) ethanol. Wings with a wild-type phenotype (MH) from both crosses and sexes were removed, mounted on glass slides with Faure's solution (30 g gum arabic, 20 mL glycerol, 50 g chloral hydrate, and 50 mL distilled water), and analyzed under a compound microscope at 400x magnification.

Unique clones (mwh or flr^3) may result from mitotic recombination, mutation, or chromosomal aberrations. Twin spots (mwh and flr^3) are exclusively produced by mitotic recombination between the proximal marker flr^3 and the marker mwh, or between the flr^3 locus and the centromere of chromosome 3. For each treatment, wings of adult trans-heterozygotes for the recessive markers mwh and flr^3 were analyzed.

Trichome analysis on the dorsal and ventral wing surfaces allowed the identification of mutant hair spots (Oliveira, 2003), classified into: (I) Single spots (mwh or flr^3), when only one marker is presente; (II) Twin spots, when both mutant phenotypes — multiple hairs (mwh) and broad-base hairs (flr^3) — are present.

2.5. Data analysis

Cell growth percentage was calculated as described by Monks et al. (1991), and nonlinear regression graphs were generated in Origin 6.0 software to determine GI50 values. Statistical analysis of SMART assay data was performed using chi-square (X^2) tests for proportions, two-tailed, with a significance level of $p \leq 0.05$, comparing frequencies between treated groups and the negative control of each cross.

3. Results

3.1. In vitro antiproliferative activity assessment

Essential oils OEEP (*Endlicheria paniculata*), OESG (*Siparuna guianensis*), OEMG (*Matayba guianensis*), and OECC (*Cymbopogon citratus*) were tested against neoplastic cell lines (MCF7, B16-F10, and U251) and normal cell lines (NIH/3T3 and HUVEC) to evaluate their cytotoxicity. The chemotherapeutic agent Doxorubicin (DXR) was used as the positive control for these experiments. The main results, including GI50, LC50, and TGI values, are summarized in Table 2.

The antitumor activity of the compounds was expressed as GI50, representing the concentration required to inhibit 50% of cell growth. Oils with GI50 values higher than 250 µg/mL were classified as inactive. Among the tested samples, OEEP, OESG, and OEMG demonstrated significant activity against the U251 cell line, with GI50 values ranging from 2.55 to 6.15 µg/mL.

OEEP exhibited selective cytotoxicity, with a GI50 of 2.71 µg/mL for U251 cells, while being inactive against B16-F10 and MCF7. However, it showed cytotoxic effects in the normal cell lines 3T3 and HUVEC. The cytotoxic profile of OEEP, including its GI50, LC50, and TGI values, is visually represented in Figure 1.

OESG demonstrated significant activity against U251 (GI50 = 2.55 µg/mL) and moderate activity against B16-F10 (GI50 = 28.93 µg/mL), while being inactive against MCF7 and the normal cell lines HUVEC and 3T3. These results are detailed in Figure 2, which highlights the cytotoxic selectivity of OESG for tumor cells.

Table 2. Cytotoxic activity and GI50 values (µg/mL) of essential oils from *Endlicheria paniculata* (OEEP), *Siparuna guianensis* (OESG), *Matayba guianensis* (OEMG), and *Cymbopogon citratus* (OECC) against cancer cell lines (B16-F10, MCF7, U251, 786) and normal cell lines (HUVEC and NIH/3T3). GI50 represents the concentration required to inhibit 50% of cell growth, calculated using nonlinear regression analysis (ORIGIN 6.0 software).

	Cell Lines					
Samples	**B16-F10**	**MCF7**	**U251**	**786**	**HUVEC**	**NIH/3T3**
OEEP	>250	>250	2.71	>250	54.54	3.67
OESG	28.93	82.27	2.55	>250	>250	44.32
OEMG	56.24	25.11	6.15	82.89	30	33.52
OECC	67.68	>250	82.94	80.75	24.20	25.57

The concentration that inhibits 50% of cell growth was determined by nonlinear regression analysis using ORIGIN 6.0 software.

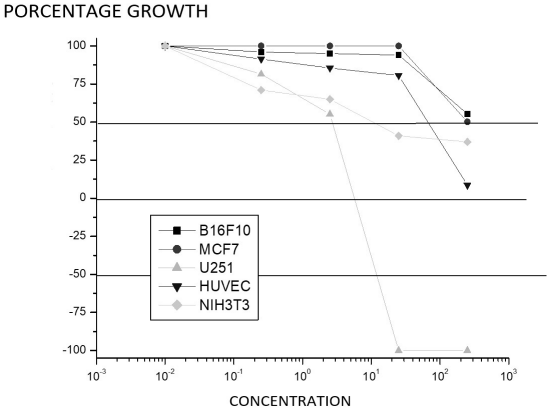

Figure 1. Representation of the antiproliferative activity in B16F10 (murine melanoma), MCF7 (human breast adenocarcinoma), U251 (human glioblastoma), HUVEC (human umbilical vein endothelial cells), and NIH/3T3 (murine fibroblast) treated with OEEP (essential oil of *Endlicheria paniculata*). Results are expressed as the percentage of cell growth as a function of treatment concentration (0.25, 2.5, 25, 250 µg/mL) over 48 hours (log_{10} scale). Software: Origin 6.0.

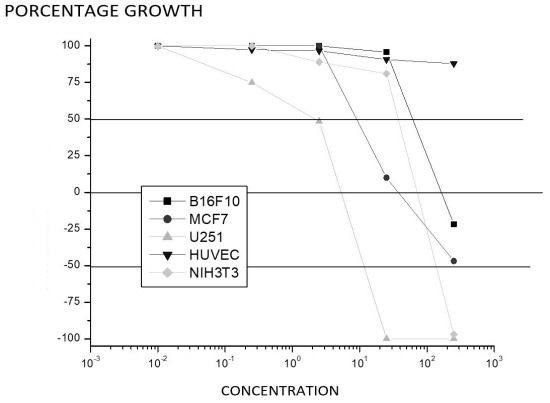

Figure 2. Representation of the antipSroliferative activity in B16F10 (murine melanoma), MCF7 (human breast adenocarcinoma), U251 (human glioblastoma), HUVEC (human umbilical vein endothelial cells), and NIH/3T3 (murine fibroblast) treated with OESG (essential oil of *Siparuna guianensis*). Results are expressed as the percentage of cell growth as a function of treatment concentration (0.25, 2.5, 25, 250 µg/mL) over 48 hours (log_{10} scale). Software: Origin 6.0.

OEMG exhibited antiproliferative activity across all tested cell lines. It showed significant effects against U251 (GI50 = 6.15 µg/mL) and moderate activity against MCF7 (GI50 = 25.11 µg/mL), while demonstrating lower activity against B16-F10, HUVEC, and 3T3. The detailed antiproliferative activity of OEMG is illustrated in Figure 3.

OECC displayed cytotoxic activity exclusively in the normal HUVEC (GI50 = 24.20 µg/mL) and 3T3 (GI50 = 25.57 µg/mL) cell lines, with no significant effects on neoplastic cells. Figure 4 presents the cytotoxic profile of OECC across all tested lines.

The total growth inhibition (TGI) values for the essential oils were also evaluated, with DXR used as the positive control. Oils were considered active if TGI ≤ 50 µg/mL. OEEP demonstrated weak inhibition in normal 3T3 cells (TGI = 41.4 µg/mL), while OESG exhibited potent inhibition exclusively in U251 cells (TGI = 4.02 µg/mL). OEMG showed potent inhibition in U251 cells (TGI = 5.64 µg/mL) and moderate inhibition in MCF7 (TGI = 26.38 µg/mL) and 3T3 (TGI = 46.01 µg/mL). OECC exhibited weak activity only in non-tumoral HUVEC cells (TGI = 25.73 µg/mL). The complete TGI results are outlined in Table 3.

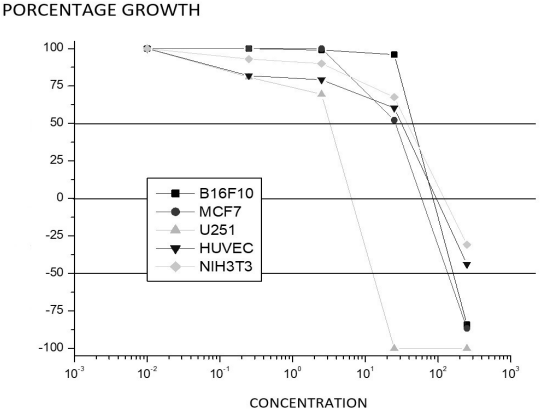

Figure 3. Representation of the antiproliferative activity in B16F10 (murine melanoma), MCF7 (human breast adenocarcinoma), U251 (human glioblastoma), HUVEC (human umbilical vein endothelial cells), and NIH/3T3 (murine fibroblast) treated with OEMG (essential oil of *Matayba* guianensis). Results are expressed as the percentage of cell growth as a function of treatment concentration (0.25, 2.5, 25, 250 µg/mL) over 48 hours (log_{10} scale). Software: Origin 6.0.

Among the tested samples, OEMG demonstrated the most significant overall activity, with potent inhibition in U251 cells and moderate effects on MCF7 and 3T3 lines.

3.2. Selectivity index

The selectivity index (SI) of the essential oils was evaluated to determine their specificity for neoplastic cell lines in comparison to normal cells. None of the four samples exhibited selectivity for the murine B16-F10 cell line, indicating a lack of specificity for this lineage.

For human neoplastic cell lines (MCF7, U251, and 786) compared to the non-tumoral HUVEC line, the results varied among the samples. OEEP showed no selective activity, with low SI values for MCF7 (SI = 0.22), U251 (SI = 0.20), and 786 (SI = 0.22). This suggests that OEEP does not preferentially target tumor cells over normal ones.

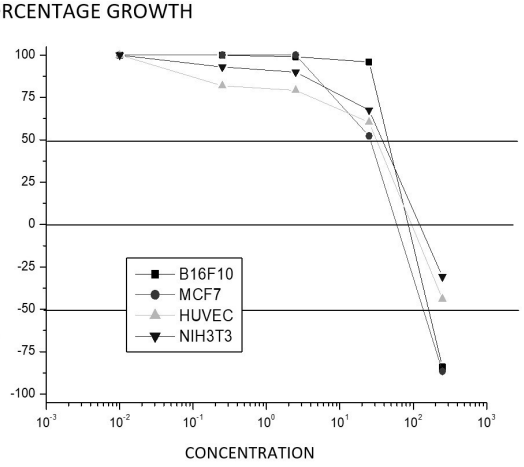

Figure 4. Representation of the antiproliferative activity in B16F10 (murine melanoma), MCF7 (human breast adenocarcinoma), U251 (human glioblastoma), HUVEC (human umbilical vein endothelial cells), and NIH/3T3 (murine fibroblast) treated with OECC (essential oil of *Cymbopogon citratus*). Results are expressed as the percentage of cell growth as a function of treatment concentration (0.25, 2.5, 25, 250 µg/mL) over 48 hours (log_{10} scale). Software: Origin 6.0.

OESG demonstrated significant selectivity for U251 (SI = 264), representing its strongest activity, and moderate selectivity for MCF7 (SI = 8.18). These results indicate that OESG preferentially targets glioblastoma cells while maintaining limited effects on normal cells.

OEMG exhibited moderate selectivity for U251, with an SI of 4.99, but no significant activity for the other cell lines. OECC, on the other hand, showed no selectivity for any of the tested cell lines, with SI values below the threshold for significance.

According to established standards, an SI value ≥ 10 is considered significant for therapeutic relevance. Among the samples, only OESG surpassed this threshold, with its pronounced selectivity for U251. The detailed SI values for all samples and cell lines are summarized in Table 4.

3.3. SMART assay – mutagenic activity

This study evaluated the mutagenic activity of the essential oil of *Siparuna guianensis* (OESG) in vivo using SMART assays on somatic cells of *Drosophila melanogaster*. Three concentrations of OESG (1.25, 2.5, and 5.0 mg/mL) were tested, selected based on preliminary survival tests that ensured suitable tolerance. These tests, summarized in Table 5 and Figure 5, indicate the frequency of genetic damage induced by OESG under standard (ST) and high-bioactivation (HB) conditions.

The survival percentage of adult flies was calculated for each OESG concentration, relative to the total number of flies hatched following larval treatment. Data from both ST and HB crosses revealed no evidence of toxicity at the tested concentrations. The survival rate for the negative control (ultrapure water) was 80%, confirming the validity of the experimental setup.

Microscopic analysis of the wings of 20 individuals (10 males and 10 females) per group, including controls, was conducted to detect mutant spots—categorized as small (MSP), large (MSG), twin (MG), and total (TM). Across all OESG treatments, the frequency of mutant spots did not differ significantly from that of the negative controls in either ST or HB crosses.

In the ST crosses, mutant spot frequencies for the negative control averaged 0.25 per individual, while OESG-treated groups ranged from 0.15 to 0.30. Similarly, in the HB crosses, mutation frequencies ranged from

Table 3. Total Growth Inhibition (TGI) values (µg/mL) of essential oils from *Endlicheria paniculata* (OEEP), *Siparuna guianensis* (OESG), *Matayba guianensis* (OEMG), and *Cymbopogon citratus* (OECC) after 48 hours of exposure to cancer cell lines (B16-F10, MCF7, U251, 786) and normal cell lines (HUVEC and NIH/3T3).

	Cell Lines					
Samples	**B16-F10[b]**	**MCF7[a]**	**U251[a]**	**786[a]**	**HUVEC[c]**	**3T3[d]**
OEEP	362.18 **I**	260.83 **I**	4.16 **P**	250 **I**	265.27 **I**	41.37 **F**
OESG	230.31 **I**	240.73 **I**	4.02 **P**	250 **I**	796.20 **I**	56.80 **I**
OEMG	169.07 **I**	26.38 **F**	5.64 **P**	240.70 **I**	51.43 **I**	46.01 **F**
OECC	227.11 **I**	263.29 **I**	219.20 **I**	221.64 **I**	25.73 **F**	285.23 **I**

TGI values were calculated using nonlinear regression analysis (ORIGIN 8.0 software) and are classified as inactive (I), weak (F), moderate (M), or potent (P) according to CSIR criteria TGI: Total Growth Inhibition after 48 hours of exposure. TGI values were calculated by nonlinear regression analysis using ORIGIN 8.0 (OriginLab Corporation). [a]Human tumor cell line; [b]Murine tumor cell line; [c]Human non-tumoral cell line; [d]Murine normal cell line. CSIR Criteria: inactive (I, TGI > 50 µg/mL), weak activity (F, 15 µg/mL < TGI < 50 µg/mL), moderate activity (M, 6.25 µg/mL < TGI < 15 µg/mL), and potent activity (P, TGI < 6.25 µg/mL).

0.20 to 0.45 in the treated groups, compared to 0.30 in the negative control. These results indicate consistency across both crosses, showing no statistically significant differences ($p \leq 0.05$).

The absence of significant changes in mutant spot frequencies suggests that OESG does not exhibit direct or indirect mutagenic activity. This effect was consistent across both ST crosses, characterized by basal cytochrome P450 levels, and HB crosses, which involved high enzymatic activity related to xenobiotic metabolism.

3.4. SMART assay - genotoxicity

Crosses and treatments with *Siparuna guianensis* essential oil (OESG) did not exhibit statistically significant mutagenic activity, as observed in the SMART assay. However, patterns of mutant spot appearance or suppression varied across the tested concentrations (1.25, 2.5, and 5.0 mg/mL), as illustrated in Graph 1.

Table 4. Selectivity Index (SI) values of essential oils from *Endlicheria paniculata* (OEEP), *Siparuna guianensis* (OESG), *Matayba guianensis* (OEMG), and *Cymbopogon citratus* (OECC) for tumor cell lines (B16-F10, MCF7, U251, 786).

	Cell Lines			
Samples	**B16-F10[a]**	**MCF7[b]**	**U251[b]**	**786[b]**
OEEP	0.01	0.22	0.20	0.22
OESG	1.53	8.18*	264*	1.00
OEMG	0.59	1.22	4.99*	0.36
OECC	0.38	0.09	0.29	0.30

SI values were calculated by comparing the IC50 of normal (HUVEC) and tumor cell lines. Values of SI ≥ 10 are considered significant for therapeutic applications (Indrayanto et al., 2021). [a]Murine tumor cell line; [b]Human tumor cell line; *Significant SI values for ≥ 10 (Indrayanto et al., 2021).

In the standard cross (ST), OESG at 1.25 mg/mL reduced the frequency of small spots (MSP) and total spots (TM) compared to the negative control. At 2.5 mg/mL, an increase in twin spots (MG) was observed, while TM frequencies remained stable. At the highest concentration (5.0 mg/mL), MSP frequencies decreased, while increases were noted in large spots (MSG), MG, and TM.

In the high-bioactivation cross (HB), OESG demonstrated different effects. At 1.25 mg/mL, there was an increase in MSP frequency, a reduction in MSG, and stability in MG and TM compared to the negative control. At 2.5 mg/mL, MSP frequencies increased, while MSG and MG decreased, and TM remained unchanged. At 5.0 mg/mL, MSP frequencies were stable, while MSG, MG, and TM decreased compared to the negative control.

4. Discussion

4.1. In vitro antiproliferative activity and selectivity of the essential oil of Endlicheria paniculata (OEEP)

The species investigated in this study are widely used in traditional medicine in the Brazilian Cerrado and Pantanal regions. However, to date, neither these species nor the genus *Endlicheria* have been studied for antineoplastic activity. In this study, the essential oil of *Endlicheria paniculata* exhibited cytotoxic activity specifically against the U251 neoplastic cell line, while showing no activity in the other tested cell lines. Similar findings were reported by Dantas et al. (2022), who studied *Ocotea minarum*, another Lauraceae species, and found no evidence of cytotoxicity or mutagenicity in most evaluated cell lines. These results reinforce the therapeutic potential of *Endlicheria paniculata*'s selective action against U251 cells.

In another study, Chethankumara et al. (2021) investigated the bark and leaves of *Alseodaphne semecarpifolia*, a

Table 5. Frequencies of mutant spots observed in *Drosophila melanogaster* somatic cells after treatment with different concentrations (0.125, 0.25, 0.50 mg/mL) of *Siparuna guianensis* essential oil (OESG).

		Mutant spots per individual (no. of spots) and statistical diagnosis[a]												Total
Genotypes and Treatments (mg/mL)	**Nº of Ind. (*N*)**	**MSP**			**MSG**			**MG**			**TM[b]**			**Spot mwh[c] (*n*)**
		(1-2 cels)[b] *m* = 2			**(>2 cels)[b] *m* = 5**			***m* = 5**			***m* = 2**			
Cross ST														
OESG [1.25]	20	0.10	(02)	-	0.05	(01)	-	0.00	(01)	-	0.15	(03)	-	3
OESG [2.5]	20	0.15	(03)	-	0.05	(01)	-	0.05	(01)	-	0.25	(05)	-	5
OESG [5.0]	20	0.10	(02)	-	0.10	(02)	-	0.10	(02)	-	0.30	(06)	-	6
Cross HB														
OESG [1.25]	20	0.20	(04)	-	0.05	(01)	-	0.05	(01)	-	0.30	(06)	-	6
OESG [2.5]	20	0.25	(05)	-	0.05	(01)	-	0.00	(00)	-	0.30	(06)	-	6
OESG [5.0]	20	0.15	(03)	-	0.05	(01)	-	0.00	(00)	-	0.20	(04)	-	4

Data are presented for standard (ST) and high-bioactivation (HB) crosses, including comparisons with negative controls (ultrapure water) and positive controls (DXR 0.125 mg/mL). Spot types include small (MSP), large (MSG), twin (MG), and total (TM) spots. MSP, small simple spots; MSG, large simple spots; MG, twin spots; TM, total spots; OESG, essential oil of *Siparuna guianensis*; CN, Negative Control. ST and HB Crosses: *mwh/flr3*. [a]Statistical diagnosis according to Frei and Würgler (1988): -, negative; m, multiplication factor for evaluating significantly negative results. Significance levels $\alpha = b = 0.05$. [b]Includes rare *flr3* simple spots. [c]Considers *mwh* clones for *mwh* simple and twin spots.

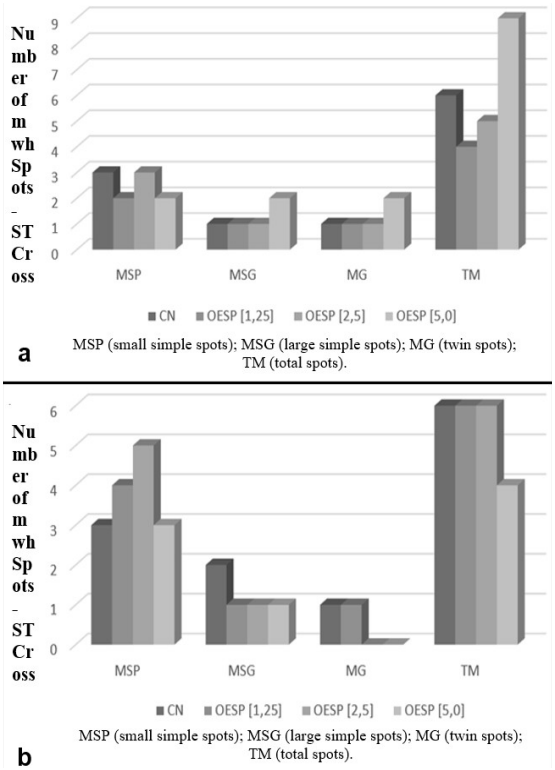

Figure 5. (a) Frequencies of mutant spots in *Drosophila melanogaster* from standard crosses (ST) treated with *Siparuna guianensis* essential oil (OESG); (b) Frequencies of mutant spots in *Drosophila melanogaster* from high-bioactivation crosses (HB) treated with *Siparuna guianensis* essential oil (OESG).

Lauraceae species cultivated in clayey soils of India, and observed selectively toxic activity against the B16-F10 cell line, with low toxicity to normal cells. Comparing this with the results for *Endlicheria paniculata*, which is native to Cerrado soils, it can be inferred that selectivity for specific cell lines may be associated with the metabolites produced, which are influenced by the soil and environmental conditions where the plant grows (Morais et al., 2017).

The GI50 value of the essential oil of *Endlicheria paniculata* was 2.71 µg/mL for the U251 cell line. Unlu et al. (2010) reported anticancer activity of EOs from *Cinnamomum zeylanicum* (Lauraceae) bark, with GI50 values below 20 µg/mL for H-Ras (5RP7) and embryonic fibroblast (F2408) cell lines. This suggests that the essential oil of *Endlicheria paniculata* is approximately 10 times more active than that of *C. zeylanicum* bark.

Lillo et al. (2021), studying secondary metabolites from *Persea lingue* (Lauraceae), observed that the essential oils from its leaves and fruits, containing avocado furans and acetogenins, induced cell death in Jurkat and Katsumi-1 T lymphocyte leukemia cell lines, without significantly affecting normal cells. These findings corroborate this study, which demonstrated the selective cytotoxicity of the essential oil of *Endlicheria paniculata* against U251 neoplastic cells, further emphasizing its therapeutic potential.

4.2. In vitro antiproliferative activity and selectivity of the essential oil of Siparuna guianensis (OESG)

Studies on the species *Siparuna guianensis* and its genus are scarce. In this study, the essential oil of *Siparuna guianensis* exhibited cytotoxic activity against B16-F10 and U251 cell lines but was inactive in normal cells. Cavalieri et al. (2011) investigated α-bisabolol, a sesquiterpene alcohol found in *Siparuna guianensis*, and observed cell growth inhibition in several neoplastic cell lines, including melanoma, breast adenocarcinoma, liver, lung carcinoma, pancreatic cancer, and leukemia, using ethanolic extracts. Similarly, Silva et al. (2020) reported cytotoxic effects of *Siparuna guianensis* essential oil against leukemia cells.

Andrade (2013) found that the essential oil of *Siparuna grandiflora* exhibited cytotoxicity in MCF-7 cells (GI50 = 3.16 µg/mL), identifying compounds such as germacrone, germacrene B, cadinene, trans-β-elemenone, and β-elemene, which are also present in *Siparuna guianensis*. In this study, *Siparuna guianensis* demonstrated comparable GI50 values for B16-F10 (28 µg/mL) and U251 (2.55 µg/mL). Andrade also highlighted the cytotoxic activity of ethanolic extracts of *Siparuna guianensis* leaves in RAW 264.7 murine macrophages.

Grecco et al. (2015) observed that the essential oils from *Siparuna guianensis* leaves contain compounds such as β-myrcene (13.14%) and germacrene-D (8.68%, with 5.16% in this study). Bicyclogermacrene, the major compound in Grecco's study (16.71%) and this study (13.12%), is a sesquiterpene with known cytotoxic activity and may explain the observed effects on B16-F10 and U251 tumor cell lines. This sesquiterpene, common in essential oils, is recognized for its antimicrobial and anti-inflammatory properties (Cascaes et al., 2021), and its cytotoxic potential may contribute to anticancer effects (Abdoul-Latif et al., 2023).

Gonçalves et al. (2012) also reported cytotoxic effects in the essential oil of *Siparuna tortuosum*, attributed to α- and β-pinene, which are also found in *Siparuna guianensis*, supporting the findings of this study. Perés et al. (2009) reported cytotoxic effects in *Piper gaudichaudianum* (Siparunaceae) against normal cell lines, with sesquiterpenes recognized for inhibiting tumor cell lines through allelopathic mechanisms (Silva et al., 2019). The presence of sesquiterpenes in *Siparuna guianensis* may explain its high antineoplastic activity while showing low cytotoxicity in normal cells.

For normal cell lines, *Siparuna guianensis* was not cytotoxic to 3T3 (GI50 = 44.3 µg/mL) and HUVEC (GI50 = 673 µg/mL), whereas *Piper gaudichaudianum* was cytotoxic to V79 cells (GI50 = 2 µg/mL). The essential oil of *Siparuna guianensis* demonstrated selectivity for MCF7 and U251, being more cytotoxic to neoplastic cells than to normal cells.

Espiña (2015) identified pyrimidobenzimidazoles as compounds with selective antitumor effects on MCF-7, suggesting that selective compounds are promising for in vivo studies as they ideally inhibit neoplastic cells without affecting normal cells. Delgado et al. (2020) emphasized that selective molecules remain stable against specific cell types, justifying further research funding for these compounds.

4.3. In vitro antiproliferative activity and selectivity of the essential oil of Matayba guianensis (OEMG)

Limited studies have been conducted on the species *Matayba guianensis*. In their research on bark extracts of *Matayba elaeagnoides* (200 µg/mL), Zandonai (2007) identified diglycoside ethers, termed matayosides, which are also found in *Matayba guianensis* (Bhattacharyya et al., 2017). These compounds exhibit antimicrobial activity and suppress cell growth by activating the intrinsic apoptotic pathway and arresting the cell cycle at the G1 phase. These findings align with the results of the present study, where the essential oil of *Matayba guianensis* demonstrated antiproliferative activity in all tested cell lines.

Pato (2003) reported that lupeol, identified in leaf extracts of *Matayba elaeagnoides*, inhibits the migration of certain inflammatory cells. Similarly, *Matayba guianensis* contains lupeol (Bhattacharyya et al., 2017), which has been shown to suppress neoplastic cells in head and neck cancers (Saleem, 2009), supporting the total growth inhibition observed in two of the three cell lines tested in this study.

The essential oil of *Matayba guianensis* displayed antiproliferative activity across all tested cell lines and exhibited cytotoxicity in 3T3 and HUVEC cells. Studies on essential oils from *Paullinia pinnata* and *Dissotis multiflora*, both from the Sapindaceae family, in Vero cells (normal kidney cell line of *Chlorocebus aethiops*) revealed cytotoxicity in the former and an absence of genotoxic effects in the latter (Afagnigni et al., 2020). Similarly, *Matayba guianensis* demonstrated toxicity in normal cells in this study (HUVEC GI50 = 30 µg/mL and 3T3 GI50 = 33.5 µg/mL), indicating potential risks associated with its use.

In contrast to the current findings, Zhang et al. (2016) in China reported a GI50 of 50 µg/mL for normal REC-293 cells (human embryonic kidney) with no cytotoxic activity. The discrepancies may stem from differences in the tested cell lines and the soil where the plant was cultivated.

Vasconcelos Silva et al. (1999) noted that the chemical composition and yield of essential oils vary throughout the day, influenced by light and water stress, characteristics of the Cerrado biome. Such stress, more prevalent in the Cerrado than in Chinese soils, could explain the greater potency of the *Matayba guianensis* essential oil from the Brazilian Cerrado.

The essential oil of *Matayba guianensis* contains 25 of the 39 identified compounds, with major components including β-caryophyllene (15.45%), germacrene D (28.39%), bicyclogermacrene (31.32%), and germacrene B (5.19%). β-caryophyllene, a selective agonist of the CB2 receptor in the endocannabinoid system, shows promise for treating pain and inflammation (Ricardi et al., 2024) and exhibits anticancer potential by modulating inflammatory responses and promoting apoptosis in cancer cells (Di Sotto et al., 2020; Shabana et al., 2023).

Unlike the essential oil of *Siparuna guianensis* (OESG), the essential oil of *Matayba guianensis* (OEMG) contains high concentrations of germacrene B and D—compounds with anticancer potential that can induce apoptosis and inhibit the proliferation of various cancer cell lines (Zhang et al., 2020). Although research on their anticancer properties is still in its early stages, these compounds, like other sesquiterpenes, have demonstrated cytotoxic effects against tumor cells (Adio, 2009).

The presence of these compounds in the essential oil of *Matayba guianensis* underscores the therapeutic potential of the oil, particularly for anticancer activity, with the greatest efficacy observed in U251 cells.

These findings underscore the importance of investigating the selectivity index of essential oils, particularly in distinguishing cytotoxic effects on tumor versus normal cells. While cytostatic responses may offer therapeutic advantages in certain oncological settings, compounds that also affect non-neoplastic cells must be approached with caution. In the present study, the essential oils of *Siparuna guianensis* and *Matayba guianensis* emerged as the most promising, exhibiting strong antiproliferative activity in tumor cell lines—*S. guianensis* notably with low toxicity in normal cells. Therefore, the extrapolation of these results to practical applications requires further validation through in vivo models and, eventually, clinical trials, to ensure both the efficacy and safety of the compounds under investigation.

4.4. In vitro antiproliferative activity and selectivity of the essential oil of Cymbopogon citratus (OECC)

The compounds α-citral and β-citral found in *Cymbopogon citratus* are well-documented in the literature for their antitumor properties in in vitro studies, demonstrating antineoplastic activity in colorectal cancer cell lines. These include reducing cell confluence, inducing apoptosis, and inhibiting migration in colorectal cancer cells (Ruvinov et al., 2019; Dolghi et al., 2021).

Similarly, Sousa et al. (2010) observed in an in vivo study using *Lactuca sativa* that high concentrations of aqueous extracts of *Cymbopogon citratus* (5, 10, 20, and 30 mg/mL) reduced the mitotic index, seed germination rate, and root development. Aqueous extracts of *Cymbopogon citratus* were also used in in vivo biological assays against the protozoan *Plasmodium*, the malaria parasite, revealing a mitodepressive effect that diminished as extract concentrations decreased (Williams and Omoh, 1996).

Rojas-Armas et al. (2020) reported the cytotoxicity of *Cymbopogon citratus* essential oil against breast cancer (MCF-7), prostate cancer (PC-3), and human glioblastoma (SF-767) cells. They attributed this activity to citral, a characteristic compound of the essential oil, recognized for its antiproliferative activity (Almeida et al., 2018). Comparatively, the results of this study showed that the essential oil was inactive against B16-F10 and MCF7, suggesting that species cultivated at high altitudes in Peru, as in the study by Rojas-Armas et al. (2020), may exhibit compositional variations compared to those grown at sea level, such as in the Cerrado and Pantanal regions.

Gobbo-Neto and Lopes (2007) emphasized that factors such as growth stage, seasonality, rainfall, temperature, and altitude influence the secondary metabolism of plants. For instance, lower temperatures in high-altitude regions significantly affect the levels of secondary metabolites.

Valarini et al. (1996) observed inhibitory effects and total mitotic inhibition of seeds from *Digitaria horizontalis*, *Sorghum halepense*, *Bidens pilosa*, *Euphorbia heterophylla*,

and *Raphanus raphanistrum* with suspensions of *Cymbopogon citratus* essential oil. In another study, Suaeyun et al. (1997) proposed that *Cymbopogon citratus* could act as a protective agent against cancer, observing significant inhibition of cancerous crypts in rodents during both initiation and promotion stages, suggesting its potential to inhibit cell proliferation.

Ruvinov et al. (2019) highlighted *Cymbopogon citratus* as a potential anticancer agent with additive effects when combined with chemotherapeutic drugs, without altering their efficacy. In in vivo studies with mice, *Cymbopogon citratus* polysaccharides were associated with tumor inhibition and stimulation of IL-2, IL-6, IL-12, and TNF-α secretion, whereas in vitro studies did not demonstrate direct cytotoxicity (Bao et al., 2014), aligning with the findings of this study.

4.5. SMART assay – genotoxicity of the essential oil of Siparuna guianensis (OESG)

The genus *Drosophila* is widely used in genetic research due to its low maintenance cost, high reproductive rate, and ease of result analysis (Moratore et al., 2009). In both standard crosses (ST) and high-bioactivation crosses (HB) using the essential oil (OE) of *Siparuna guianensis*, the results indicated an absence of toxic activity, possibly due to the low concentrations of the OE employed. Despite its frequent use in traditional medicine, few studies substantiate the mutagenic or antimutagenic efficacy of *Siparuna guianensis*.

Thomé et al. (2012) evaluated hydroalcoholic extracts of the plant (0.68 to 10.90 mg/plate) and observed no mutagenic activity in non-tumor cells. Studies on *Drosophila melanogaster* involving compounds from *Siparuna guianensis* are scarce, making this study a pioneering contribution with novel data on cytotoxicity and mutagenicity.

Research on the family Siparunaceae has demonstrated significant biological activity for sesquiterpenes such as α-bisabolol, a major component of *Siparuna guianensis* essential oil. Diniz (2014) reported significant growth inhibition in *Rhipicephalus microplus* larvae and females when treated with *Siparuna guianensis* essential oil, highlighting its deleterious effects.

In this study, the highest tested concentration (5.0 mg/mL) showed a slight increase in large simple spots, twin spots, and total spots, which may be attributed to α-bisabolol. According to Amaral et al. (2021), this compound inhibits nitric oxide and prostaglandin production and reduces the expression of certain genes.

Carmona et al. (2017), studying *Peumus boldus* (Siparunaceae), observed that aqueous extracts (2.28 to 9.12 mg/mL) did not induce mutagenic effects in *Drosophila melanogaster*, but reduced mutant spots in somatic cells, indicating desmutagenic effects. The authors associated these antimutagenic effects with antioxidant compounds such as flavonoids and sesquiterpenes present in the family.

In another study, Ferreira et al. (2017) observed that a concentration of 0.08 µg/mL of *Siparuna guianensis* essential oil exhibited repellent effects against larvae and adults of *Galleria mellonella* and *Achroia grisella*, suggesting its potential as a substitute for synthetic insecticides. This indicates that small concentrations of *Siparuna guianensis* essential oil can cause cellular changes, unlike *Cymbopogon. citratus*, which requires higher concentrations for mutagenic or antimutagenic activity.

Ferreira et al. (2019) also reported larvicidal activity of *Siparuna guianensis* essential oil against *Aedes aegypti*, with effects increasing with oil concentration. At lower concentrations, the oil exhibited mitodepressive activity, positioning *Siparuna guianensis* as a promising alternative for larvicide and biological control.

Lourenço et al. (2018) demonstrated insecticidal activity of *Siparuna guianensis* against larvae of *Spodoptera frugiperda* and *Anticarsia gemmatalis*, linking its larvicidal effects to necrosis and apoptosis in vitro. The authors observed inhibition of feeding, larval development, and locomotion, reinforcing the potential of *Siparuna guianensis* in managing lepidopteran pests.

The antimicrobial activity of *Siparuna guianensis* essential oil was also assessed by Andrade (2013), who reported inhibitory effects against fungi (*Aspergillus* and *Penicillium*), but limited effects on Gram-negative bacteria, suggesting selectivity in its antimicrobial properties.

Studies on other Siparunaceae species involving *Drosophila melanogaster* have yielded notable findings. Pina (2016) evaluated ethanolic extracts of *Siparuna poeppigii* (50 µg/mL) and observed only 25% inhibition but a CI50 of 12.41 µg/mL, indicating antiplasmodial activity. While other species in the genus exhibit low cytotoxicity, *Siparuna guianensis* essential oil demonstrated significant results in this study, being considered cytotoxic.

5. Conclusions

The essential oil of *Matayba guianensis* (OEMG) demonstrated the most promising antiproliferative activity among the tested samples, significantly inhibiting the neoplastic cell lines B16-F10, MCF-7, and U251. It also achieved total cell growth inhibition after 48 hours, showing a pronounced effect on the U251 glioblastoma line and moderate effects on MCF-7 breast carcinoma and normal 3T3 cells. Despite its potency, the essential oil of *Matayba guianensis* exhibited cytotoxicity in normal cells as well, highlighting the need for further investigations to optimize its therapeutic index.

The essential oils of *Endlicheria paniculata* and *Siparuna guianensis* also exhibited noteworthy activity against U251 cells. However, *Endlicheria. paniculata* and *Cymbopogon citratus* displayed cytotoxic effects primarily in normal 3T3 and HUVEC cells, indicating limited tumor specificity. None of the oils demonstrated selectivity toward the murine B16-F10 melanoma cell line. In contrast, *Endlicheria paniculata* showed preferential activity against human breast carcinoma (MCF-7) and glioblastoma (U251) cells, underscoring its potential for targeted cancer therapies.

Overall, the essential oils of *Matayba guianensis* and *Siparuna guianensis* demonstrated significant antitumor potential, warranting further studies to elucidate their mechanisms of action and evaluate their clinical applicability as therapeutic agents.

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Data Availability Statement

This research did not produce novel raw datasets; all findings are comprehensively reported in this paper. Thus, a statement on data availability is not applicable.

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