



Systematic Review

Activity of Brazilian Cerrado Plants in Tumor Cell Lines: A Systematic Review



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Abstract

Background and objectives: Medicinal plants have been recognized as a promising alternative treatment against some types of cancer, being rich sources of effective biochemical agents. The aim of this study, therefore, was to gather, through a systematic literature review, articles related to plants from the Brazilian Cerrado biome that have an action on different tumor cells.

Methods: Different keywords were used in the search mechanisms of Pubmed, Scielo, Science Direct, Scopus, and Lilacs databases. Of the studies found, titles that did not reflect the purpose of this review, those that did not provide access to the full text, and those that were published before 2005 were excluded. Articles referring to the activity of Cerrado plants in tumor cells published in the last sixteen years were selected, totaling thirty-nine articles. Registration number of this review: #CRD42020205579.

Results: The extracts from the studied plants demonstrated significant antiproliferative effects against several tumor cell lines. 39 species of plants were identified belonging to the families: Combretaceae, Annonaceae, Celastraceae, Verbenaceae, Solanaceae, Myrtaceae, Rubiaceae, Bignoniaceae, Erythroxylaceae, Sapotaceae, Asteraceae, Elaeocarpaceae, Apocynaceae, Anacardiaceae, Calophyllaceae, Lythraceae, Mimosaceae, and Morseraceae. The extracts were obtained from different parts of the plants and different fractions were used.

Conclusion: It can be concluded that the Cerrado contains a wide variety of plants with antitumor actions, and further studies are needed to discover other species with anticancer potential, in addition to *in vivo* studies.

Introduction

Cancer is characterized by uncontrolled cell growth or cell proliferation capable of invading other tissues. There are approximately one hundred types that are named for the tissue, organ, or cell type in which the disease begins. Chemicals, radiation, inadequate diet, infection, environmental factors, and smoking are some of the main risk factors.¹ The disease is a relevant problem for public health and the treatment represents an obstacle, as it is often unsuccessful. It is considered the main cause of death in developed

countries and the second in developing countries, leading to a considerable increase in health costs and the great need for a better understanding of its mechanisms to control the disease through the development of more effective therapies.^{2,3}

Concerning cancer treatment, medicinal plants represent a promising alternative. These are a source of important bioactive molecules with wide structural diversity that generally demonstrate less toxicity and greater selectivity against tumor cells.⁴ Furthermore, they have also been shown to decrease the side effects induced by synthetic drugs and increase the survival rate for many patients.⁵ Moreover, it is recognized that many natural products have a rich chemical diversity, being a source for the identification of new structures and, consequently, for the manufacture of new drugs.⁶ Currently, the sources of natural products used for developing drugs against cancer include, in addition to plants, marine organisms and microorganisms, being more diversified now than in the past. However, plants remain a promising source of natural products for chemoprevention, as about 25% of currently available therapies derive from plants.^{7,8}

Keywords: Cerrado; Medicinal plants; Cancer; Tumor cell.

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The Cerrado, known as the “Savanna of the Tropical Lands”, is a Brazilian biome that occupies about 20% of the national territory. The vegetation, quite heterogeneous, with taxonomic biodiversity that is even greater than that of the Amazon Forest, occurs especially in the states of Mato Grosso, Goiás, Minas Gerais, São Paulo, and Ceará. The region is considered a global biodiversity hotspot and contains several plant species that are widely used in folk medicine and scientific research. Due to its considerable diversity, there is a growing interest in the Cerrado regarding the discovery of new medicinal plants with bioactive compounds (<http://www.mma.gov.br/biomas/Cerrado>).^{9,10} The species present in the biome are already used by local communities for the treatment of several diseases and research with biological models has already demonstrated the promising potential of several molecules from these species.¹¹ The beneficial action of its plants has already been proven in inflammatory processes against microorganisms and cancer, among other diseases.¹²

The search for new drugs that exhibit action against various types of tumors is one of the most interesting topics in the field of natural product research.¹³ In this area, plants are considered very promising, since their derivatives are widely used for cancer control. An example is *Catharanthus roseus* (Apocynaceae), a plant from which Vinblastine (Velban®) and Vincristine (Oncovin®) were isolated and used in the treatment of various types of tumors.¹⁴ Interruption of the cell cycle, induction of apoptosis, and inhibition of angiogenic factors in cancer cells are important effects associated with these plant-based drugs.¹⁵ In this sense, the Cerrado stands out, as many compounds with important biological activities have already been obtained from plants in this biome.¹³

Given the importance of the above subject, this study aimed to gather and discuss, through a systematic literature review, articles related to plants from the Brazilian Cerrado biome that have action on different tumor cells.

Methods

The present systematic review is registered in the PROSPERO database (International Prospective Register of Systematic Reviews) under registration number #CRD42020205579.

Types of study

Articles related to the effects of plants from the Brazilian Cerrado biome on human and animal tumor cells that used plausible control groups for the study (untreated, vehicle, treated vehicle, and standard chemotherapeutics), *in vitro*, published between 2005 and 2020, in English or Portuguese languages were included. Methods, time, and concentration of extracts/compounds were not considered. The information about the plants gathered in this article includes species, popular name, part of the plant used, type of extract, target cell, probable main active of the extracts, and mode of action.

Search strategy

Our research on the action of Brazilian Cerrado plants on tumor cells was carried out using Pubmed, Science Direct, and Scopus. Date filter (2005–2020), full text, and article type (research articles) were applied. The search included free text and medical subject heading terms: 1) Cerrado plants and Tumor Cell Lines; 2) Medicinal Plants and Cerrado and Tumor Cell Lines; 3) Medicinal Herbs and Cerrado and Tumor Cell Lines; 4) Phytotherapy and Cerrado and Tumor Cell Lines, and 5) Pharmaceutical Plants and

Cerrado and Tumor Cell lines. The last survey update was in January/2021 (Fig. 1).

Results

A total of 225 scientific articles were selected from the five databases consulted. After excluding duplicate titles, unrelated abstracts, and “not open access” articles, 35 articles remained. After a free search, 4 articles were included, totaling 39 scientific articles. Thirty-nine plant species are cited, along with the popular name, part of the plant used, type of extract, target cell, and reference (Table 1).^{8,12,16–53} The species are distributed among 33 genera and 20 families. The families include: Combretaceae (*Terminalia fagifolia*), Annonaceae (*Annona coriacea*, *Annona crassiflora*, *Cardiopetalum calophyllum*), Celastraceae (*Austroplenckia populnea*, *Salacia crassifolia*, *Maytenus ilicifolia*), Verbenaceae (*Lippia salviaefolia*), Solanaceae (*Solanum lycocarpum*), Myrtaceae (*Myrcia falax*, *Myrcia bella*, *Campomanesia adamantium*, *Myrcia guianensis*, *Psidium guineense*), Rubiaceae (*Palicourea rigidum*, *Ixora brevifolia*), Bignoniaceae (*Pyrostegia venusta*, *Tabebuia avellanadae*), Erythroxylaceae (*Erythroxylum suberosum*, *Erythroxylum daphnites* and *E. subrotundum*), Sapotaceae (*Pouteria pie*, *Pouteria ramiflora*), Asteraceae (*Calea pinatifida*, *Chresta sphaerocephala*, *Eremanthus matogrossensis*, *Eremanthus seidelii* and *Lychnophora trichocarpha*), Elaeocarpaceae (*Sloanea garckeana*), Apocynaceae (*Calotropis procera*), Anacardiaceae (*Anacardium humile*), Calophyllaceae (*Kielmeyera coriacea*), Lythraceae (*Lajfoensia pacari*), Mimosaceae (*Mimosa caesalpiniiifolia*), Burseraceae (*Protium ovatum*), Fabaceae (*Senna velutina*, *Dipteryx alata* Vog, *Stryphnodendron adstringens* and *Zornia brasiliensis*) and Moraceae (*Brosimum gaudichaudii*) (Table 1).

The major components of the extracts and probable mode of action on tumor cells are presented in Table 2. In general, the major effects of plant compounds are on the modulation of the cellular cycle (proliferation, DNA synthesis, and apoptosis) of tumor cell lines. Some compounds (flavonoids) have free radicals scavenging and antioxidant capacities (Table 2, Fig. 2).^{16,18–21,24–26,30,31,33,36–46,48–53}

All plants and their main information (photos, geographic distribution, *etc.*) can be found on the main platform: <http://florado-brasil.jbrj.gov.br>.

Discussion

A total of thirty-nine species of medicinal plants from the Brazilian Cerrado biome that have antitumor properties were identified. The species are distributed among 33 genera and 20 families. In most previous studies leaves were used to carry out the tests, and their use as sources of active compounds is a relevant strategy for the sustainable management of endemic species, since it does not compromise the survival of the species.⁵⁴ In addition to the leaves, stem, trunk bark, root bark, flowers, fruits, seeds, essential oils, and isolated compounds were also used. It must be considered here that different parts of the same plant can synthesize and accumulate different secondary metabolites or different amounts of a certain compound.⁵⁵

The main compounds responsible for the antitumor potential and for several other pharmacological activities, such as antimicrobial, antioxidant, anti-inflammatory effects against intestinal and respiratory diseases include cardiotonic glycoside steroids (*C. procera*), phenolic compounds and tannins (*A. humile*), al-

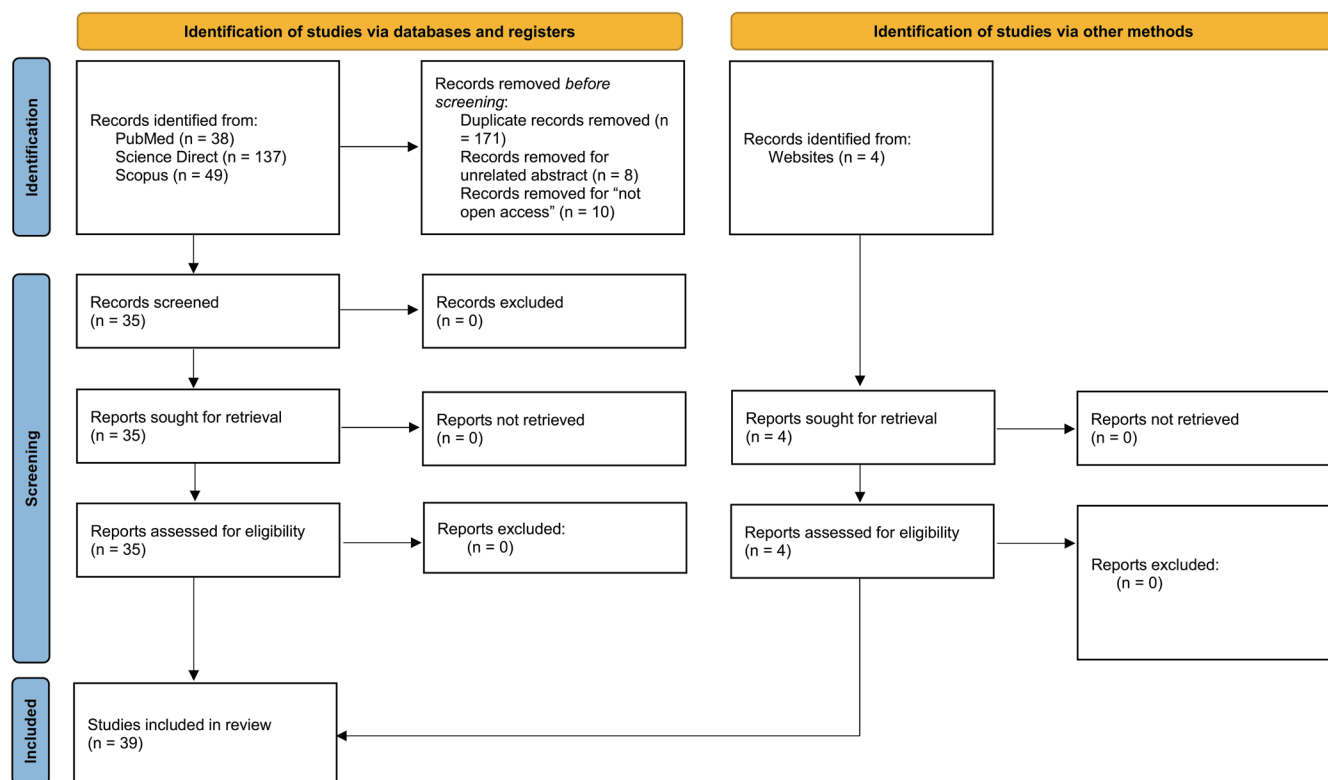


Fig. 1. Flowchart of study selection.

kaloids (*S. lycocarpum*), phenolic acids (*A. coriacea*), flavonoids - quercetin (*A. crassiflora*), triterpenes (*M. ilicifolia*, *P. torta*, *C. sphaerocephala*), sesquiterpenes – germacranolides - (*C. pinatifida*), flavonoids (*E. suberosum*, *A. populnea*, *A. coriacea*, *T. avellanadae*, *L. salviaefolia*, *C. procerca*; *E. suberosum*; *M. caesalpiniifolia*, *M. bella*, *M. falax*, *S. velutina*; *E. subrotundum*, *P. ramiflora*), spathulenol, germacrene-B and β -caryophyllene oxide (*C. adamantium* leaves); spathulenol, β -caryophyllene, and β -myrcene (*P. ovatum* leaves); β -myrcene, α -pinene and limonene (*P. ovatum* green fruits), spathulenol, viridiflorol, and (Z,E)-farnesol (*C. calophyllum* leaves), oleic acid and phenolic compounds - gallic acid (*D. alata* Vog., *S. adstringens*), sesquiterpene lactones (*L. trichocarpha*, *E. matogrossensis*; *E. seidelii*), triterpenes (*E. daphnites*), catechins (*E. suberosum*), lignan syringaresinol and cyclopeptide alkaloids (*I. brevifolia*), D- germacrene, neo-intermedeol, bicyclogermacrene, Viridiflorol, Globulol, Epi- α -muurolol and δ -cadinene (*K. coriacea*), δ -tocotrienol and its dimer (*K. coriacea*), 1-cicosanol, 1-docosanol, and 2- nonadecane (*K. coriacea*), ellagic acid and others (*L. pacari*), isomers of galoyl glucose (*M. guianensis*), monoterpene indole alkaloid (*P. rigida*), sesquiterpene alcohol spathulenol (*P. guineense*), alkane (*P. venusta*), triterpenes, quinonamethides (*S. crassifolia*), phenolic compounds (*S. garckeana*, *S. adstringens*; *T. fagifolia*; *Z. brasilienses*), polyphenols (*S. adstringens*) and zornioside (*Z. brasilienses*).

Of all the compounds with antitumor properties presented above, flavonoids appear most frequently. The anticancer action of flavonoids occurs through their effect on the scavenging of free radicals, DNA repair, and stimulation of the immune system.⁸ In general, the compounds present different modes of action: 1) Arrest of cell cycle progression/induction (triterpenes, gallic acid,

element-type sesquiterpenes, δ -tocotrienol and dimer, ellagic acid, monoterpene indole alkaloid, alkanes)^{20,25,31,33,41,42,45}; 2) Inducer apoptosis (sesquiterpenes, cardiotoxic glycoside steroids, Triterpenes, δ -tocotrienol and dimer, elagitannins, pristimerin, alkanes, alkaloids)^{20,21,25,31,33,38,42,45}; 3) Inhibition of nuclear factor kappa B (sesquiterpenes, gallotannins)^{20,52}; 4) Inhibition of DNA synthesis (sesquiterpene lactones, pristimerin),^{37,38} and 5) DNA repair (flavonoids).¹⁶ Table 2 presents the major component of the species and the probable mode of action in inhibiting tumor cells. It is noteworthy that plant extracts have thousands of active compounds; here we have gathered just a few of the compounds that were identified in the research.

Cancer cell lines used in previous research include breast, brain, colon, lung, blood, skin, liver, kidney, prostate, ovary, mouth, larynx, and stomach cells, the majority of which are of human origin. According to Caneschi *et al.*¹⁹ and as mentioned by Liu *et al.*,⁵⁶ some cell types, such as lung and breast, are more frequently used because they are widely studied in research involving analysis. cytotoxic and because they can be easily used for comparison with different compounds. Regarding the nature of the study, the research used *in vitro* assays, or more specifically, cell culture. This is an accepted substitute for animal models as its application reduces the number of animal experiments, which is a relevant characteristic of this method.⁵⁷ Furthermore, these methods are inside the 3Rs principles: replacement, reduction, and refinement, providing stimulation for alternative research, reduction of the use of animals, and an ethical framework for researchers.^{58,59}

Regarding the type of extract, we can verify that ethanolic, methanolic, phenolic, hexane, aqueous, chloroform, hydroalcoholic, hydroethanolic, heptanoic, glycoalkaloid, ethyl acetate,

Table 1. Description of details about plant species of Brazilian Cerrado, popular name, parts used, type of extract (fraction), tumor cell lines, and references

Species	Popular name	Used part of the plant	Extract type	Target cell	References
<i>Anacardium humile</i> <i>Brosimum gaudichaudii</i> <i>Tabebuia avellanedae</i>	'Cajuzinho' 'Inharé' 'Purple ipé'	Bark (c) and leaves (f) Bark (c) and leaves (f) Bark (c) and leaves (f)	Ethanollic	NCI-H292 (lung) (-) HEp-2 (larynx) (-) HT-29 (colon) (-) HL-60 (promyelocytic leukemia) (-) MCF-7 (breast) (C, F,+) NCI-H292 (F,+), HEP-2 (-) HT-29 (F,+), HL-60 (-) MCF-7 (C,+) NCI-H292 (-), HEP-2 (F,+) HT-29 (-), HL-60 (F,+) MCF-7 (-)	16
<i>Annona coriácea</i>	'Marola' 'Araticum-liso'	Seeds	Methanollic	UACC-62 (melanoma), MCF-7 (breast), NCI/ADR/RES (ovary), 786-O (kidney), NCI-H460 (lung), OVCAR-3 (ovary), HT-29 (colon), K562 (leukemia), UA251 (glioma) (+)	17
<i>Annona crassiflora</i>	'Araticum'	Seeds and bark	Phenolic	NCI/ADR/RES (ovary) (+) U251 (glioma) (+) MCF-7 (breast) (+) NCI-H460 (lung) (-) PC-3 (prostate) (+) OVCAR-03 (ovary) (+) HT-29 (colon) (+) K562 (leukemia) (+)	18
<i>Austroplenckia Populnea</i>	'Mangabarana' 'Marmelo-do-campo' 'Mangabeira-brava'	Fruit	Pure compounds (proanthocyanidin A and 4'-O-methyl-epigallocatechin) Three pure extracts (ethanol, ethyl acetate and chloroform)	A549 (lung) (+) H5578T (breast) (+) MCF-7 (breast) (+) A549 (-) H5578T (-), MCF-7 (-)	19
<i>Calea pinnatifida</i>	'Quebra-tudo' 'Cipó-cruz' 'Aruca'	Leaves	Dichloromethane	UACC-62 (melanoma) (+) MCF-7 (breast) (+) 786-O (kidney) (+) NCI-ADR/RES (ovary) (+) NCI-H460 (lung) (+) PC-3 (prostate) (+) OVCAR-3 (ovary) (+) HT29 (colon) (+) K-562 (leukemia) (+)	20
<i>Calotropis procera</i>	'Algodão de seda' 'Leiteiro' 'Queimadeira' 'Ciúme'	Bark	Ethyl acetate, acetone Hexane, methanollic dichloromethane	B-16/F10 (melanoma - murine) (+) HCT-8 (human colon) (+) CEM (human leukemia) (+) B-16/F10 (-) HCT-8 (-) CEM (-)	21

(continued)

Table 1. (continued)

Species	Popular name	Used part of the plant	Extract type	Target cell	Refer-ences
<i>Campomanesia adamantium</i>	'Guavira'	Leaves	Essential oil	MCF-7 (breast) (+)	22
<i>Cardiopetalum calophyllum</i>	'Imbirinha'	Leaves		HeLa (cervical) (+)	
<i>Protium ovatum</i>	'Almecega'	Leaves		M059J (glioblastoma) (+)	
		Green fruits		MCF-7 (+), HeLa (+), M059J (+) MCF-7 (-), HeLa (-), M059J (+) MCF-7 (-), HeLa (-), M059J (-)	
<i>Chresta sphaerocephala</i>	'João-bobo'	Leaves	Hexanic (L)	U251 (glioma) (+), UACC-62 (melanoma) (+)	12
		Bark (B)	Hexanic (B)	MCF7 (breast) (-), NCI-ADR/RES (ovary) (+)	
			Methanolic	786-0 (kidney) (+), NCI-H460 (lung) (+)	
			Ethyl acetate	OVCAR-3 (ovary) (+), PC-03 (prostate) (+)	
				HT29 (colon) (+) e K-562 (leukemia) (+)	
				U251 (-), UACC-62 (+), MCF-7 (+)	
				NCI-ADR/RES (-), 786-0 (-), NCI-H460 (-)	
				OVCAR-3 (+), PC-3 (+), HT29 (-), K-562 (+)	
				Showed no antiproliferative effect	
				Showed no antiproliferative effect	
<i>Dipteryx alata</i> Vog.	'Barú'	Seeds	Phenolic	HT29 (colon) (+)	23
<i>Eremanthus matogressensis</i>	Uninformed	Leaves	Isolated compound	T98G (+) e U87MG (+) (glioblastoma)	24
<i>Eremanthus seidelii</i>	Uninformed	Leaves	isolated compound	T98G (-), U87MG (-)	
<i>Erythroxylum daphnites</i>	'Fruta-de-pomba'	Leaves	Hexanic	SCC-9 (oral) (+)	25
<i>Erythroxylum daphnites</i>	'Mercurinho'	Leaves	Aqueous	FaDu (-), SCC-25 (-), SCC-9 (-)	26,27
<i>Erythroxylum suberosum</i>	'Fruta-de-veado'	Leaves	Ethanollic	FaDu (-), SCC-25 (-), SCC-9 (-)	
<i>Erythroxylum subtrotundum</i>		Leaves	Hexanic	FaDu (-), SCC-25 (+), SCC-9 (+)	
<i>Pouteria ramiflora</i>		Leaves	Aqueous	FaDu (+), SCC-25 (+), SCC-9 (-)	
<i>Pouteria torta</i>		Leaves	Ethanollic	FaDu (+), SCC-25 (-), SCC-9 (-)	
			Hexanic	FaDu (+), SCC-25 (-), SCC-9 (+)	
			Aqueous	FaDu (-), SCC-25 (-), SCC-9 (-)	
			Ethanollic	FaDu (+), SCC-25 (-), SCC-9 (-)	
			Hexanic	FaDu (+), SCC-25 (-), SCC-9 (-)	
			Hexanic	FaDu (+), SCC-25 (-), SCC-9 (-)	
<i>Erythroxylum suberosum</i>	'Cabelo-de-negro'	Leaves	Aqueous	SCC-25, SCC-9 (tongue)/FaDu (hypopharynx)	28
			Ethanollic	FaDu (+), SCC-25 (-), SCC-9 (-)	
			Hexanic	FaDu (+), SCC-25 (-), SCC-9 (-)	
			Hexanic	FaDu (-), SCC-25 (-), SCC-9 (-)	
<i>Ixora brevifolia</i>	'Ixora-arborea'	Twigs	Crude and hydroethanolic extract, hexanic	SCC-9 (oral) (+) FaDu (hypopharynx) (+) SCC-9 (-), FaDu (+) SCC-9 (-), FaDu (-)	29

(continued)

Table 1. (continued)

Species	Popular name	Used part of the plant	Extract type	Target cell	References
<i>Kielmeyera coriacea</i>	'Pau-santo'	Fruits and Leaves	Essential oil	MDA-MB-231 (breast) (+) DU-145 (prostate) (+) MDA-MB-231 (-) DU-145 (-)	30
<i>Kielmeyera coriacea</i>	'Pau-santo'	Root bark	Hexanic	HL-60 (leukemia) (+) HCT-8 (colon) (+) MDA-MB-435 (breast) (+) SF-295 (glioblastoma) (+)	31
<i>Kielmeyera coriacea</i>	Uninformed	Leaves	Chloroform Hydroalcoholic Ethyl acetate Hexanic Heptane	B16F10-Nex2 (melanoma murino) (+) HCT (colon) (+), Siha (cervical) (+) A2058 (melanoma) (+), SKmel28 (melanoma) (+) and MeWO (melanoma) (+) B16F10-Nex2 (-) B16F10-Nex2 (-) B16F10-Nex2 (-) B16F10-Nex2 (-)	32
<i>Lafoensia pacari</i>	'Dedaleira' 'Mangava-brava'	Stem bark	Methanolic	TRH- 18 (+) (colorectal)	33
<i>Lafoensia pacari</i>	'Dedaleira' 'Mangava-brava'	Stem bark	Ethanollic	H460 Human NSCLC (lung) (+) A549 (NSCLC, adenocarcinoma) (+) H2023 (NSCLC, adenocarcinoma) (+) E9 murina (lung) (+)	34
<i>Lafoensia pacari</i>	'Dedaleira' 'Mangava-brava'	Stem bark	Methanolic and fractions	U-937 (+), Jurkat Daudi (leukemia) (+)	35
<i>Lippia salviaefolia</i>	Uninformed	Aerial parts	Aromadendrin Phloretin	HEK-293 (kidney) (-) M14 (melanoma) (+) HEK-293 (+)	36
<i>Lychnophora trichocarpa</i> Spreng.	'Arnica brasileira'	Aerial parts	Ethanollic Lychnopholide	30 human tumor cell lines	37
<i>Maytenus ilicifolia</i>	'Espinheira santa'	Root bark	Ethanollic	HL-60 (leukemia) (+) K-562 (chronic myelocytic leukemia) (+) SF-295 (glioblastoma) (+) HCT- 8 (colon) (+) MDA/MB-435 (melanoma) (+)	38
<i>Mimosa caesalpinjifolia</i>	'Sabiá' 'Sansão-do-campo'	Leaves	Ethanollic	MCF-7 (breast) (+)	39

(continued)

Table 1. (continued)

Species	Popular name	Used part of the plant	Extract type	Target cell	References
<i>Myrcia bella</i>	'Mercurinho'	Leaves	Hydroalcoholic	ACP02 (gastric) (+)	40
<i>Myrcia bella</i>	'Jacarezinho'	Leaves	Hydroethanolic	K562 (+), MCF-7 (+), 786-0 (-), NCI-H460 (-)	27,41
<i>Myrcia faxax</i>	Uninformed	Leaves		PC-3 (-), HT-29 (-)	
<i>Myrcia guianensis</i>	Uninformed	Leaves		K562 (+), MCF-7 (-), 786-0 (-), NCI-H460 (-)	
				PC-3 (-), HT-29 (-)	
<i>Palicourea rigida</i>	'Douradão'	Leaves	Ethanolic extract (isolated compound)	K562 (leukemia) (+), MCF-7 (breast) (+) 786-0 (kidney) (-), NCI-H460 (lung) (-) PC-3 (prostate) (-), HT-29 (colon) (-)	42
<i>Pouteria torta</i> ^a	'Guapeva'	Leaves	Hexanic Ethanolic Aqueous	OSCC-3 (oral) (+) MCF-7 (breast) (+) OSCC-3 (+) MCF-7 (+) OSCC-3 (+) MCF-7 (+)	43
<i>Psidium guineense</i>	'Goiabinha-araçá' 'Araçá-do-campo' 'Araçá verdadeiro' 'Goiabinha selvagem'	Leaves	Essential oil	OVCAR-3 (ovary) (+) U251 (glioma) (+), MCF-7 (breast) (+) NCI-ADR/RES (ovary) (+), 786-0 (kidney) (+) NCI-H460 (lung) (+), PCO-3 (prostate) (+) HT-29 (colon) (+), K-562 (leukemia) (+)	44
<i>Pyrostegia venusta</i>	'St. John vine'	Flowers	Heptane Hydroalcoholic	B16F10-Nex2 (murine melanoma) (+) B16F10-Nex2 (-)	45
<i>Salacia crassifolia</i>	'Bacupari-do-Cerrado' 'Saputá' 'Seputá'	Stem bark	Hexanic Dichloromethane Ethyl acetate Hydroalcoholic Hexanic Dichloromethane Ethyl acetate Hydroalcoholic Hexanic Dichloromethane Ethyl acetate Hydroalcoholic	MDA-MB-435 (melanoma) (+) MDA-MB-435 (-) MDA-MB-435 (-) MDA-MB-435 (-) HCT-8 (colon) (+) HCT-8 (-) HCT-8 (+) HCT-8 (-) SF-295 (central nervous system) (+) SF-295 (-) SF-295 (-) SF-295 (-)	46

(continued)

Table 1. (continued)

Species	Popular name	Used part of the plant	Extract type	Target cell	References
<i>Salacia crassifolia</i>	'Bacupari-do-Cerrado'	Root wood	Hexanic	Colo205 e KM12 (colon) (+) A498 e U031 (kidney) (+) HEP3B and SKHEP (liver) (-) MG63 and MG63.3 (osteosarcoma) (+)	47
<i>Senna velutina</i>	'Fedegão'	Leaves	Ethanollic	Jurkat (+) e K562 (+) (leukemia)	27,48
<i>Solanum lycocarpum</i>	'Fruit-of-wolf' 'Lobeira' or 'Jurubebão'	Fruit	Glycoalkaloid	HepG2 (liver) (+) B16F10 (murine melanoma) (+) HT29 (colon), MCF-7 (breast) (+) Hela (cervical) (+), HepG2 (liver) (+) MO59J, U343 e U251 (glioblastoma) (+)	49
<i>Sloanea garckeana</i> ^a	'Urucurana Brava'	Leaves	Methanolic Hexanic Chloroform Ethyl acetate	UACC-62 (melanoma) (+), NCI-460 (lung) (+) MCF-7(breast) (+), NCI-ADR (breast) (+) HT-29 (colon) (+), OVCAR (ovary) (+) C786-0 (kidney) (+) e PCO-3 (prostate) (+)	50
<i>Stryphnodendron adstringens</i>	'Barbatimão' or 'Casca-da-mocidade'	Stem bark	Aqueous	B16F10Nex-2 (melanoma) (+)	51
<i>Terminalia fagifolia</i>	'Capitão-do-mato' 'Mirindiba' 'Pau-de-bicho'	Bark and leaves	Ethanollic	PC3 (prostate) (+) B16F10 (murine melanoma) (+)	52
<i>Terminalia fagifolia</i>	'Capitão' 'Capitão -do-Cerrado' 'Capitão-do-campo' 'Mirindiba'	Stem bark	Ethanollic and fractions	MCF-7 (breast) (+)	8
<i>Zornia brasiliensis</i>	'Urinária' 'Urinana' 'Carrapicho'	Aerial parts	Ethanollic	HL60 (promyelocytic leukemia) (+) MCF-7 (breast) (-) HCC1954 (breast) (-) T-47D (breast) (-) 4T1 (breast) (-) HL60 (promyelocytic leukemia) (-)	53

Data set from all relevant studies. ^aSource: <https://www.sibbr.gov.br/>. (+), effect on tumor cells; (-), null or very low effect.

Table 2. Description of details of Brazilian Cerrado plant species, major compounds, and probable mode of action

Species	Compound and mode of action	References	
<i>Anacardium humile</i>	Phenolic compounds - free radical scavenging (<i>A. humile</i>) (<i>T. fagifolia</i>)	16,50,53	
<i>Erythroxylum suberosum</i>	Flavonoids - free radical scavenging, prevention of cancer progression, DNA repair and stimulation of the immune system, and an ability to effect the pathway that regulates cell growth and proliferation and tumor formation (<i>T. avelanadae</i>)		
<i>Myrcia falax</i>			
<i>Sloanea garckeana</i>			
<i>Tabebuia avellanadae</i>			
<i>Terminalia fagifolia</i>			
<i>Zornia brasiliensis</i>			
<i>Annona crassiflora</i>	Flavonoids - antioxidant; free radical scavenging, DNA repair, and immune system stimulation		16,18,19, 36,40,48
<i>Austroplenckia populnea</i>			
<i>Brosimum gaudichaudii</i>			
<i>Lippia salviaefolia</i>			
<i>Myrcia bella</i>			
<i>Senna velutina</i>			
<i>Calea pinnatifida</i>	Sesquiterpenes (germacranolides) - potent induction of apoptosis and inhibition of nuclear factor kappa B	20	
<i>Calotropis procera</i>	Cardiotonic glycoside steroids - activation of apoptotic pathways	21	
<i>Chresta sphaerocephala</i>	Triterpenes - inhibition of tumor growth and cell cycle progression and	25,43,46	
<i>Erythroxylum daphnites</i>	induction of apoptosis of tumor cells <i>in vitro</i> and <i>in vivo</i>		
<i>Erythroxylum subrotundum</i>			
<i>Pouteria ramiflora</i>			
<i>Pouteria torta</i>			
<i>Salacia crassifolia</i>			
<i>Dipteryx alata</i>	Phenolic compounds		
<i>Myrcia spp</i>	Gallic acid (GA) - regulation of several signaling pathways; inhibit proliferation Gallotannins (GT) - suppression of NFkB activation induced by tumor necrosis factor (TNF-α) Antioxidants		
<i>Eremanthus matogressensis</i>	Sesquiterpene lactones (goyazensolide and lychnofolide) - possible interference in angiogenesis internally		24
<i>Eremanthus seidelii</i>	and in tumor microenvironment remodeling externally through the ability to degrade proteoglycans		
<i>Erythroxylum suberosum</i>	Catechins - antioxidant	26,39	
<i>Mimosa caesalpinjifolia</i>			
<i>Kielmeyera coriacea</i>	Elemen-type sesquiterpenes - inhibition of cell proliferation, stimulation of apoptosis, and induction of cell cycle arrest in the malignant cell	30	
<i>Kielmeyera coriacea</i>	δ-tocotrienol and dimer - arrest of cell cycle progression/induction of cell apoptosis	31	
<i>Lafoensia pacari</i>	Elagitannins - apoptogenic effects Ellagic acid - regulation of cyclin E (up-regulation), A and B1 (down-regulation) levels, ability to retain cells in the G1/S phase of the cell cycle	33	

(continued)

Table 2. (continued)

Species	Compound and mode of action	References
<i>Lychnophora trichocarpa</i>	Sesquiterpene lactones - inhibition of enzymes involved in essential biological processes such as DNA and RNA synthesis, protein and purine synthesis, glycolysis, the citric acid cycle, and the mitochondrial electron transport chain.	37
<i>Maytenus ilicifolia</i>	Pristimerin (triterpenoid) - inhibition of DNA synthesis and ability to trigger apoptosis	38
<i>Palicourea rigida</i>	Monoterpenic indole alkaloid called vallesiachotamine - promotion of G0/G1 cell cycle arrest, apoptosis, and necrosis.	42
<i>Psidium guineense</i>	Sesquiterpene alcohol - induction of apoptosis	44
<i>Pyrostegia venusta</i>	Alkanes - induction of cell cycle arrest and apoptosis	45
<i>Senna velutina</i>	Flavonoids (epigallocatechin, epicatechin, kaempferol heteroside, rutin) and dimeric and trimeric proanthocyanidin derivatives - induction of leukemic cell death by activating intracellular calcium and caspase-3, ability to decrease mitochondrial membrane potential and interrupt the cell cycle in S and C phases G2.	48
<i>Solanum lycocarpum</i> <i>Ixora brevifolia</i>	Alkaloids - ability to change cell morphology and DNA - irreversible apoptosis, regulation of caspases, regulation of death receptor expression (Example: Tumor necrosis factor receptor 1 (TNFR-1)).	29,49
<i>Stryphnodendron adstringens</i>	Phenolic compounds and polyphenols Gallic acid, galloocatechin, epigallocatechin, dimeric and trimeric proanthocyanidins - antioxidant activity through direct scavenging of free radicals, oxidative hemolysis, inhibition of lipid peroxidation in human erythrocytes, apoptosis-induced cell death through increased levels of intracellular reactive oxygen species (ROS), and induction of mitochondrial membrane potential dysfunction and caspase-3 activation	51

Each compound, found in a specific plant, has a possible mode of action or a target.

and acetone extracts were used depending on the solvent used to prepare the extract as different solvents produce higher or lower extractive yields and show differences in polarity and, consequently, in the class of compounds extracted from the extract; ethanolic and aqueous extracts, for example, which are the most polar, are rich in polyphenols.²⁸ Table 1 shows the types of extracts and details that were discussed in this review, which include species, common name, plant part used, and target cell. In front of each cell line, a positive or negative sign was placed; the sign (+) means that the extract inhibited the tumor cell (regardless of the method) and the sign (-) indicates a null or very low effect. Differences are seen according to the solvent used and this fact is due to the compounds that are extracted according to the solvent, as discussed above.

Conclusion

In view of the data, we conclude that the Brazilian Cerrado biome contains a wide variety of species with antitumor properties and more detailed research is needed to isolate bioactive secondary metabolites with cytotoxic properties. The evaluation of the chemical structure of these compounds is capable of enabling more extensive biological evaluations; thus, additional studies with the fractionated extracts and isolated compounds should be carried out to determine the complete antitumor therapeutic potential of these plants and, also, as future studies, *in vivo* assays. Moreover, further studies are needed to discover other Cerrado species with antitumor potential.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

Study concept and design (GSNO, RCO), acquisition of data (GSNO, CS), analysis and interpretation of data (GSNO), drafting of the manuscript (GSNO, CS), critical revision of the manuscript for important intellectual content (GSNO, CS, RCO). All authors have made a significant contribution to this study and have approved the final manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

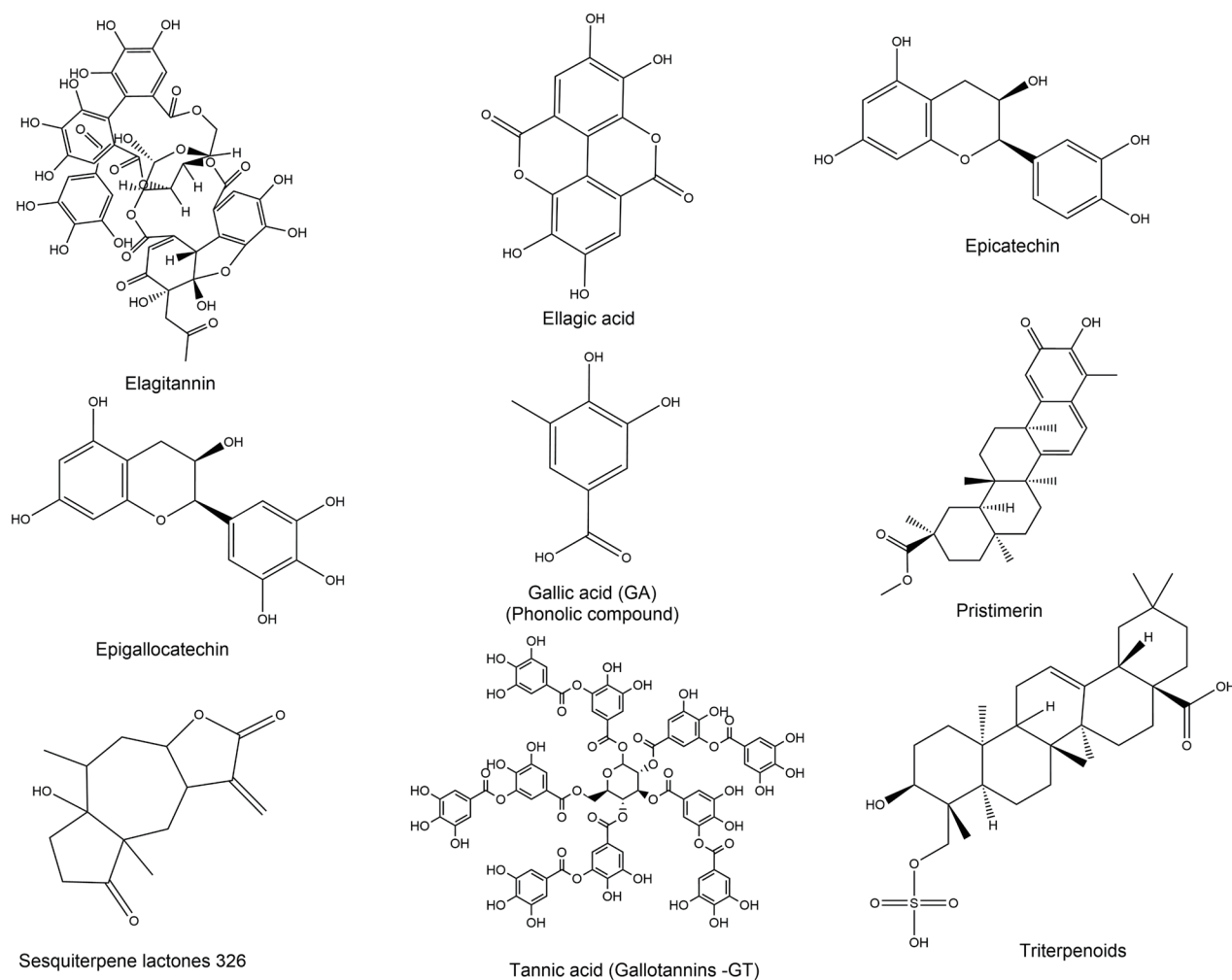


Fig. 2. Chemical structures of some of the major compounds mentioned in Table 2.

References

- Ahmad R, Ahmad N, Naqvi AA, Shehzad A, Al-Ghamdi MS. Role of traditional Islamic and Arabic plants in cancer therapy. *J Tradit Complement Med* 2017;7(2):195–204. doi:10.1016/j.jtcm.2016.05.002, PMID:28417090.
- Orang-Ojong BB, Mulyangaju JE, Wei MS, Lin M, Wei FG, Foukounang C, *et al*. Impact of natural resources and research on cancer treatment and prevention: A perspective from Cameroon. *Mol Clin Oncol* 2013;1(4):610–620. doi:10.3892/mco.2013.132, PMID:24649217.
- Inacio KK, Pessoa AS, Tokuhara CK, Pagnan AL, Sanches MLR, Fakhoury VS, *et al*. Menadione and protocatechuic acid: A drug combination with antitumor effects in murine osteosarcoma cells. *Arch Biochem Biophys* 2024;751:109840. doi:10.1016/j.abb.2023.109840, PMID:38040223.
- Torquato HF, Goettert MI, Justo GZ, Paredes-Gamero EJ. Anti-Cancer Phytometabolites Targeting Cancer Stem Cells. *Curr Genomics* 2017;18(2):156–174. doi:10.2174/1389202917666160803162309, PMID:28367074.
- Yu Z, Zhang T, Zhou F, Xiao X, Ding X, He H, *et al*. Anticancer Activity of Saponins from *Allium chinense* against the B16 Melanoma and 4T1 Breast Carcinoma Cell. *Evid Based Complement Alternat Med* 2015;2015:725023. doi:10.1155/2015/725023, PMID:26146506.
- Pessoa AS, Tokuhara CK, Fakhoury VS, Pagnan AL, Oliveira GSN, Sanches MLR, *et al*. The dimerization of methyl vanillate improves its effect against breast cancer cells via pro-oxidant effect. *Chem Biol Interact* 2022;361:109962. doi:10.1016/j.cbi.2022.109962, PMID:35523312.
- Pagnan AL, Pessoa AS, Tokuhara CK, Fakhoury VS, Oliveira GSN, Sanches MLR, *et al*. Anti-tumour potential and selectivity of caffeic acid phenethyl ester in osteosarcoma cells. *Tissue Cell* 2022;74:101705. doi:10.1016/j.tice.2021.101705, PMID:34864499.
- de Araujo AR, Quelemes PV, Perfeito ML, de Lima LI, Sá MC, Nunes PH, *et al*. Antibacterial, antibiofilm and cytotoxic activities of *Terminalia fagifolia* Mart. extract and fractions. *Ann Clin Microbiol Antimicrob* 2015;14:25. doi:10.1186/s12941-015-0084-2, PMID:25902872.
- Correia AF, Silveira D, Fonseca-Bazzo YM, Magalhães PO, Fagg CW, da Silva EC, *et al*. Activity of crude extracts from Brazilian cerrado plants against clinically relevant *Candida* species. *BMC Complement Altern Med* 2016;16:203. doi:10.1186/s12906-016-1164-3, PMID:27401815.
- Fakhoury VS, Pessoa AS, Tokuhara CK, Pagnan AL, Oliveira GSN, Liessa MRS, *et al*. Evaluation of *Myrcia bella* in murine osteosarcoma cells: Effect of the extract and enriched fractions of tannins and flavonoids. *Nat Prod Res* 2022;36(22):5823–5827. doi:10.1080/14786419.2021.2018431, PMID:34930089.

- [11] Albernaz LC, de Paula JE, Romero GA, Silva Mdo R, Grellier P, Mambu L, *et al*. Investigation of plant extracts in traditional medicine of the Brazilian Cerrado against protozoans and yeasts. *J Ethnopharmacol* 2010;131(1):116–121. doi:10.1016/j.jep.2010.06.011, PMID: 20600775.
- [12] Costa LSD, Andrezza NL, Correa WL, Cunha IBDS, Ruiz ALTG, Carvalho JED, *et al*. Antiproliferative activity, antioxidant capacity and chemical composition of extracts from the leaves and stem of *Chresta sphaerocephala*. *Rev Bras Farmacogn* 2015;25(4):369–374. doi:10.1016/j.bjp.2015.04.005.
- [13] de Mesquita ML, de Paula JE, Pessoa C, de Moraes MO, Costa-Lotufo LV, Grougnet R, *et al*. Cytotoxic activity of Brazilian Cerrado plants used in traditional medicine against cancer cell lines. *J Ethnopharmacol* 2009;123(3):439–445. doi:10.1016/j.jep.2009.03.018, PMID:19501276.
- [14] dos Santos Júnior HM, Oliveira DF, de Carvalho DA, Pinto JM, Campos VA, Mourão AR, *et al*. Evaluation of native and exotic Brazilian plants for anticancer activity. *J Nat Med* 2010;64(2):231–238. doi:10.1007/s11418-010-0390-0, PMID:20127421.
- [15] Mohammadi-Motlagh HR, Shokohinia Y, Mojarrab M, Rasouli H, Mostafaie A. 2-Methylpyridine-1-ium-1-sulfonate from *Allium hirtifolium*: An anti-angiogenic compound which inhibits growth of MCF-7 and MDA-MB-231 cells through cell cycle arrest and apoptosis induction. *Biomed Pharmacother* 2017;93:117–129. doi:10.1016/j.biopha.2017.06.013, PMID:28624423.
- [16] Araújo TADS, Sobrinho TJDS, Aguiar JDS, Silva ACOD, Brito FU, Silva GD, *et al*. Phytochemical, antioxidant and cytotoxic analysis of Brazilian Cerrado plants: Preliminary evidence of their antitumor activity. *J Med Plants Res* 2015;9(9):310–319. doi:10.5897/JMPR2015.5741.
- [17] Formagio AS, Vieira MC, Volobuff CR, Silva MS, Matos AI, Cardoso CA, *et al*. In vitro biological screening of the anticholinesterase and antiproliferative activities of medicinal plants belonging to Annonaceae. *Braz J Med Biol Res* 2015;48(4):308–315. doi:10.1590/1414-431X20144127, PMID:25714885.
- [18] Prado LG, Arruda HS, Peixoto Araujo NM, de Oliveira Braga LE, Banzato TP, Pereira GA, *et al*. Antioxidant, antiproliferative and healing properties of araticum (*Annona crassiflora* Mart.) peel and seed. *Food Res Int* 2020;133:109168. doi:10.1016/j.foodres.2020.109168, PMID:32466931.
- [19] Caneschi CM, Muniyappa MK, Duarte LP, Silva GD, Dos Santos OD, Spillane C, *et al*. Effect of constituents from samaras of *Austroplenckia populnea* (Celastraceae) on human cancer cells. *J Intercult Ethnopharmacol* 2015;4(1):6–11. doi:10.5455/jice.20141006105747, PMID:26401377.
- [20] Marchetti GM, Silva KA, Santos AN, Sousa IM, Tinti SV, Figueira GM, *et al*. The anticancer activity of dichloromethane crude extract obtained from *Calea pinnatifida*. *J Exp Pharmacol* 2012;4:157–162. doi:10.2147/JEP.S37135, PMID:27186128.
- [21] Magalhães HI, Ferreira PM, Moura ES, Torres MR, Alves AP, Pessoa OD, *et al*. In vitro and in vivo antiproliferative activity of *Calotropis procera* stem extracts. *An Acad Bras Cienc* 2010;82(2):407–416. doi:10.1590/s0001-37652010000200017, PMID:20563422.
- [22] Alves CCF, Oliveira JD, Estevam EBB, Xavier MN, Nicoletta HD, Furtado RA, *et al*. Antiproliferative activity of essential oils from three plants of the Brazilian Cerrado: *Campomanesia adamantium* (Myrtaceae), *Protium ovatum* (Burseraceae) and *Cardiopetalum calophyllum* (Annonaceae). *Braz J Biol* 2020;80(2):290–294. doi:10.1590/1519-6984.192643, PMID:31017239.
- [23] Oliveira-Alves SC, Pereira RS, Pereira AB, Ferreira A, Mecha E, Silva AB, *et al*. Identification of functional compounds in baru (*Dipteryx alata* Vog.) nuts: Nutritional value, volatile and phenolic composition, antioxidant activity and antiproliferative effect. *Food Res Int* 2020;131:109026. doi:10.1016/j.foodres.2020.109026, PMID:32247467.
- [24] Izumi C, Laure HJ, Barbosa NG, Thomé CH, Ferreira GA, Sousa JPB, *et al*. Sequesterpene Lactones Isolated from a Brazilian Cerrado Plant (*Eremanthus* spp.) as Anti-Proliferative Compounds, Characterized by Functional and Proteomic Analysis, are Candidates for New Therapeutics in Glioblastoma. *Int J Mol Sci* 2020;21(13):4713. doi:10.3390/ijms21134713, PMID:32630308.
- [25] Elias ST, Macedo CC, Simeoni LA, Silveira D, Magalhães PO, Lofranco-Porto A, *et al*. Cytotoxic effect of *Erythroxylum daphnites* extract is associated with G1 cell cycle arrest and apoptosis in oral squamous cell carcinoma. *Cell Cycle* 2016;15(7):948–956. doi:10.1080/15384101.2016.1151583, PMID:26918580.
- [26] Elias ST, Borges GA, Amorim DA, Rêgo DF, Simeoni LA, Silveira D, *et al*. Radiation induced a supra-additive cytotoxic effect in head and neck carcinoma cell lines when combined with plant extracts from Brazilian Cerrado biome. *Clin Oral Investig* 2015;19(3):637–646. doi:10.1007/s00784-014-1289-z, PMID:25096669.
- [27] Loverde-oliveira SM, Freitas MN, Araújo PKB, Costa IBC. Urban Cerrado fragment of the Federal University of Mato Grosso, Rondonópolis Campus, Mato Grosso. *Revista Biodiversidade* 2010;9(1):74.
- [28] Macedo TB, Elias ST, Torres HM, Yamamoto-Silva FP, Silveira D, Magalhães PO, *et al*. Cytotoxic Effect of *Erythroxylum suberosum* Combined with Radiotherapy in Head and Neck Cancer Cell Lines. *Braz Dent J* 2016;27(1):108–112. doi:10.1590/0103-6440201600014, PMID:27007356.
- [29] Medina RP, de Moura VM, da Silva CC, de Oliveira CMA, Kato L, Pomini AM, *et al*. Anti-inflammatory and antiproliferative activities of *Ixora brevifolia* Benth. (Rubiaceae). *Nat Prod Res* 2018;32(11):1357–1360. doi:10.1080/14786419.2017.1344654, PMID:28641452.
- [30] Lemes RS, Costa GCS, Silva DCS, Becceneri AB, Bicalho KU, Miranda MLD, *et al*. Essential oils of *Kielmeyera coriacea* fruits and leaves: antitumor activity and chemical study. *Rev Virtual Quim* 2017;9(3):1245–1257. doi:10.21577/1984-6835.20170073.
- [31] de Mesquita ML, Araújo RM, Bezerra DP, Filho RB, de Paula JE, Silveira ER, *et al*. Cytotoxicity of δ -tocotrienols from *Kielmeyera coriacea* against cancer cell lines. *Bioorg Med Chem* 2011;19(1):623–630. doi:10.1016/j.bmc.2010.10.044, PMID:21094611.
- [32] Figueiredo CR, Matsuo AL, Massaoka MH, Girola N, Azevedo RA, Rabaça AN, *et al*. Antitumor activity of *Kielmeyera coriacea* leaf constituents in experimental melanoma, tested in vitro and in vivo in syngeneic mice. *Adv Pharm Bull* 2014;4(Suppl 1):429–436. doi:10.5681/apb.2014.063, PMID:25364658.
- [33] Reichert CL, Silva DB, Carollo CA, Weffort-Santos AM, Santos CAM. Metabolic profiling and correlation analysis for the determination of killer compounds of proliferating and clonogenic HRT-18 colon cancer cells from Lafoensia pacari. *J Ethnopharmacol* 2018;224:541–552. doi:10.1016/j.jep.2018.06.021, PMID:29928972.
- [34] Cordeiro YdeG, Rochetti AL, Souza VC, da Silva ER, Scatolini AM, Genovese MI, *et al*. Antineoplastic effect of procyanidin-rich extract of *Lafoensia Pacari* in lung carcinoma cells. *Braz Arch Biol Technol* 2019;62(7):e19160638. doi:10.1590/1678-4324-2019160638.
- [35] da Silva Marcondes DB, Reichert CL, de Andrade LF, de Moraes Santos CA, Weffort-Santos AM. Cytotoxicity and apoptogenic effects of *Lafoensia pacari*. *J Ethnopharmacol* 2014;157:243–250. doi:10.1016/j.jep.2014.09.018, PMID:25311274.
- [36] Funari CS, Passalacqua TG, Rinaldo D, Napolitano A, Festa M, Capasso A, *et al*. Interconverting flavanone glucosides and other phenolic compounds in *Lippia salviaefolia* Cham. ethanol extracts. *Phytochemistry* 2011;72(16):2052–2061. doi:10.1016/j.phytochem.2011.07.004, PMID:21871644.
- [37] Saúde-Guimarães DA, Raslan DS, Oliveira AB. In Vitro antitumor activity of Sesquiterpene lactones from *Lychnophora trichocarpha*. *Rev Bras Plantas Med* 2014;16(2):275–282. doi:10.1590/S1516-05722014000200017.
- [38] Costa PM, Ferreira PM, Bolzani Vda S, Furlan M, de Freitas Formen-ton Macedo Dos Santos VA, Corsino J, *et al*. Antiproliferative activity of pristimerin isolated from *Maytenus ilicifolia* (Celastraceae) in human HL-60 cells. *Toxicol In Vitro* 2008;22(4):854–863. doi:10.1016/j.tiv.2008.01.003, PMID:18296021.
- [39] Silva MJD, Carvalho AJS, Rocha CQ, Vilegas W, Silva MA, Gouvêa CMCP. Ethanolic extract of *Mimosa caesalpinifolia* leaves: Chemical characterization and cytotoxic effect on human breast cancer MCF-7 cell line. *S Afr J Bot* 2014;93:64–69. doi:10.1016/j.sajb.2014.03.011.
- [40] Serpeloni JM, Specian AF, Ribeiro DL, Tuttis K, Vilegas W, Martínez-López W, *et al*. Antimutagenicity and induction of antioxidant defense by flavonoid rich extract of *Myrcia bella* Cambess. in normal and tumor gastric cells. *J Ethnopharmacol* 2015;176:345–355. doi:10.1016/j.jep.2015.11.003, PMID:26549270.
- [41] Dos Santos C, Galaverna RS, Angolini CFF, Nunes VVA, de Almeida LFR, Ruiz ALTG, *et al*. Antioxidative, Antiproliferative and Antimi-

- icrobial Activities of Phenolic Compounds from Three *Myrcia* Species. *Molecules* 2018;23(5):986. doi:10.3390/molecules23050986, PMID:29695037.
- [42] Soares PR, de Oliveira PL, de Oliveira CM, Kato L, Guillo LA. In vitro antiproliferative effects of the indole alkaloid vallesiachotamine on human melanoma cells. *Arch Pharm Res* 2012;35(3):565–571. doi:10.1007/s12272-012-0320-7, PMID:22477204.
- [43] Elias ST, Salles PM, de Paula JE, Simeoni LA, Silveira D, Guerra EN, *et al.* Cytotoxic effect of *Pouteria torta* leaf extracts on human oral and breast carcinomas cell lines. *J Cancer Res Ther* 2013;9(4):601–606. doi:10.4103/0973-1482.126454, PMID:24518703.
- [44] Nascimento KF, Moreira FMF, Alencar Santos J, Kassuya CAL, Croda JHR, Cardoso CAL, *et al.* Antioxidant, anti-inflammatory, antiproliferative and antimycobacterial activities of the essential oil of *Psidium guineense* Sw. and *spathulenol*. *J Ethnopharmacol* 2018;210:351–358. doi:10.1016/j.jep.2017.08.030, PMID:28844678.
- [45] Figueiredo CR, Matsuo AL, Pereira FV, Rabaça AN, Farias CF, Girola N, *et al.* *Pyrostegia venusta* heptane extract containing saturated aliphatic hydrocarbons induces apoptosis on B16F10-Nex2 melanoma cells and displays antitumor activity in vivo. *Pharmacogn Mag* 2014;10(Suppl 2):S363–S376. doi:10.4103/0973-1296.133284, PMID:24991116.
- [46] De Oliveira CR, Menezes ACS, de Moraes MO, Vieira LDM, Pereira AG, Lima RS, *et al.* Cytotoxic evaluation in three tumor cell lines of fractions obtained from the stem bark of *Salacia crassifolia* (MART. ex. Schult.) G. Dom. (Celastraceae). *Rev Colomb Cienc Quim Farm* 2012;41(2):133–142.
- [47] Espindola LS, Dusi RG, Demarque DP, Braz-Filho R, Yan P, Bokesch HR, *et al.* Cytotoxic Triterpenes from *Salacia crassifolia* and Metabolite Profiling of Celastraceae Species. *Molecules* 2018;23(6):1494. doi:10.3390/molecules23061494, PMID:29925807.
- [48] Campos JF, de Castro DT, Damião MJ, Vieira Torquato HF, Paredes-Gamero EJ, Carollo CA, *et al.* The Chemical Profile of *Senna velutina* Leaves and Their Antioxidant and Cytotoxic Effects. *Oxid Med Cell Longev* 2016;2016:8405957. doi:10.1155/2016/8405957, PMID:27803764.
- [49] Munari CC, de Oliveira PF, Campos JC, Martins Sde P, Da Costa JC, Bastos JK, *et al.* Antiproliferative activity of *Solanum lycocarpum* alkaloidic extract and their constituents, solamargine and solasonine, in tumor cell lines. *J Nat Med* 2014;68(1):236–241. doi:10.1007/s11418-013-0757-0, PMID:23475509.
- [50] Romero AL, Fontana A, da Silva CC, de Souza MC, de Carvalho JE, Faria EO, *et al.* Antiproliferative activity of *Sloanea garckeana* K. Schum. *Quím Nova* 2008;31(6):1359–1361. doi:10.1590/S0100-40422008000600016.
- [51] Baldivia DDS, Leite DF, Castro DTH, Campos JF, Santos UPD, Paredes-Gamero EJ, *et al.* Evaluation of In Vitro Antioxidant and Anticancer Properties of the Aqueous Extract from the Stem Bark of *Stryphnodendron adstringens*. *Int J Mol Sci* 2018;19(8):2432. doi:10.3390/ijms19082432, PMID:30126115.
- [52] Rodrigues PSDM, Bertolin AO, Fucase TM, Galluzzi FM, Silva EC, Marumo Maria HB. Assessment of the cytotoxic activity of ethanol extracts from the bark and leaves of *Terminalia fagifolia* mart. on normal and tumor cells. *J Health Biol Sci* 2017;5(1):16–23. doi:10.12662/2317-3076jhbs.v5i1.1068.p16-23.2017.
- [53] Nascimento YM, Abreu LS, Lima RL, Silva ADS, Costa VCO, Melo JIM, *et al.* Zornioside, a dihydrochalcone C-glycoside, and other compounds from *Zornia brasiliensis*. *Rev Bras Farmacogn* 2018;28(2):3. doi:10.1016/j.bjp.2018.02.003.
- [54] Seito LN, Ruiz AL, Vendramini-Costa D, Tinti SV, de Carvalho JE, Bastos JK, *et al.* Antiproliferative activity of three methoxylated flavonoids isolated from *Zeyheria montana* Mart. (Bignoniaceae) leaves. *Phytother Res* 2011;25(10):1447–1450. doi:10.1002/ptr.3438, PMID:21351299.
- [55] Karabegovic IT, Stojicevic SS, Velickovic DT, Todorovic ZB, Nikolic NC, Lazic ML. The effect of different extraction techniques on the composition and antioxidant activity of cherry laurel (*Prunus laurocerasus*) leaf and fruit extracts. *Ind Crops Prod* 2014;54:142–148. doi:10.1016/j.indcrop.2013.12.047.
- [56] Liu JM, Haroun-Bouhedja F, Boisson-Vidal C. Analysis of the in vitro inhibition of mammary adenocarcinoma cell adhesion by sulphated polysaccharides. *Anticancer Res* 2000;20(5A):3265–3271. PMID:11062752.
- [57] Toropainen E, Ranta VP, Talvitie A, Suhonen P, Urtti A. Culture model of human corneal epithelium for prediction of ocular drug absorption. *Invest Ophthalmol Vis Sci* 2001;42(12):2942–2948. PMID:11687540.
- [58] Hubrecht RC, Carter E. The 3Rs and Humane Experimental Technique: Implementing Change. *Animals (Basel)* 2019;9(10):754. doi:10.3390/ani9100754, PMID:31575048.
- [59] Daniyan MO, Omisore NO, Adeyemi OI, Olusa AS, Olaniran SF, Oyemitan IA, *et al.* An Improved Method for Toxicological Profiling of Chemical Substances. *Toxicol Mech Methods* 2024;12:1–50. doi:10.1080/15376516.2024.2310012, PMID:38267361.