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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 coriaceae, Annona crassiflora, Cardiopetalum calophyllu*m), Celastraceae (*Austroplenckia populnea, Salacia crassifolia, Maytenus ilicifolia*), Verbenaceae (*Lippia salviaefolia*), Solanaceae (*Solanum lycocarpu*m), Myrtaceae (*Myrcia falax, Myrcia bella, Campomanesia adamantium, Myrcia guianensis, Psidium guineense*), Rubiaceae (*Palicourea rigidum, Ixora brevifolia*), Bignoniaceae (*Pyrostegia venusta, Tabebuia avellanedae*), Erythroxylaceae (*Erythroxylum suberosum, Erythroxylum daphnites* and *E. subrotundum*), Sapotaceae (*Pouteria pie, Pouteria ramiflora*), Asteraceae (*Calea pinnatifida, Chresta sphaerocephala, Eremanthus matogrossensis, Eremanhus seidelii* and *Lychnophora trichocarpha*), Elaeocarpaceae (*Sloanea garckeana*), Apocynaceae (*Calotropis procera*), Anacardiaceae (*Anacardium humile*), Calophyllaceae (*Kielmeyera coriacea*), Lythraceae (*Lafoensia pacari*), Mimosaceae (*Mimosa caesalpiniifolia*), Burseraceae (*Protium ovatum*), Faba ceae (*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://floradobrasil.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-

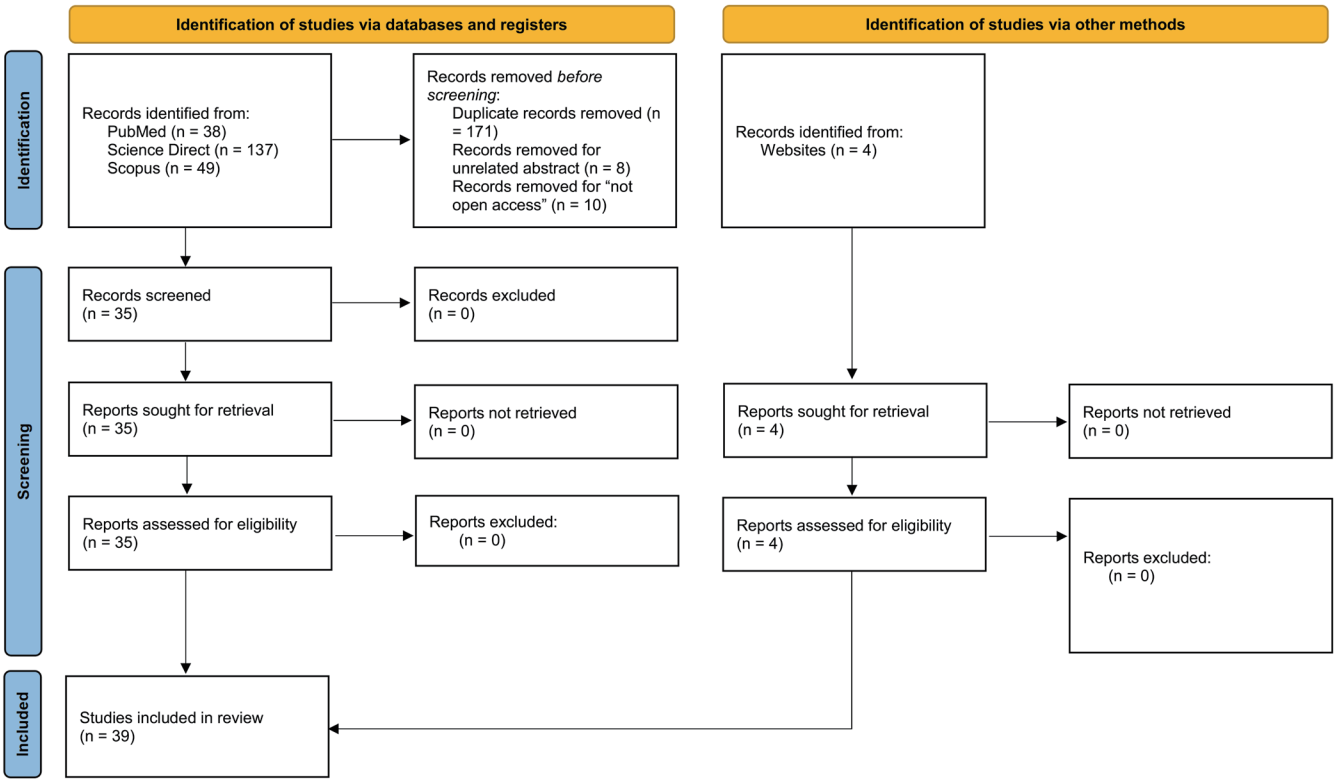

Fig. 1. Flowchart of study selection.

kaloids (*S. lycocarpum*), phenolic acids (*A. coriacea*), flavonoids - quercetin (*A. crassiflora*), triterpenes (*M. ilicifolia, P. torta, C. sphaerocephala*), sesquiterpenes – germacranolides - (*C. pinnatifida*), flavonoids (*E. suberosum, A. populnea, A. coriacea, T. avellanedae, L. salviaefolia, C. procera; 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. matogressensis; 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-eicosanol, 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, monoterpenic indole alkaloid, alkanes)[20,25,31,33,41,42,45]; 2) Inducer apoptosis (sesquiterpenes, cardiotonic 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
Anacardium humile *Brosimum gaudichaudii* *Tabebuia avellanedae*	'Cajuzinho' 'Inharé' 'Purple ipê'	Bark (c) and leaves (f) Bark (c) and leaves (f) Bark (c) and leaves (f)	Ethanolic	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
Annona coriácea	' Marola' 'Araticum-liso'	Seeds	Methanolic	UACC-62 (melanoma), MCF-7 (breast), NCI/ADR/RES (ovary), 786-0 (kidney), NCI-H460 (lung), OVCAR-3 (ovary), HT-29 (colon), K562 (leukemia), UA251 (glioma) (+)	17
Annona crassiflora	'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
Austroplenckia Populnea	'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) (+) HS578T (breast) (+) MCF-7 (breast) (+) A549 (−) HS578T (−), MCF-7 (−)	19
Calea pinnatifida	'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
Calotropis procera	*'Algodão de seda'* 'Leiteiro' 'Queimadeira' 'Ciúme'	Bark	Ethyl acetate, acetone Hexane, methanolic 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	References
Campomanesia adamantium *Cardiopetalum calophyllum* *Protium ovatum*	'Guavira' 'Imbirinha' 'Almecega'	Leaves Leaves Leaves Green fruits	Essential oil	MCF-7 (breast) (+) HeLa (cervical) (+) M059J (glioblastoma) (+) MCF-7 (+), HeLa (+), M059J (+) MCF-7 (−), HeLa (−), M059J (+) MCF-7 (−), HeLa (−), M059J (−)	22
Chresta sphaerocephala	'João-bobo'	Leaves Bark (B)	Hexanic (L) Hexanic (B) Methanolic Ethyl acetate	U251 (glioma) (+), UACC-62 (melanoma) (+) MCF7 (breast) (−), NCI-ADR/RES (ovary) (+) 786-0 (kidney) (+), NCI-H460 (lung) (+) 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	12
Dipteryx alata Vog.	'Baru'	Seeds	Phenolic	HT29 (colon) (+)	23
Eremanthus matogressensis *Eremanthus seidelii*	Uninformed Uninformed	Leaves Leaves	Isolated compound isolated compound	T98G (+) e U87MG (+) (glioblastoma) T98G (−), U87MG (−)	24
Erythroxylum daphnites	'Fruta-de-pomba'	Leaves	Hexanic	SCC-9 (oral) (+)	25
Erythroxylum daphnites *Erythroxylum suberosum* *Erythroxylum subrotundum* *Pouteria ramiflora* *Pouteria torta*	'Mercurinho' 'Fruta-de-veado'	Leaves Leaves Leaves Leaves Leaves	Aqueous Ethanolic Hexanic Aqueous Ethanolic Hexanic Aqueous Ethanolic Hexanic Aqueous Ethanolic Hexanic	FaDu (−), SCC-25 (−), SCC-9 (−) FaDu (−), SCC-25 (−), SCC-9 (−) FaDu (−), SCC-25 (+), SCC-9 (+) FaDu (+), SCC-25 (+), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (+) FaDu (−), SCC-25 (−), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (−) FaDu (−), SCC-25 (−), SCC-9 (−) FaDu (−), SCC-25 (−), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (−) SCC-25, SCC-9 (tongue)/FaDu (hypopharynx) FaDu (+), SCC-25 (−), SCC-9 (−) FaDu (+), SCC-25 (−), SCC-9 (−) FaDu (−), SCC-25 (−), SCC-9 (−)	26,27
Erythroxylum suberosum	'Cabelo-de-negro'	Leaves	Aqueous Ethanolic Hexanic	SCC-9 (oral) (+) FaDu (hypopharynx) (+) SCC-9 (−), FaDu (+) SCC-9 (−), FaDu (−)	28
Ixora brevifolia	'Ixora-arborea'	Twigs	Crude and hydroethanolic extract, hexanic	U251 (glioma) (+) K562 (leukemia) (+)	29

(continued)

Table 1. *(continued)*

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

(continued)

Table 1. *(continued)*

Species	Popular name	Used part of the plant	Extract type	Target cell	References
Myrcia bella	'Mercurinho'	Leaves	Hydroalcoholic	ACP02 (gastric) (+)	40
Myrcia bella *Myrcia falax* *Myrcia guianensis*	'Jacarezinho' Uninformed Uninformed	Leaves Leaves Leaves	Hydroethanolic	K562 (+), MCF-7 (+), 786-0 (−), NCI-H460 (−) PC-3 (−), HT-29 (−) K562 (+), MCF-7 (−), 786-0 (−), NCI-H460 (−) PC-3 (−), HT-29 (−) K562 (leukemia) (+), MCF-7 (breast) (+) 786-0 (kidney) (−), NCI-H460 (lung) (−) PC-3 (prostate) (−), HT-29 (colon) (−)	27,41
Palicourea rígida	'Douradão'	Leaves	Ethanolic extract (isolated compound)	SK-MEL-37 (melanoma) (+)	42
Pouteria torta[a]	'Guapeva'	Leaves	Hexanic Ethanolic Aqueous	OSCC-3 (oral) (+) MCF-7 (breast) (+) OSCC-3 (+) MCF-7 (+) OSCC-3 (+) MCF-7 (+)	43
Psidium guineense	'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
Pyrostegia venusta	'St. John vine'	Flowers	Heptane Hydroalcoholic	B16F10-Nex2 (murine melanoma) (+) B16F10-Nex2 (−)	45
Salacia crassifolia	'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
Salacia crassifolia	'Bacupari-do-Cerrado'	Root wood	Hexanic	Colo205 e KM12 (colon) (+) A498 e U031 (kidney) (+) HEP3B and SKHEP (liver) (−) MG63 and MG63.3 (osteosarcoma) (+)	47
Senna velutina	'Fedegosão'	Leaves	Ethanolic	Jurkat (+) e K562 (+) (leukemia)	27,48
Solanum lycocarpum	'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
Sloanea garckeana[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
Stryphnodendron adstringens	'Barbatimão' or 'Casca-da-mocidade'	Stem bark	Aqueous	B16F10Nex-2 (melanoma) (+)	51
Terminalia fagifolia	'Capitão-do-mato' 'Mirindiba' 'Pau-de-bicho'	Bark and leaves	Ethanolic	PC3 (prostate) (+) B16F10 (murine melanoma) (+)	52
Terminalia fagifolia	'Capitão' 'Capitão -do-Cerrado' 'Capitão-do-campo' 'Mirindiba'	Stem bark	Ethanolic and fractions	MCF-7 (breast) (+)	8
Zornia brasiliensis	'Urinária' 'Urinana' 'Carrapicho'	Aerial parts	Ethanolic	HL60 (promyelocytic leukemia) (+) MCF-7 (breast) (−) HCC1954 (breast) (−) T-47D (breast) (−) 4T1 (breast) (−) HL60 (promyelocytic leukemia) (−)	53

Data set from all relevant studies. [a]Source: https://www.sibbr.gov.br/. (+) , effect on tumor cells; (−), null or very low effect.

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

Species	Compound and mode of action	References
Anacardium humile *Erythroxylum suberosum* *Myrcia falax* *Sloanea garckeana* *Tabebuia avellanedae* *Terminalia fagifolia* *Zornia brasiliensis*	Phenolic compounds - free radical scavenging (*A. humile*) (*T. fagifolia*) 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 (*T. avellanedae*)	16,50,53
Annona crassiflora *Austroplenckia populnea* *Brosimum gaudichaudii* *Lippia salviaefolia* *Myrcia bella* *Senna velutina*	Flavonoids - antioxidant; free radical scavenging, DNA repair, and immune system stimulation	16,18,19, 36,40,48
Calea pinnatifida	Sesquiterpenes (germacranolides) - potent induction of apoptosis and inhibition of nuclear factor kappa B	20
Calotropis procera	Cardiotonic glycoside steroids - activation of apoptotic pathways	21
Chresta sphaerocephala *Erythroxylum daphnites* *Erythroxylum subrotundum* *Pouteria ramiflora* *Pouteria* torta *Salacia crassifólia*	Triterpenes - inhibition of tumor growth and cell cycle progression and induction of apoptosis of tumor cells *in vitro* and *in vivo*	25,43,46
Dipteryx alata *Myrcia spp*	Phenolic compounds Gallic acid (GA) - regulation of several signaling pathways; inhibit proliferation Gallotannins (GT) - suppression of NFκB activation induced by tumor necrosis factor (TNF-α) Antioxidants	41,52
Eremanthus matogressensis *Eremanthus seidelii*	Sesquiterpene lactones (goyazensolide and lychnofolide) - possible interference in angiogenesis internally and in tumor microenvironment remodeling externally through the ability to degrade proteoglycans	24
Erythroxylum suberosum *Mimosa caesalpiniifolia*	Catechins - antioxidant	26,39
Kielmeyera coriacea	Elemen-type sesquiterpenes - inhibition of cell proliferation, stimulation of apoptosis, and induction of cell cycle arrest in the malignant cell	30
Kielmeyera coriacea	δ-tocotrienol and dimer - arrest of cell cycle progression/induction of cell apoptosis	31
Lafoensia pacari	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
Lychnophora trichocarpha	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
Maytenus ilicifolia	Pristimerin (triterpenoid) - inhibition of DNA synthesis and ability to trigger apoptosis	38
Palicourea rigida	Monoterpenic indole alkaloid called vallesiachotamine - promotion of G0/G1 cell cycle arrest, apoptosis, and necrosis.	42
Psidium guineense	Sesquiterpenic alcohol - induction of apoptosis	44
Pyrostegia venusta	Alkanes - induction of cell cycle arrest and apoptosis	45
Senna velutina	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
Solanum lycocarpum	Alkaloids - ability to change cell morphology and DNA - irreversible apoptosis, regulation of caspases,	29,49
Ixora brevifolia	regulation of death receptor expression (Example: Tumor necrosis factor receptor I (TNFR-I)).	
Stryphnodendron adstringens	Phenolic compounds and polyphenols Gallic acid, gallocatechin, 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 interest.

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.

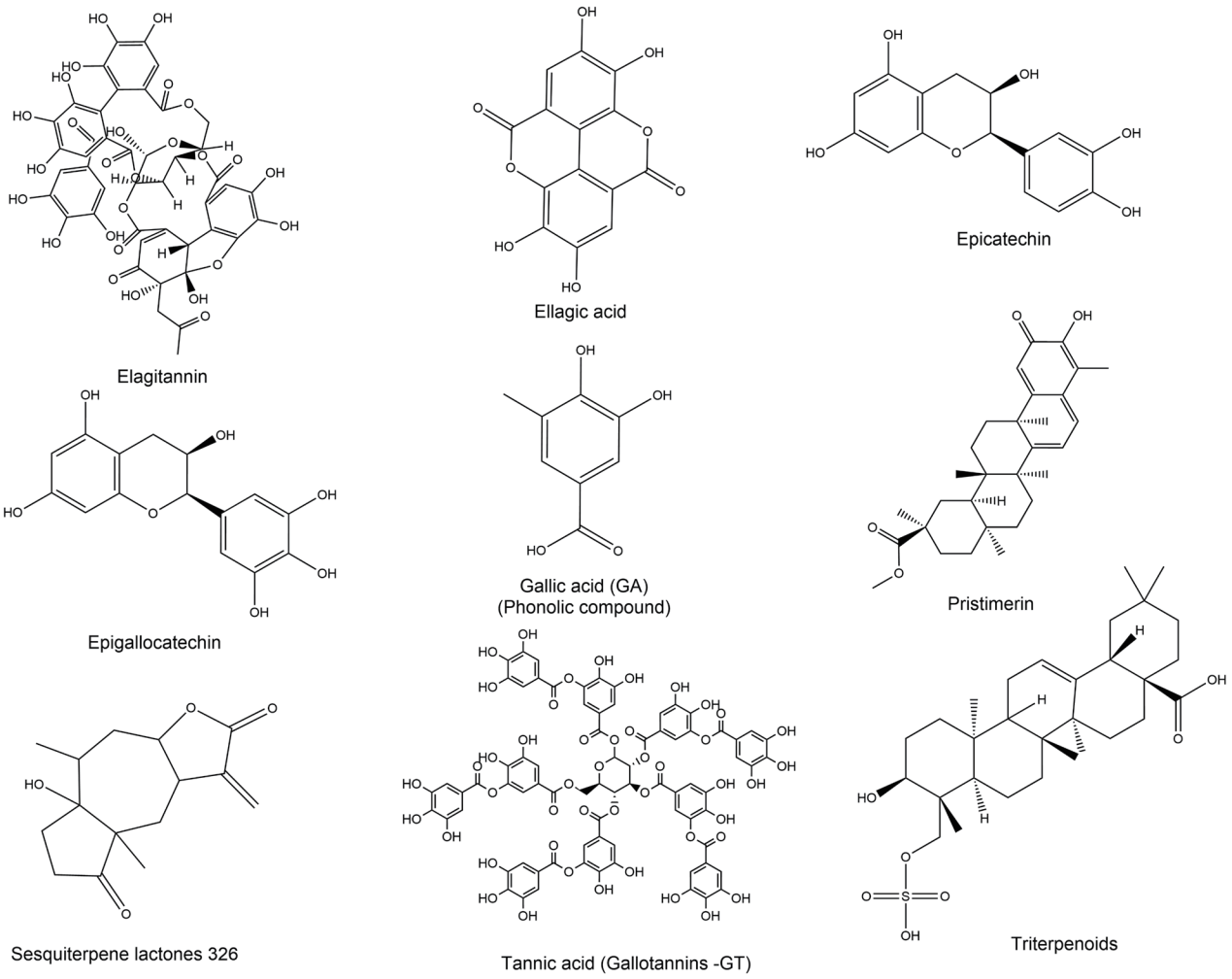

Fig. 2. Chemical structures of some of the major compounds mentioned in Table 2**.**

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