

Supplementary material

South American Medicinal Plants as Sources of Antiglioblastoma Agents: A Systematic Review of *In Vitro* Evidence and Cell Death Mechanisms

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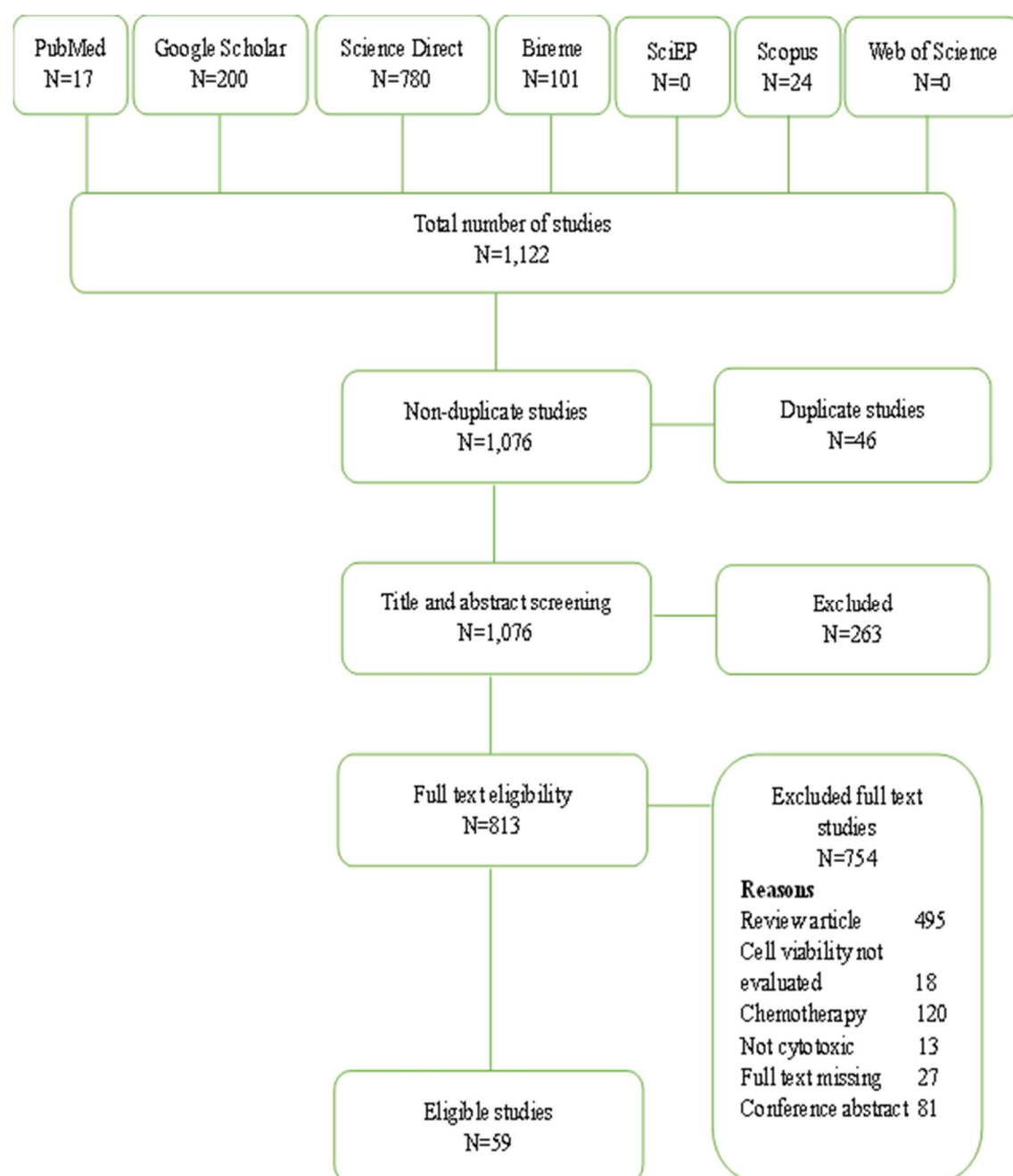


Fig S1 Study selection process

Table S1 Synthesis of studies that used South American plants in the treatment of Glioblastoma

Species	Plant part	Extract/Compound	Dose/Time	IC ₅₀	Cell line	Ref.
<i>Myracrodruon urundeuva</i> Allem., Anacardiaceae	Seeds	Ethanollic extract	17.3-36.6 µg/ml 72 h	25.1 µg/ml	SF-295	(Ferreira et al. 2011)
<i>Annona coriacea</i> Mart., Annonaceae	Leaves	Ethyl acetate extract (AcL-1, AcL-2, AcL-3, AcL-4)	1 – 25 µg/ml 24 h	<7 µg/ml	U251, GAMG	(Sousa et al. 2023)
<i>Cardiopetalum calophyllum</i> Schltldl., Annonaceae	Leaves	Hydrodistillate	3.91 – 500 µg/ml 72 h	311.4 µg/ml	M059J	(Alves et al. 2020)
<i>Guatteropsis blepharophylla</i> Mart., Annonaceae	Leaves	Hydrodistillate	0.024 – 50 µg/ml 72 h	24.3 µg/ml	SF-295	(Ribeiro et al. 2012)

<i>Araucaria angustifolia</i> (Bertol.) Kuntze, Araucariaceae	Seeds	Coat extract	25 – 300 µg/ml 48 and 72 h	120 µg/ml 48 h, 73 µg/ml 72 h	C6	(Fonseca et al. 2020)
<i>Achyrocline</i> <i>satureioides</i> (Lam.) DC., Asteraceae	Stem	Ethyl acetate extract	12.5 – 200 µg/ml 24, 48 and 72 h	C6 121.2, 42.36, 37.30 µg/ml	C6, U87	(Pedra et al. 2018)
				U87 177.7, 81.13, 55.12 µg/ml		
		DCM extract	0.625 – 10 µg/ml 24, 48 and 72 h	C6 3.31, 2.86, 1.60 µg/ml		
				U87 3.12, 2.35, 1.63 µg/ml		
	Inflorescence			U251 80 µg/ml		

		Hydroethanolic extract (Achyrobichalcone, Luteolin, 3-O-methyl-quercetin, Quercetin)	10 - 500 µg/ml 72 h	C6 180 µg/ml U87 220 µg/ml	U251, C6, U87	(Souza et al. 2018)
<i>Baccharis uncinella</i> DC., Asteraceae	Aerial part	Methanolic extract	10 – 200 µg/ml 24 h	213.9 µg/ml	U87	(Lucas et al. 2021)
<i>Eremanthus crotonoides</i> (DC.) Sch.Bip., Asteraceae	Leaves	DCM extract	0.005 – 160 µg/ml 24 h	3.57 µg/ml 8.06 µg/ml	U87 U251	(Lobo et al. 2012)
<i>Eremanthus seidelii</i> MacLeish & H.Schumacher, Asteraceae	Leaves	Methanolic extract (Sesquiterpene Lactone)	17.3 – 36.3 µg/ml 72 h	25.1 µg/ml	SF-295	(Izumi et al. 2020)
<i>Eupatorium laevigatum</i> (Lam.) R.M.King & H.Rob., Asteraceae	Leaves, stem, flowers, roots	Ethanolic extract	0.1 – 100 µg/ml 0.2 72 h	0.32 – 45.0 µg/ml	U373	(Monks et al. 2002)

<i>Dittrichia graveolens</i> (L.) Greuter, Asteraceae	Aerial part	Hydrodistillate	125 - 1000 µg/ml 48 h	1000 µg/ml	U87	(Koc et al. 2021)
<i>Pyropia endiviifolia</i> (A. Gepp & E. Gepp) H. G. Choi & M. S. Hwang, Bangiaceae	-	Hexane	10 – 1000 µg/ml 24 and 48 h	10 µg/ml	C6	(de Souza et al. 2022)
<i>Fridericia platyphylla</i> (Cham.) L.G.Lohmann, Bignoniaceae	Leaves	Ethanolic extract (Luteolin)	5 – 314 µM 48 h	16.7 µM	U251	(Franco et al. 2021)
<i>Handroanthus ochraceus</i> (Cham.) Mattos, Bignoniaceae	Leaves	Ethanolic	0.78 – 50 µg/ml 72 h	18.2 µg/ml	SF-295	(Silva et al. 2020)
<i>Lepidium meyenii</i> Walp., Brassicaceae	Roots	Ethyl acetate extract	1 – 100 µg/ml 24 h	>100 µg/ml	C6	(Carvalho et al. 2021)
<i>Protium ovatum</i> Engl., Burseraceae	Leaves	Hydrodistillate	3.91 – 500 µg/ml 24 h	191.3 µg/ml, 276.1 µg/ml	M059J, GM07492A	(Alves et al. 2020)

	Fruits			583.5 µg/ml, 306.0 µg/ml		
<i>Kielmeyera rugosa</i> Choisy, Calophyllaceae	Leaves, Stems, Fruits	Methanolic extract	0.024 – 50 µg/ml 72 h	3.5 µg/ml	SF-295	(Ribeiro et al. 2012)
<i>Kielmeyera argentea</i> Choisy, Calophyllaceae	Stems and roots	Hexane extract (Prenylated 4- phenylcoumarins, 4-alkylcoumarins)	0.6 – 200 µM 72 h	6.6, 52.0, 37.0 µM	U251	(Boness et al. 2021)
<i>Kielmeyera coriacea</i> Mart., Calophyllaceae	Root bark	Hexane extract	0.02 – 25.0 µg/ml 72 h	23.58 µg/ml	SF-295	(de Mesquita et al. 2011)
<i>Crataeva tapia</i> Capparaceae Juss.	Bark	Ethanolic extract (CrataBL Lectin)	5 – 100 µM 48 h	51 µM	U87	(Bonturi et al. 2019)
<i>Clusia burle-marxii</i> Bittrich., Clusiaceae	Trunk	Hexane extract (Polyprenylated benzophenone)	72 h	31.96 µM Sampsonine 26.0 µM	GL-15	(Ferraz et al. 2019)
	Fruit epicarp		10 – 40 µM	23 µM	U251	

<i>Garcinia brasiliensis</i> Mart., Clusiaceae		Ethanollic extract (7- epiclusianone)	48 h	18.52 µM	U138	(Sales et al. 2015)
<i>Platonia insignis</i> Mart., Clusiaceae	Stem bark	DCM extract	0.78 – 50 µg/ml 72 h	22.3 µg/ml	SF-295	(Silva et al. 2020)
<i>Combretum duarteanum</i> Cambess., Combretaceae	Leaves	Ethanollic extract	0.78 – 50 µg/ml 72 h	6.4 µg/ml	SF-295	(Silva-Filho et al. 2020)
<i>Combretum mellifluum</i> Eichler, Combretaceae	Leaves	Ethanollic extract	0.78 – 50 µg/ml 72 h	23.5 µg/ml	SF-295	(Silva-Filho et al. 2020)
<i>Combretum leprosum</i> Mart., Combretaceae	Leaves	DCM extract (Triterpene)	1.19 – 1.74 µg/ml 72 h	1.44 µg/ml	SNB19	(Silva-Filho et al. 2020)
<i>Gaultheria hispida</i> R.Br., Ericaceae	Leaves	Hydrodistillate	0.024 – 50 µg/ml 72 h	5.7 µg/ml	SF-295	(Ribeiro et al. 2012)

<i>Croton betulaster</i> Müll.Arg., Euphorbiaceae	Leaves	DCM and Ethyl acetate extracts (Dimethoxyflavone, Casticin, Penduletin)	10 – 100 µM 72 h	Penduletin 10 µM, Casticin 100 µM after 72 h	GL-15	(Coelho et al. 2016)
<i>Jatropha curcas</i> L., Euphorbiaceae	Leaves	Methanolic extract	0.024 – 50 µg/ml 72 h	>50 µg/ml	SF-295	(Ribeiro et al. 2012)
<i>Bauhinia acuruana</i> Moric., Fabaceae	Leaves	Ethanolic	0.39 – 25.0 µg/ml 72 h	37.85 µM	SF-295	(Góis et al. 2017)
<i>Canavalia brasiliensis</i> Mart. ex Benth., Fabaceae	Seeds	Hydrodistillate (Lectin)	1– 50 µg/ml 24 h	30 µg/ml	U87, GBM1, C6	(Wolin et al. 2021)
<i>Canavalia ensiformis</i> (L.) DC., Fabaceae	Seeds	Ammonium precipitate (Lectin)	10 – 100 µg/ml 48 h	56.02 µg/ml	C6	(Nascimento et al. 2018)
<i>Canavalia gladiata</i> (Jacq.) DC., Fabaceae	Seeds	Ammonium precipitate (Lectin)	10 – 100 µg/ml 48 h	50 µg/ml	C6	(Cavada et al. 2018)

<i>Dioclea violacea</i> (Mart. ex Benth.), Fabaceae	Seeds	Ammonium precipitate	10 – 100 µg/ml 48 h	58.84 µg/ml	C6	(Nascimento et al. 2018)
<i>Erythrina verna</i> Vell., Fabaceae	Stem bark	Ethanolic extract (Erythraline)	0.016 – 5 µg/ml 72 h	-	SF-295	(Guaratini et al. 2014)
<i>Glycine max</i> (L.) Merr., Fabaceae	Seeds	Phenolic	220.2 µg/ml 24 h	F1 6.74 µg/ml F2 2.57 µg/ml	U87	(Freitas et al. 2019)
<i>Mimosa caesalpiniiifolia</i> Benth., Fabaceae	Stem bark	DCM extract	0.78 – 50 µg/ml 72 h	5.4 µg/ml	SF-295	(Silva et al. 2020)
<i>Dimorphandra mollis</i> Benth., Fabaceae	Leaves	Rutin, Quercetin	Rutin: 50 µM 48 h Quercetin: 1- 100 µM 48 h	-	U251, GL- 15	(Santos et al. 2015)

<i>Mimosa pteridifolia</i> Benth., Fabaceae	Bark	Ethanolic extract	0.39 – 50 µg/ml 72 h	>50 µg/ml	SF-295	(Silva et al. 2020)
<i>Mimosa tenuiflora</i> Benth., Fabaceae	Bark	Ethanolic extract	0.39 – 50 µg/ml 72 h	>50 µg/ml	SF-295	(Silva et al. 2020)
<i>Prosopis juliflora</i> (Sw.) DC., Fabaceae	Pods	Phenolic extract	0.03 – 30.0 µg/ml 24 and 48 h	0.03 µg/ml (24 h) 2.0 µg/ml (48 h)	GL-15	(Hughes et al. 2005)
<i>Tephrosia egregia</i> Sandwith, Fabaceae	Leaves, roots, stems	Ethanolic extract(5- hydroxy-8-(1",2"- epoxy-3"-hydroxy- 3"-methylbutyl)-7- methoxyflavone)	0.19 – 25 µg/ml 72 h	>20 µg/ml	SF-295	(Teixeira et al. 2018)
<i>Casimirella ampla</i> (Miers) R.A.Howard, Icacaceae	Roots	Ethylacetate (Annonalide)	5 µg/ml 72 h	2.18 µg/ml	SF-295	(Marques et al. 2018)

<i>Mentha crispa</i> L., Lamiaceae	Leaves	Oil	0.78 – 50 µg/ml 48 h	16.26 µg/ml	U87	(Turkez et al. 2018)
<i>Plectranthus grandis</i> (L.H.Cramer) R.H.Willemse, Lamiaceae	Roots	Hydrodistillate	25 µg/ml 72 h	20.2 µg/ml	SF-295	(Camelo et al. 2019)
	Leaves			15.91 µg/ml		
<i>Nectandra megapotamica</i> (Spreng.) Mez, Lamiaceae	Leaves	Hydrodistillate	3.91 – 500 µg/ml 24 h	79.14 µg/ml	M059J	(Almeida et al. 2020)
<i>Persea fulva</i> L.E.Kopp, Lamiaceae	Leaves	Ethyl acetate extract (Majoranolide B, Majoranolide, Majorenolide, Majorynolide	1-50 µM 24 h	9.06 µM, 6.69 µM, 12.04 µM, 41.90 µM	C6	(Reis et al. 2019)

<i>Eleutherine plicata</i> (Sw.) Herb., Iridaceae	Bulb	Ethanolic extract (Eleutherin)	0.5 – 50 µM 24 h	4.98 µM	C6	(Shinkai et al. 2022)
<i>Miconia albicans</i> (Sw.) Steud., Melastomataceae	Leaves	Ethanolic extract	1.5 - 300 µg/ml 72 h	12.05, 19.94, 70.21, 23.08, 38.07, 30.05 µg/ml	NHA, GAMG, U251, SF188, RES259, HCB151	(Silva et al. 2023)
<i>Miconia chamissois</i> Naudin, Melastomataceae	Leaves	Chloroform extract (Matteucinol)	28 µg/ml 72 h	28 µg/ml	U251	(Netto et al. 2022)
<i>Miconia chamissois</i> Naudin, Melastomataceae	Leaves	Chloroform extract (Matteucinol)	1.5 – 100 µg/ml 72 h	GAMG 5.7 µg/ml U251 26.57 µg/ml 72 h	GAMG, U251	(Silva et al. 2020)

<i>Miconia cuspidata</i> Naudin, Melastomataceae	Leaves	Ethanolic extract	1.5 - 300 µg/ml 72 h	2.9, 25.7, 28.9, 13.6, 29.3, 30.2 µg/ml	NHA, GAMG, U251, SF188, RES259, HCB151	
<i>Carapa guianensis</i> Aubl., Meliaceae	Seeds	Oil	30 – 120 µg/ml 48 h	FAA1 70 µg/ml FAA2 30 µg/ml	C6	(Silva et al. 2024)
<i>Bagassa guianensis</i> Aubl., Moraceae	Stem bark	Ethanolic extract (1- deoxynojirimycin)	0.5 – 32 mM 72 h	5.3 mM	A172	(Fonseca et al. 2024)
<i>Brosimum acutifolium</i> Huber, Moraceae	Bark	Hexane-acetone extract (BAS-1, BAS- 4)	25 – 150 µM 24 h	BAS-1 75 µM BAS-4 72 µM	C6	(Maués et al. 2019)
<i>Campomanesia adamantium</i> (Cambess.) O.Berg, Myrtaceae	Leaves	Hydrodistillate	3.91 – 500 µg/ml 24 h	M059J 79.9 µg/ml GM07492A 369.8 µg/ml	M059J, GM07492A	(Alves et al. 2020)

<i>Eugenia uniflora</i> L., Myrtaceae	Leaves	Oil	3.12 – 400 µg/ml 24 h	84.5 µg/ml	M059J	(da Silva et al. 2018)
<i>Eucalyptus grandis</i> W.Hill ex Maiden, Myrtaceae	Leaves	Ethanolic	30 – 300 µg/ml 24 h	300 µg/ml	U87	(Wouters et al. 2023)
<i>Plinia cauliflora</i> (Mart.) Kausel, Myrtaceae	Leaves	Oil	3.12 – 400 µg/ml 24 h	79.1 µg/ml	M059J	(da Silva et al. 2018)
<i>Rapanea ferruginea</i> (Ruiz & Pav.) Mez, Primulaceae	Leaves	Methanolic extract	10 – 1000 µg/ml 48 h	250 µg/ml	C6	(Dos Santos et al. 2018)
<i>Richardia brasiliensis</i> Gomes, Rubiaceae	Aerial part	Ethanolic extract	75 – 1000 24 h	932.30 µg/ml	U87	(Dornelles et al. 2022)
<i>Physalis pubescens</i> L., Solanaceae	Pulp and Seeds	Ethanolic extract	500 – 2000 µg/ml 48 and 72 h	>2000 µg/ml	C6, GL261	(Zimmer et al. 2021)
<i>Solanum lycocarpum</i> A.St.-Hil., Solanaceae	Fruits	Glycoalkaloid extract	1-128 µg/ml 24 h	9.60 – 40.82 µg/ml		(Munari et al. 2014)

		Solasonine (SS)	0.45 – 58 µg/ml 24 h	6.01 – 26.21 µg/ml	M059J, U343, U251	
		Solamargine (SM)		4.58 – 18.23 µg/ml		
<i>Cecropia pachystachya</i> Trécul, Urticaceae	Leaves	Ethanolic extract	25 – 500 µg/ml 72 h	377.1 µg/ml	C6	(Bona et al. 2024)
<i>Aloysia gratissima</i> (Gillies & Hook.) Tronc., Verbenaceae	Leaves	Aqueous extract	0 – 100 µg/ml 72 h	45.5 µg/ml	U87	(Lopes da Silva et al. 2023)
<i>Lippia gracilis</i> Schauer, Verbenaceae	Leaves, stems	Hexane and Methanolic extracts	0.024 – 50 µg/ml 72 h	6.1 µg/ml	SF-295	(Ribeiro et al. 2012)
<i>Drimys brasiliensis</i> Miers, Winteraceae	Leaves	Hydrodistillate	125 – 500 µg/ml 24 h	250 µg/ml	U-138	(Gomes et al. 2013)
<i>Drimys angustifolia</i> Miers, Winteraceae	Leaves	Hydrodistillate	125 – 500 µg/ml 24 h	500 µg/ml	U-138	(Gomes et al. 2013)

<i>Alpinia zerumbet</i> (Pers.) B.L.Burt & R.M.Sm., Zingiberaceae	Leaves	DCM extract (5,6- dehydrokavain)	0.25 – 250 µg/ml 48 h	22.89 µg/ml	U251	(Roman Junior et al. 2017)
		Chloroform fraction (pinostrobin)		32.73 µg/ml		

NHA: Normal Human Astrocytes; RES259: Pediatric Grade II Diffuse Astrocytoma

Table S2 Studies that tested isolated compounds

Classification	Compound	Source	Cell line(s)	Dose; Duration	Ref.
Acetogenins	AcL-1, AcL-2, AcL-3, AcL-4	<i>Annona coriacea</i> Mart.	U251, GAMG	1 – 25 µg/ml; 24 h	(Sousa et al. 2023)
Alkaloids	Erythraline (1)	<i>Erythrina verna</i> Vell.	SF-295	0.016 – 5 µg/ml; 72 h	(Guaratini et al. 2014)
Alkaloids	1-deoxynojirimycin (2)	<i>Bagassa guianensis</i> Aubl.	A172	0.5 – 32 nM; 72 h	(Fonseca et al. 2024)
Benzophenone	Burlemarxione A (3), Sampsonine N (4)	<i>Clusia burle-marxii</i> Bittrich.	GL-15	72 h	(Ferraz et al. 2019)

Benzophenones	7-epiclusianone (5)	<i>Garcinia brasiliensis</i> Mart.	U251, U138	10 – 40 µM; 48 h	(Sales et al. 2015)
Butanolides	Majoranolide B (6), Majoranolide (7), Majorenolide (8), Majorynolide (9)	<i>Persea fulva</i> L.E.Kopp	C6	1 – 50 µM; 24 h	(Reis et al. 2019)
Flavanones	Matteucinol (10)	<i>Miconia chamissois</i> Naudin	U251	28 µg/ml; 72 h	(J. B. Netto et al. 2022)
Flavanones	Matteucinol (10)	<i>Miconia chamissois</i> Naudin	GAMG, U251	1.5 – 100 µg/ml; 72 h	(Silva et al. 2020)
Flavonoids	Rutin (11)	<i>Citrus</i>	C6, U251	1 – 50 µM; 24 and 48 h	(da Silva et al. 2020)

Flavonoids	Brachydin E (13), Brachydin F (14)	<i>Fridericia</i> <i>platyphylla</i> (Cham.) L.G.Lohmann	U251	1.6 – 100 µg/ml; 48 h	(de Lima et al. 2022)
Flavonoids	Luteolin (15)	<i>Dittrichia graveolens</i> (L.) Greuter	U251	5 – 314 µM; 48 h	(Franco et al. 2021)
Flavonoids	Penduletin (16), Casticin (17)	<i>Croton betulaster</i> Müll.Arg.	GL-15	10 – 100 µM; 24 and 72 h	(Coelho et al. 2016)
Flavonoids	Rutin (11), Quercetin (12)	<i>Dimorphandra</i> <i>mollis</i> Benth.	U251, GL-15	50 µM, 1 - 100 µM; 48h	(Santos et al. 2015)
Flavonoids	BAS-1 (18), BAS-4 (19)	<i>Brosimum</i> <i>acutifolium</i> Huber	C6	25 - 150 µM; 24 h	(Maués et al. 2019)

Flavonoids	Pinostrobin (20), 5,6-dehydrokavain (21)	<i>Alpinia zerumbet</i> (Pers.) B.L.Burt & R.M.Sm.	U251	0.25 – 250 µg/ml; 48 h	(Roman Junior et al. 2017)
Flavonoids	5-hydroxy-8-(1",2"- epoxy-3"-hydroxy- 3"-methylbutyl)-7- methoxyflavone (22)	<i>Tephrosia egregia</i> Sandwith	SF-295	0.19 - 25 µg/ml; 72 h	(Teixeira et al. 2018)
Flavonoids	Achyrobichalcone (23), Luteolin (15), 3-O-methyl- quercetin (24), Quercetin (12)	<i>Achyrocline</i> <i>satureioides</i> (Lam.) DC.	U251, C6, U87	10 – 500 µg/ml; 72 h	(Souza et al. 2018)

Glycoalkaloids	Solamargine (25), Solasonine (26)	<i>Solanum</i> <i>lycocarpum</i> A.St.- Hil.	M059J, U343, U251	0.45 – 58 µg/ml; 24 h	(Munari et al. 2014)
Glycoproteins	Lectin	<i>Canavalia</i> <i>brasiliensis</i> Mart. ex Benth.	U87, GBM1, C6	1 – 50 µg/ml; 24 h	(Wolin et al. 2021)
Glycoproteins	Lectin	<i>Canavalia</i> <i>ensiformis</i> (L.) DC., <i>Dioclea violacea</i> (Mart. ex Benth.)	C6	10 – 100 µg/ml; 48 h	(Nascimento et al. 2018)
Glycoproteins	Lectin	<i>Canavalia gladiata</i> (Jacq.) DC.	C6	10 – 100 µg/ml; 48 h	(Cavada et al. 2018)

Glycoproteins	CrataBL Lectin	<i>Crataeva tapia</i> (Capparaceae Juss.)	U87	5 – 100 µM; 48 h	(Bonturi et al. 2019)
Isoprenoids/ Terpenoids	Triterpene 3β,6β,16β-tri- hydroxilup-20(29)- ene (27) Sesquiterpene Lactones (goyazensolide (28) and Lychnofolide (29)	<i>Combretum</i> <i>leprosum</i> Mart. <i>Eremanthus seidelii</i> MacLeish & H.Schumacher	SNB19 T98G, U87MG	1.19 – 1.74 µg/ml; 72 h 5 – 100 µM; 24 h	(Silva-Filho et al. 2020) (Izumi et al. 2020)
Naphthoquinones	Eleutherin (30)	<i>Eleutherine plicata</i> (Sw.) Herb.	C6	0.5 – 50 µM; 24 h	(Shinkai et al. 2022)

Neoflavones	Mammea B/BA (31), Mammea B/BA cyclo F (32), Ferruol A (33)	<i>Kielmeyera argentea</i> Choisy	U251	0.6 – 200 µM; 72 h	(Boness et al. 2021)
Pimarane diterpenes	Annonalide (34)	<i>Casimirella ampla</i> (Miers) R.A.Howard	SF-295	5 µg/ml; 72 h	(Marques et al. 2018)
Tocotrienols	δ-tocotrienol (35)	<i>Kielmeyera coriacea</i> Mart.	SF-295	0.02 – 25 µg/ml; 72 h	(de Mesquita et al. 2011)