Chapter

Cytotoxicity and Antitumor Action of Lignans and Neolignans

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Abstract

Lignans and neolignans are plant's secondary metabolites, widely distributed in the plant kingdom, and have been identified in more than 70 plant families. These compounds are mainly localized in lignified tissues, seeds, and roots. Lignans and neolignans present a great variety of biological activities, such as antioxidant, anti-inflammatory, antineurodegenerative, antiviral, antimicrobial, and antitumor. By 2040, it is estimated that the number of new cancer cases per year will rise to 29.5 million; therefore, the development of new anticancer agents and adjuvants is essential. Lignans and neolignans have also indicated a reduction in the risk of cancer at different stages. The objective of this review is to search and analyze the cytotoxic and antitumor activity of lignans and neolignans that can be an important source of new antitumor drugs. We have made a comprehensive summary of 113 lignans and neolignans, obtained from 44 plants and divided between 34 families, which demonstrated cytotoxic activity in several human cancer cell lines evaluated through various in vitro studies and other in vivo models, by inducing mitochondrial apoptosis and cell cycle arrest, inhibiting NF-κβ activity and activation of metalloproteinases (MMPs), among other processes. Overall, 13 compounds, methoxypinoresinol, arctigenin, trachelogenin, 4-O-methylhonokiol, honokiol, bifidenone, (−)-trachelogeninit, deoxypodophyllotoxin, matairesinol, bejolghotin G, H, and I, and hedyotol-B, showed the best anticancer activity.

Keywords: Neolignans, cytotoxic activity, cancer, natural products

1. Introduction

Cancer produces uncontrolled cell proliferation, and one of the treatments used to stop it is chemotherapy. However, although these therapies have advanced over the years, they not only destroy cancer cells but also healthy cells, causing adverse effects in people suffering from this disease. A great variety of tumors are the cause of death in the population; the World Health Organization (WHO) reports that cancer causes approximately 10 million deaths each year, with one out of every six deaths

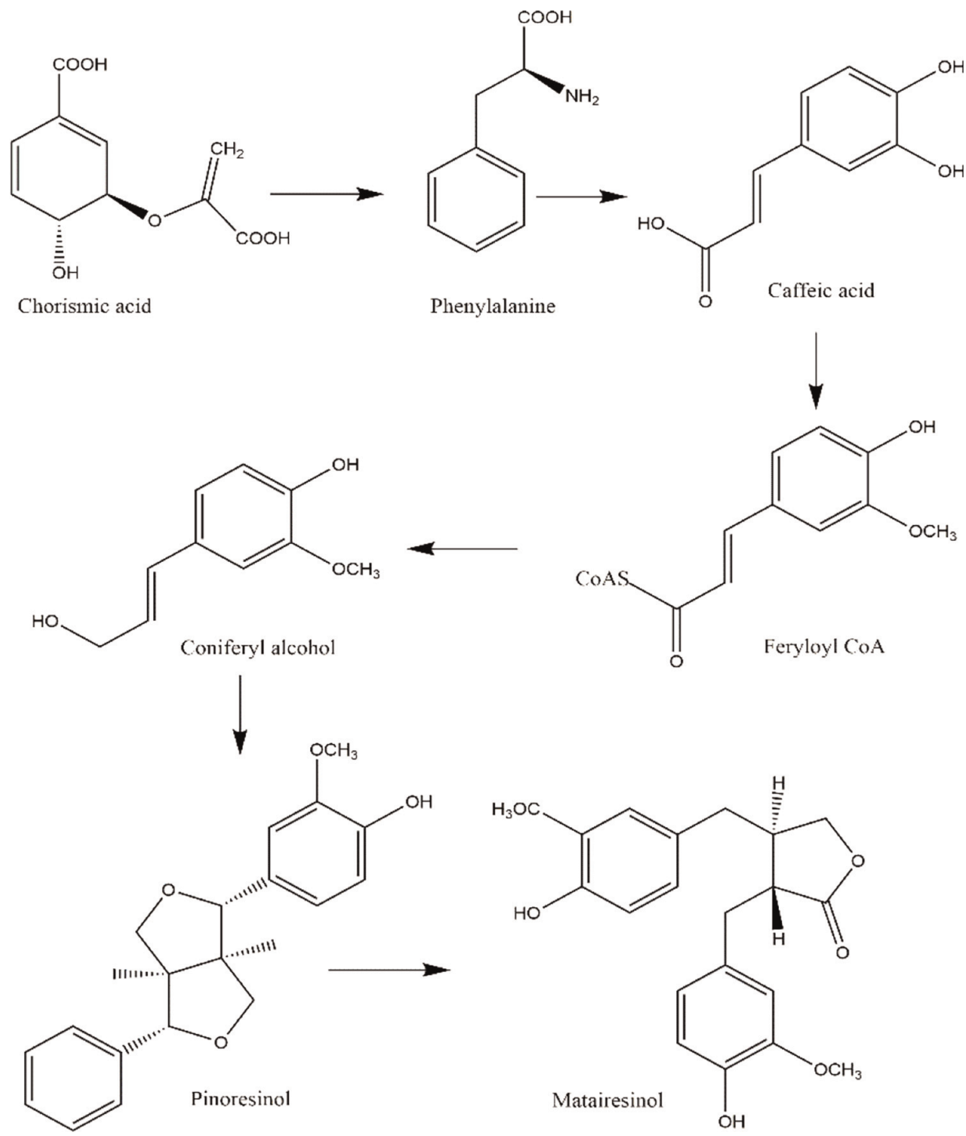


Figure 1.
Shikimic acid pathway for lignan and neolignan biosynthesis.

worldwide due to some type of cancer [1]. The main problem of this disease is that it is often detected at an advanced stage, and the lack of access to health services and the high cost of treatment are common, particularly in developing countries. The WHO suggests that 90% of the population in developed countries has access to treatment for this disease, while only 15% of the population in developing countries has access to treatment [2].

At present, the search for new chemotherapy drugs continues, with the purpose of having a wide range of compounds that help improve the quality of life of people with cancer. For many years, plants have played a very important role, as a source of compounds with biological activity. As a treatment alternative, multiple plant genera and species have demonstrated their cytotoxic potential in cancer cells and have been

Compound	Method	Results		Reference
1. 3-(1, 3-benzodioxol-5- yl methyl)-4-[(3, 4-dimethoxyphenyl)methyl] dihydro-, (3S-cis)-2(3H)- furanone **2.** 4-[(R)-1, 3-benzodioxol-5-ylhydroxymethyl]-3-(1, 3-benzodioxol-5-ylmethyl)dihydro-, (3S, 4R)-2(3H)-furanone **3.** (−)-Dihydrosesamin **4.** Phenol, 4, 4′-(2R, 3S, 4S)-tetrahydro2-methoxy-3, 4-furandiyl]bis(methylene)] bis[2-methoxy **5.** 4, 4′-dihydroxy-3, 3′, 9-trimethoxy-9, 9′-epoxylignan **6.** (+)-1-hydroxypinoresinol	MTT assay HL-60 SMMC-7721 A549 MCF-7 SW480	IC_{50} μM > 40		[11]
7. (+)-Nortrachelogenin **8.** -(3″-methoxy-4″-hydroxybenzyl)-3-(3′-methoxy-4′- hydroxylbenzyl)-γ-butyrolactone	MTT assay	IC_{50} μM		[12]
		(7)	(8)	
	A549	19.6	17.0	
	HepG2	17.6	15.1	
	U251	39.1	23.9	
	Bcap-37	51.6	50.3	
	MCF-7	45.6	25.3	
9. Sesamin (SE)	MTT assay	Cytotoxicity %		[13]
	MCF-7	23		
	Caco-2	15		
	CCK-8 assay in EL4 Cell apoptosis assay in EL4 lymphoma (EL4) induced in BALB/c mice	% Viability (40 μM) 50 to 80 (48, 72 y 96 h) SE Induced apoptosis by increased expression levels of apoptotic markers (Bax/Bcl-2) and cleaved-Caspase 3 SE decreased the size of tumor (10 mg/kg for 21 days)		[14]
10. Methoxypinoresinol	MTT assay PANC-1	IC_{50} μM 3.7		[15]
11. Erythro-austrobailignan-6 (EA6)	MTT assay 4 T-1 MCF-7 Western blot	IC_{50} μM (24 h) 4.3 12.6 EA6 increased the levels of p38 MAPK and caspase-3, in 4 T-1 and MCF-7		[16]
12. Mappiodoinin A **13.** Mappiodoinin B **14.** Mappiodoinin C **15.** Conocarpan **16.** Odoratisol A **17.** Trichobenzolignan **18.** Prunustosanan AI **19.** Simulanol **20.** Woorenogenin	MTT assay	IC_{50} μM		[9]
	HL-60	0.8–5.8		
	SMMC-7721	1.8–8.8		
	A-549	2.2–16.2		
	MCF-7	1.3–15.9		
	SW480	0.2–12.5		

Compound	Method	Results		Reference
21. Noralashinol B **22.** Noralashinol C	MTT assay HepG2	IC_{50} μM		[17]
		21	22	
		31.7	15.8	
23. Arctigenin (ATN)	MTT assay	IC_{50}μM		[18] [19]
	MCF-7	40.8		
	MCF-10A	24.1		
	SK-BR-3	20.7		
	MDA-MB-435S	3.8		
	MDA-MB-453	2.9		
	MDA-MB-231	0.8		
	MDA-MB-468	0.3		
	SRB assay in MCF-7 Colony formation assay. Cell cycle analysis by flow cytometry	At 200 μM arctigenin inhibited cell viability around 50%. ATN induced autophagy in MCF-7cells. The lignan might inhibit downstream effector molecules of the TOR resulting in a decreased expression of Erα in ER-positive MCF-7		
	Cell Count Reagent Western blot. JC-1 mitochondrial membrane potential	CC_{50} μM		[20]
		BC3	BCBL1	
		2.8	2.3	
		ATN induced the caspase-9-mediated apoptosis of glucose-starved PEL cells (BC3). ATN induced mitochondrial disruption in glucose-starved BC3 cells by decreasing ATP levels and disrupting the mitochondrial membrane, and suppressed ERK and p38 MAPK signaling		
24. Honokiol (HNK)	CCK-8 assay OC2 OCSL Apoptosis by annexin Xenograft nude mice model	GI_{50} μM at 48 h 22 13 This compound induced apoptosis cell death HNK had antitumour activity		[21]
	MTT assay	IC_{50} μg/mL		[22]

Compound	Method	Results	Reference
	KKU-213 L5 Apoptosis by Muse™ Cell Analyzer Western blot Flow cytometer analysis	24 (h) 48 (h) 50.0 26.3 % apoptosis 50 μM 70 μM 30.4 52.0 HNK increased apoptosis by decrease of intact caspase-3, whereas cleaved caspase-3 increased The antitumor activity of dendritic cells (DC) is increased using a lysate derived from a cell line (KKU-2113 L5) treated with HNK HNK increased antitumor activity of DCs stimulated with cell lysates derived from KKU-213 L5	
25.1-(2′,6′-dimethoxy-7′,8′-peroxyphenylpropyl)-2,10-dimethoxybibenzyl-6,9′-diol **26.** Aloifol I **27.** Moscatilin **28.** Moniliformine **29.** Balanophonin	MTT assay HL-60	IC_{50} μM 25 26 27 28 29 4.5 4.5 5.1 10.7 11.0	[23]
30. (−)-Trachelogenin (TA)	MTT assay HL-60 OVCAR-8 HCT-116 HCT-8 PC-3 SF-295 Membrane integrity and viability by the exclusion of propidium iodide	IC_{50} μM 32.4 3.5 1.9 5.2 15.0 0.8 TA did not induce apoptosis, but it was induced by autophagic death mediated by the increase of LC3 activation. Also promoted changes in the expression of Beclin-1 levels	[24]
31. 4-O-methylhonokiol (MH)	MTT assay OSCC PE/CA-PJ41	IC_{50} μM 1.3	[25]
32. Bifidenone (BF)	Sequoia Sciences Assay NCI-H460 Caspase-Glo 3/7 assay LDH assay Tubulin Polymerization assay Tubulin	IC_{50} μM 0.26 BF increased the levels of caspase (2.5-fold) BF increased the level of LDH released BF inhibits tubulin polymerization in a dose-dependent manner BF interfered with mitosis by	[26]

Compound	Method	Results	Reference
	competition assay PC-3 SF-295 ACHN	disrupting the microtubule dynamics necessary for cell division IC_{50} μM 0.49 0.25 0.36	
	M14 A375 UACC-62 SKMEL-2 HCC-2998	0.064 0.075 0.044 0.095 1.41	
33. (+)-Hinokinin	WST-8 Assay PANC-1 MIA-PaCa2 CAPAN-1 SN-1 KLM-1	PC_{50} μM 64.1 21.3 50.1 60.1 92.5	[27]
34. (−)-Deoxypodophyllotoxin (DPT)	MTT assay U2OS Annexin-V/ propidium iodide (PI) assay Acridine orange assay	IC_{50} nM 40 DPT induced apoptosis related with proteins Annexin-V positive cells were increased in DPT-treated cells, compared with control group. Formation of acidic vesicular organelles (AVOs) was significantly increased in DPT-treated cells in a dose-dependent manner	[28]
35. Lariciresinol (LA)	CCK-8 assay HepG2 Flow cytometry Immuno-fluorescence staining Annexin V/PI double-staining assay Mitochondrial membrane potential (ΔΨm)	IC_{50} μg/mL 208 after 48 h LA exhibited an apoptosis-inducing effect LA decreased Ki-67 expression and induced apoptosis LA was a concentration- and time-dependent manner resulted in an increasing percentage of apoptosis, which might result in the cytotoxic activity of LA on HepG2 cells LA might induce HepG2 cell apoptosis through the mitochondrial-mediated apoptosis pathway	[29]
36. Burserain **37.** Picropolygamain	MTT assay HeLa	IC_{50} μM 36: 21.7 37: 9.1	[30]

Compound	Method	Results			Reference
38. Heilaohulignan C **39.** Kadsuralignan I **40.** Longipedunin B	MTT assay	IC_{50} µM			[31]
		38 39 40			
	HepG2	9.9	21.7	18.7	
	BGC-823	16.6	—	—	
	HCT-116	16.7	—	—	
41. (−)-(7′S,8S,8′R)- 4,4′-dihydroxy-3,3′,5,5′-tetramethoxy-7′,9-epoxylignan-9′-ol-7-one **42.** Burseneolignan **43.** (8R)-3,5′-dimethoxy-8,3′-neoligna-4,4′,9,9′-tetraol	MMP-9 assay	IC_{50} µM			[32]
		41	42	43	
		16.5	18.8	8.7	
44. Oryzativol C	Ez-Cytox cell kit MDA -MB -231	IC_{50} µM 24.8			[33]
45. (−)-Asarinin	MTT assay A2780 SKoV3 Annexin V-FITC/PI Double Staining	IC_{50} µM 38.4 60.9 This compound might induce apoptotic cell death in human ovarian cancer cells			[34]
46. Balanophonin **47.** Dehydrodiconiferyl (DDI) **48.** Methoxyl-balanophonin	MTT assay	IC_{50} µM			[35]
		46	47	48	
	HepG2	36.5	78.6	80.5	
	Hep3B	29.3	65.5	76.8	
	Flow cytometry				
		DDI induced apoptosis			
49. Dehydrodieugenol B **50.** Methyldehydrodieugenol B (MEB)	MTT assay	IC_{50} µg/mL			[36]
		50	51		
	SKMEL-147	4.4	43.6		
	Comet Assay CBMN on SKMEL-29	100% of apoptosis	25% of apoptosis		
		MEB increased DNA damage by cytokinesis			
51. (−)-Rabdosiin	MTT assay	IC_{50} µg/mL			[37].
	MCF-7 SKBR3 HCT-116	75 83.0 84.0			
	Flow Cytometry	% of apoptosis			
	MCF-7 SKBR3 HCT-116	44.9 40.1 43.1			
52. Kalshiolin A	SRB assay A549 MDA-MB-231 MCF-7 KB KB-VIN	IC_{50} µg/mL 35.9 to 43.3			[38]

Compound	Method	Results			Reference
34. (−)-Deoxy podophyllotoxin **53.** (−)-Matairesinol	SRB assay NB	IC_{50}			[39]
		34		53	
		1.7 ng/mL		3.7 μg/mL	
54. Phengustifols A	CCK-8 assay A375	IC_{50} μM 12.1			[40]
55. Hedyotol-B	MTT assay SGC7901 A549 MDA-MB-231 HepG2	IC_{50} μM 1.7 6.1 24.0 26.0			[41]
56. Heilaohusus C	MTT assay HepG2	IC_{50} μM			[42]
		13.0			
57. Zijusesquilignan A **58.** Zijusesquilignan B **59.** Zijusesquilignan C	MTT assay	IC_{50} μM			[43]
		57	58	59	
	MCF-7	9.8	8.8	8.4	
	HL-60	11	—	—	
60, 61. Crataegifin B (enantiomers) **62.** CrataegifinC	MTT assay	IC_{50} μM			[44]
		60	61	62	
	Hep3B	25.5	59.4		
	HepG2	—	—	34.3	
	Flow cytometry	Compound 61 at 25 μM induced apoptosis in Hep3B cell in 10.76%			
63. Bejolghotin A **64.** Bejolghotin B **65.** Bejolghotin C **66.** Bejolghotin G **67.** Bejolghotin H **68.** Bejolghotin I	MTT assay	IC_{50} μM			[45]
	HCT-116	0.8–39.9			
	A549	0.9–39.9			
	MDA-MB-231	0.8–45.6			
54. (−)-Matairesinol **23.** Arctigenin **34.** (−)-Deoxypodophyllotoxin	MTT assay	IC_{50} μg/mL			[46]
		54	23	34	
	MDA-MB-231b	—	1.1	0.07	
	A549	—	0.8	0.004	
	HepG2	15.1	2.8	—	
69. Niranthin **70.** 7-hydroxy- hinokinin	MTT assay HepG2	IC_{50} μM			[47]
		69		70	
		7.2		8.5	
71. Cleistonkinin A **72.** Cleistonkinin B **73.** Cleistonkinin C **74.** Cleistonkinin D **75.** Cleistonkinin E	MTT assay	IC_{50} μM			[48]
	A549	>20			
	PANC-1	>20			
	HeLa	>20			

Compound	Method	Results			Reference
76. Cleistonkiside A **77.** Cleistonkiside B	Hep3B	>20			
	MCF-7	>20			
78. Crataegusal A **79.** Crataegusal A	MTT assay Hep3B	IC_{50} µM			[49]
		78	79		
		34.97	17.42		
80. Miliusin A **81.** Miliusin B **82.** Miliusin 7R,8S **83.** Miliusin C **84.** Miliusin D **85.** Miliusin E **86.** Miliusin F	MTT assay	IC_{50} (µM)			[50]
	HeLa	0.2–18			
	HN22	0.2–43.1			
	HepG2	2.9–88.5			
	HCT116	4.5–107.5			
87. Pleiocarpumlignan B	MTS assay MCF-7	IC_{50} µM 18.2			[51]
88. Officinalioside (OFD)	MTT assay HepG2	OFD showed cytotoxic effect at 50 µmol/L and 100 µmol/L			[52]
89. 5-((E)-2-carboxyvinyl)-7-methoxy-2-(3′,4′-methylenedioxyphenyl) Benzofuran **90.** Egonol **91.** (−)-Machicendiol	MTT assay	IC_{50} µM			[53]
		89	90	91	
	KB	96.0	22.1	33.5	
	HepG2	86.6	18.1	31.5	
	Lu	106.9	21.5	22.2	
92. Schisphenlignan M **93.** Schisphenlignan N **94.** Gomisin G **95.** Schisantherin D **96.** Schisantherin A **97.** Epigomisin O **98.** (+)-omisin K3 (Schisanhenol) **99**. Schisanhenol B **100.** Gomisin A	MTT assay A549 HCT116 SW620	IC_{50} µM 13.5 to >50			[54]
101. Glalignin B **102.** Glalignin C **103.** Glalignin E **104.** Glaneolignin A **105.** Dihydrodehydro diconiferyl alcohol **106.** Tribulusamide A	MTT assay A549	IC_{50} µM			[55]
		13.5–100			
	HeLa	20.1–79.9			
	MCF-7	11.4–100			
107. Pinoresinol monomethyl ether-β-D-glucoside (PMG)	MTT assay HeLa MDA-MB-231	IC_{50} µg/mL 10.1 (24 h) and 3.54(48 h) >250 (24 and 48 h)			[56]
108. Methylcubebin (MB) **109.** Cubebin (CB) **110.** Dyhydrocubebin (DB) **111.** Ethylcubebin (EB)	MTT assay HEp-2 SCC-25 Transwell cell migration assay	MB and CB decreased cell proliferation at concentrations of 10 and 50 µg/mL DB, EB, and MB decreased cell migration			[57]
112. (1S,2S)-1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-[(2S,3R,	MTT assay HL-60 A549	IC_{50} µM 8.2 15.1			[58]

Compound	Method	Results	Reference
4R)-tetrahydro-4-[(4-hydroxy-3-methoxyphenyl)methyl]-3-(hydroxymethyl)-2-furanyl] phenoxy]-1,3-propanediol (MFP)	SMMC-7721 MCF-7 SW480 Flow cytometry	10.6 4.4 16.1 MFP induced dose-dependent apoptosis in MCF-7 cells	

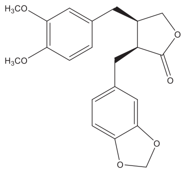
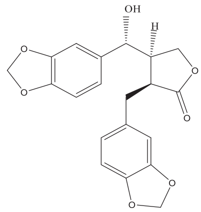
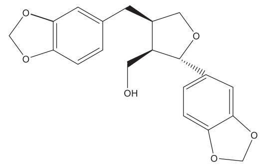
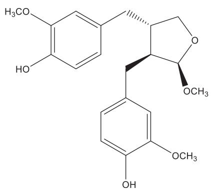
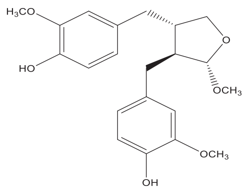
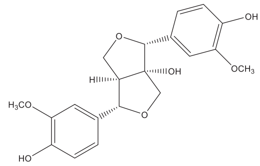
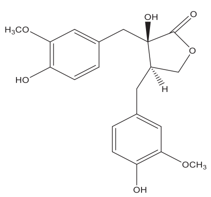
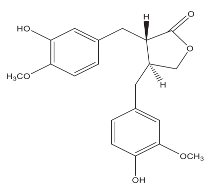
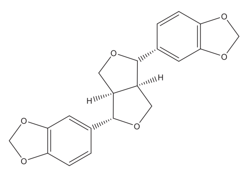
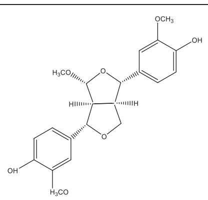
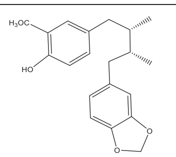
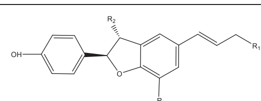
Abbreviations: PC50: Preferential cytotoxicity mean Concentration; IC50 Inhibitory mean Concentration; CC50: cytotoxic effects; GI50:Growth inhibition; LDH deshidrogenase lac tate; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; SRB: Sulforhodamine B; CCK-8: The Cell Counting Kit 8 assay; CBMNCyt: cytokinesis block micronucleus; MMP-9: Matrix metalloproteinase 9; LC3: a process that involved the bulk degradation of cytoplasmic components (positive structures are prominent in autophagy-deficient); MAPK: protein kinase; ERK: extracellular signal-regulated kinase; MYCN: proto-oncogene; MYCN2: human neuroblastoma cell with MYCN amplification; pCNA nuclear antigen of cell proliferation; STATs: Signal transducers and activators of transcription; JC-1: mitochondrial membrane assay.
Human cancer cell lines: A2780, SKOV3, OVCAR-8: ovarian; A549, NCI-H460: lung; BGC-823, SGC7901: gastric cancer; Caco-2, HCC-2998, HCT-16, HCT-116, HCT-8, SW480, SW620: colon cancer; HeLa: human cervical uterine cancer; KB, KBVIN: papillomavirus; Bcap-37: endocervical adenocarcinoma; Hep3B, HepG2, SMMC 7721: hepatocellular carcinoma; KKU-213 L5: cholangiocarcinoma; HEp-2: laryngeal cancer; HL-60: promyelocytic leukemia; SN-1: leukemia; HN22: head and neck squamous cell carcinoma; TNBC, MCF-10A, MCF-7, MDA-MB-468, MDA-MB-453, MDAMB-231, SK-BR-3: breast cancer; NB: neuroblastoma; SKMEL-147: wild-type human melanoma; SKMEL-29: human melanoma carrying the B-Raf mutation-V600E; SKMEL-2, A375: malignant melanoma skin; M14, UACC-62: melanoma; OC2, SCC-25, OSCC: squamous cell carcinoma; Lu carcinoma; MIA-PaCa2, CAPAN-1, KLM-1 PANC-1: pancreatic cancer; PC-3: prostate cancer; SF-295, U251: glioblastoma; ACHN: renal cancer; U2OS: osteosarcoma; BCBL1: lymphoma cells; muscular cancer cell lines 4 T-1.

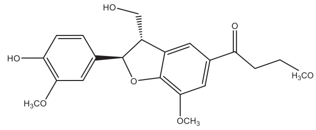
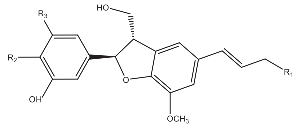
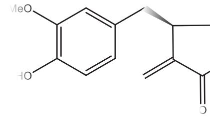
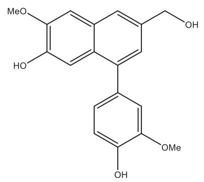
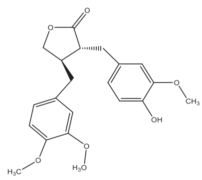
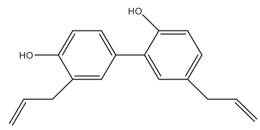
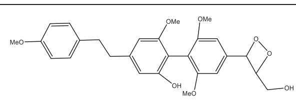
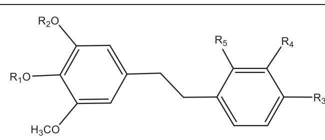
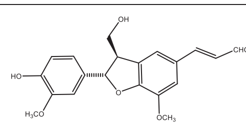
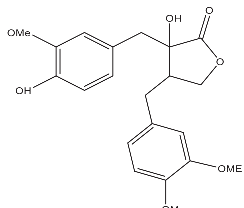
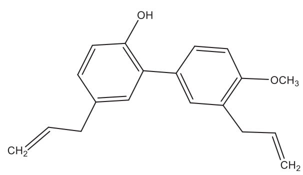
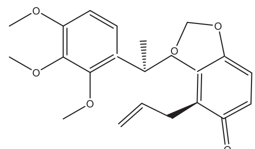
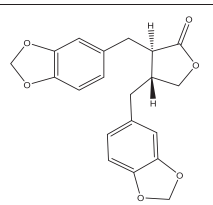
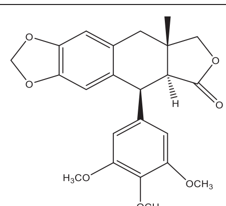
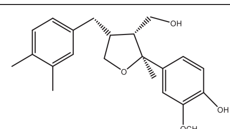
Table 1.
Anticancer activity of lignans and neolignan isolated of different plants.

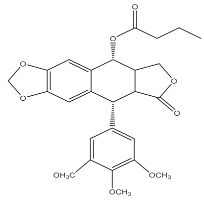
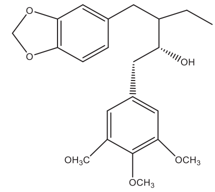
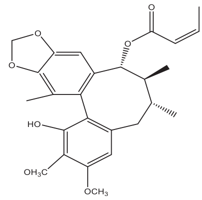
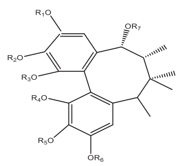
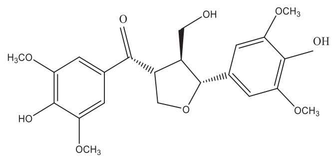
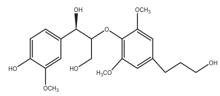
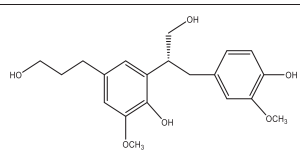
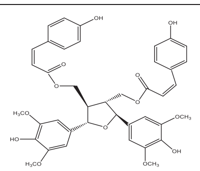
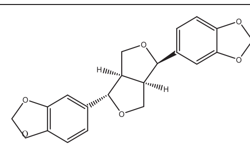
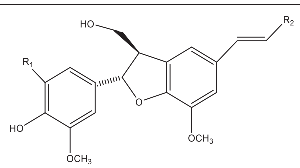
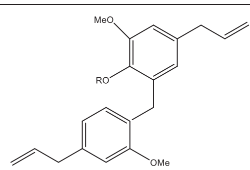
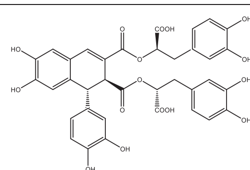
used in traditional medicine in many countries as anti-inflammatory and antirheumatic agents, among others, as well as antirhythmic and antitumor agents, since they inhibit cell proliferation and induce cytotoxicity in a large number of cell lines, as demonstrated through research [3].

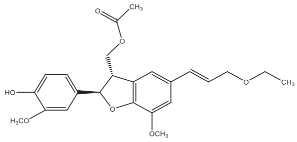
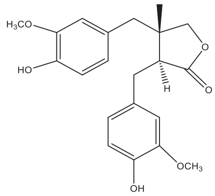
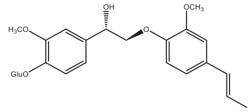
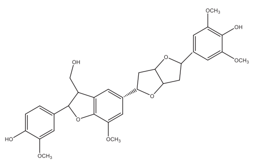
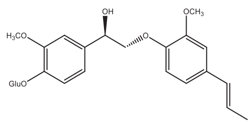
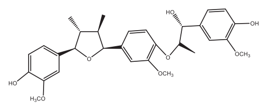
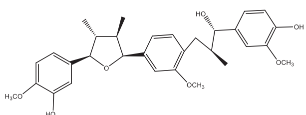
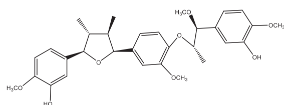
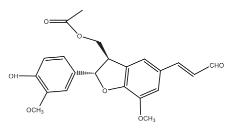
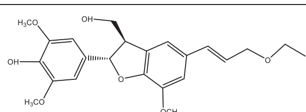
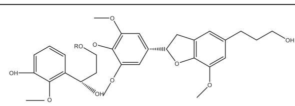
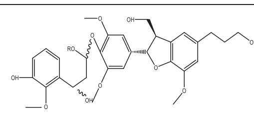
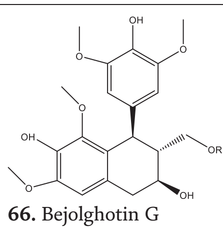
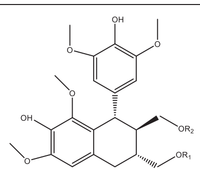
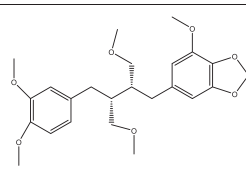
Lignans are a group of secondary metabolites found in different plant and animal species. Lignans are biologically synthesized from the shikimic acid pathway [4] and through different reactions (**Figure 1**). Despite their structural variety, lignans are dimers of phenylpropanoid units that are linked via their β-carbon atoms [5]. Dimers of phenylpropanoid units that are coupled via other linkages are named neolignans [6]. The lignan family is classified into the following eight classes, based on how oxygen is incorporated into the skeleton and the cyclization pattern: furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene, and dibenzylbutyrolactol. The neolignans have structural variety and are divided into more than 15 groups, some of them are: benzofuran, dihydrobenzofuran, diarylethane, benzodioxine, alkyl aryl ether, and bicycloctane derivatives, among others [7]. These metabolites present different biological activities, such as cytotoxicity; as an example, podophyllotoxin is used in cancer treatments today [8].

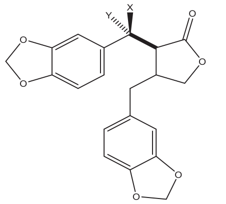
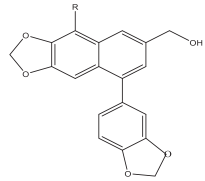
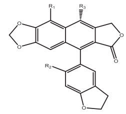
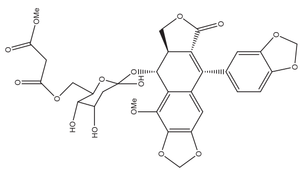
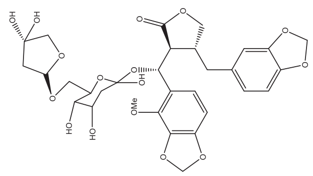
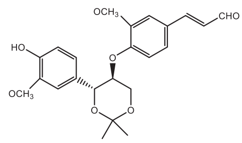
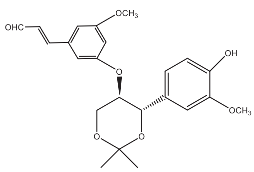
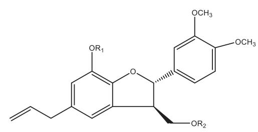
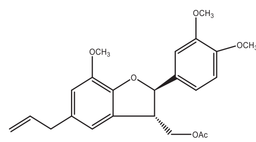
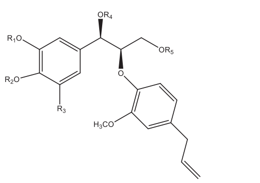
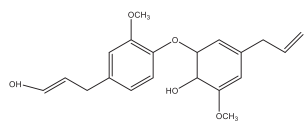
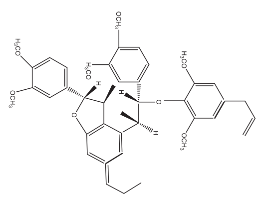
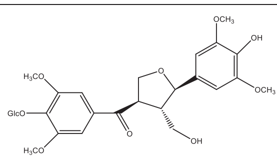
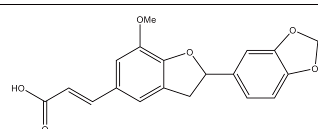
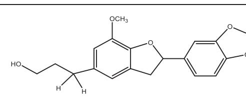
In this sense, Jiang and col. [9] have suggested that this behavior is not the same with all cell lines, where tested, and that it depends on the type of lignan for its cytotoxicity. Multiple lignans are being studied, particularly for their effectiveness against breast cancer. Because they bind to cells where there are estrogen deposits, they have been shown to be effective against breast cancer [10]. The cytotoxic activity of various lignans has also been studied on colon, pancreatic, throat, and oral cancers,

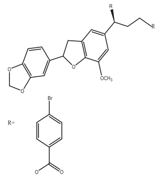
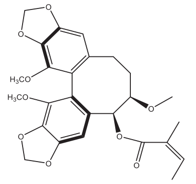
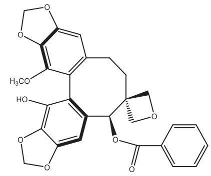
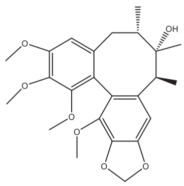
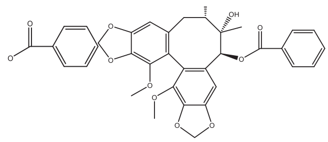
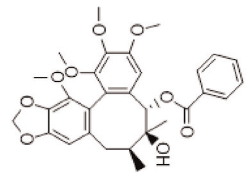
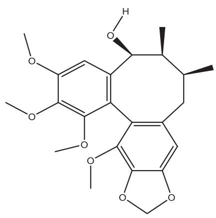
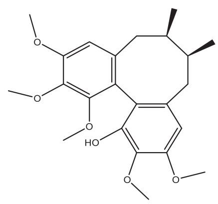
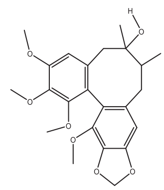
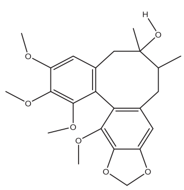
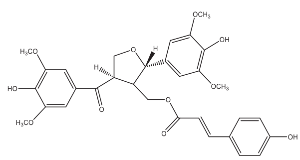
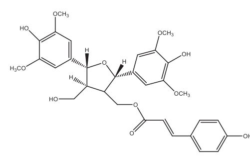
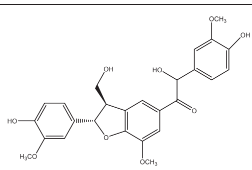
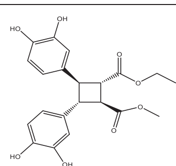
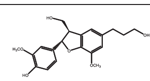
Wikstroemia scytophylla		
 **1.** 3-(1, 3-benzodioxol-5-ylmethyl)-4-[(3, 4-dimethoxyphenyl)methyl] dihydro-, (3S-cis)-2(3H)- furanone	 **2.** 4-[(R)-1, 3-benzodioxol-5-ylhydroxymethyl]-3-(1, 3-benzodioxol-5-ylmethyl)dihydro-, (3S, 4R)-2(3H)-furanone	 **3.** (−)-Dihydrosesamin
Wikstroemia scytophylla		
 **4.** Phenol, 4, 4′-(2R, 3S, 4S)-tetrahydro2-methoxy-3, 4-furandiyl]bis(methylene)]bis[2-methoxy	 **5.** 4, 4′-dihydroxy-3, 3′, 9-trimethoxy-9, 9′-epoxylignan	 **6.** (+)-1-hydroxypinoresinol
Bupleurum chinense		*Zanthoxylum capense, Sesamun* *Virola; Piper sp, Camellia sp, Magnolia sp*
 **7.** (+)-Nortrachelogenin	 **8.** -(3″-methoxy-4″-hydroxybenzyl)-3-(3′-methoxy-4′- hydroxylbenzyl)-γ-butyrolactone	 **9.** Sesamin (SE)
Calotropis gigantea	*Saururus chinensis*	*Mappianthus iodoizes*
 **10.** Methoxypinoresinol	 **11.** Erythro-austrobailignan-6 (EA6)	 **12.**Mappiodoinin A R_1 = OH, R_2 = H, R_3 = H **13.** Mappiodoinin B R_1 = OCH_3, R_2 = H, R_3 = H **14.** Mappiodoinin C R_1 = COH, R_2 = OH, R_3 = OCH_3 **15.** Conocarpan R_1 = H, R_2 = H, R_3 = H **16.** Odoratisol A R_1 = OH, R_2 = OH, R_3 = H

Wikstroemia scytophylla		
Mappianthus iodoizes		*Syringa pinnatifolia*
 **17.** Trichobenzolignan	 **18.** Prunustosanan AI R_1 = OH, R_2 = OCH_3, R_3 = OCH_3 **19.** Simulanol R_1 = OCH, R_2 = OH, R_3 = H **20.** Woorenogenin R_1 = OCH, R_2 = OCH_3, R_3 = H	 **21.** Noralashinol B
Syringa pinnatifolia	*Arctium lappa, Cupressus macrocarpa*	*Magnolia officinalis*
 **22.** Noralashinol C	 **23**. Arctigenin (ATN)	 **24.** Honokiol (HNK)
Dendrobium williamsonii		
 **25.** 1-(2′,6′-dimethoxy-7′,8′-peroxyphenylpropyl)-2,10-dimethoxybibenzyl-6,9′-diol	 **26.** Aloifol I,R_1 = R_3 = R_4 = H, R_2==CH_3, R_5 = OH **27.** Moscatilin,. R_1 = R_5 = H, R_2 = CH_3, R_3 = OH **28.** Moniliformine R_1 = R_2 = R_4 = R_5 = H, R_3 = OCH_3	 **29**. Balanophonin
Combretum fruticosum	*Magnolia officinalis*	*Beilschmiedia sp*
 **30.** (−)-Trachelogenin	 **31.** 4-O-methylhonokiol (MH)	 **32.** Bifidenone (BF)
Chamaecyparis obtusa	*Anthriscus sylvestris, C. macrocarpa*	*Patrinia scabra*
 **33.** (+)-Hinokinin	 **34.** (−)-Deoxypodophyllotoxin (DPT)	 **35.** Lariciresinol (LA)

Wikstroemia scytophylla		
Bursera microphylla		*Kadsura coccinea*
 **36.** Burserain	 **37.** Picropolygamain	 **38.** Heilaohulignan C
Kadsura coccinea	*Selaginella moellendorffii*	
 **39.** Kadsuralignan I $R_1 + R_2 = CH_2$; $R_3 = R_5 = R_6 = CH_3$; $R_7 = OH$; $R_4 = OAng$ **40.** Longipedunin B$R_1 + R_2 = CH_2$; $R_3 = R_5 = R_6 = CH_3$; $R_4 = OH$; $R_7 = OProp$	 **41.** (−)-(7′S,8S,8′R)- 4,4′-dihydroxy-3,3′,5,5′-tetramethoxy-7′,9-epoxylignan-9′-ol-7-one	 **42.** Burseneolignan
Selaginella moellendorffii	*Oryza sativa*	*Asarum sieboldii*
 **43.** (8R)-3,5′-dimethoxy-8,3′-neoligna-4,4′,9,9′-tetraol	 **44.** Oryzativol C	 **45.** (−)-Asarinin
Picrasma quassioides	*Nectandra leucantha*	*Ocimum sanctum*
 **46.** $R_1 = H$; $R_2 = CHO$ **47.** $R_1 = H$; $R_2 = OH$ **48.** $R_1 = OCH_3$; $R_2 = CHO$	 **49**. R = H Dehydroeugenol **50**. R = Me methyl	
46. Balanophonin, **47.** Dehydrodiconiferyl (DDI). **48.** Methoxyl-balanophonin	**49.** Dehydrodieugenol B **50.** Methyldehydrodieugenol B (MEB)	**51.** (−)-Rabdosiin

Wikstroemia scytophylla		
Kalimeris shimadaies	*C. macrocarpa*	*Elaeagnus angustifolia*
 **52.** Kalshiolin A	 **53.** (−)-Matairesinol	 **54.** Phengustifols A
Herpetospermum pedunculosum	*Kadsura coccinea*	*Ziziphus jujuba*
 **55.** Hedyotol-B	 **56.** Heilaohusus C	 **57.** Zijusesquilignan A
Z. jujuba	*Crataegus pinnatifida*	
 **58.** Zijusesquilignan B	 **59.** Zijusesquilignan C	 **60**−**61.** Crataegifin B
C. pinnatifida	*Cinnamomum bejolghota*	
 **62.** Crataegifin C	 **63.** Bejolghotin A	 **64.** Bejolghotin B 7”S, 8”R R = E-Feruloyl **65.** Bejolghotin C 7”R, 8”R R = E-Feruloyl
Cinnamomum bejolghota		*Euphorbia hirta*
R = E-Feruloyl		
 **66.** Bejolghotin G	 **67.** Bejolghotin H R_1 = E-Feruloyl R_2 = H **68.** Bejolghotin I R_1 = R_2 = E-Feruloyl	 **69,** Niranthin

Wikstroemia scytophylla		
E. hirta	*Cleistanthus tonkinensis*	
 **70.** 7-hydroxy- hinokinin	 **71**. *R = H* **72**. *R = OCH_3* **71.** Cleistonkinin A **72.** Cleistonkinin B	 **73**. Cleistonkinin C R_1 = OCH3, R_2 = H, R_3 = H **74**. leistonkinin D R_1 = OCH3, R_2 = H, R_3 = OH **75**. Cleistonkinin E R_1 = H, R_2 = OH, R_3 = OH
Cleistanthus tonkinensis		*C. pinnatifida*
 **76.** Cleistonkiside A	 **77.** Cleistonkiside B	 **78.** Crataegusal A
C. pinnatifida	*Miliusa sessilis*	
 **79.** Crataegusal A	 **80**. Miliusin AR_1 = H, R_2 = AC **81**. Miliusin BR_1 = H, R_2 = H **82**. Miliusin 7R,8SRR_1 = CH_3, R_2 = H	 **83.** Miliusin C
Miliusa sessilis		*Piper pleiocarpum*
 **84.** Miliusin D. *R_1 = R_2 = CH_3, R_3 = R_4 = H, R5 = Ac* **85.** Miliusin E *R_1 = R_2 = CH_3, R_3 = R_4 = R_5 = H*	 **86.** Miliusin F	 **87.** Pleiocarpumlignan B
Solanum lyratum	*Styrax argentifolius*	
 **88.** Officinalioside (OFD)	 **89.** 5-((E)-2-carboxyvinyl)-7-methoxy-2-(3′,4′-methylenedioxyphenyl) Benzofuran	 **90.** Egonol

Wikstroemia scytophylla		
Styrax argentifolius	*Schisandra sphenanthera*	
 **91.** (−)-Machicendiol	 **92.** Schisphenlignan M	 **93.** Schisphenlignan N
Schisandra sphenanthera		
 **94.** Gomisin G	 **95.** Schisantherin D	 **96.** Schisantherin A
Shisandra sphenanthera		
 **97.** Epigomisin O	 **98.** (+)-Gomisin K3	 **99.** Schisanhenol B
Schisandra sphenanthera	*Sigesbeckia glabrescens*	
 **100.** Gomisin A	 **101.** Glalignin B	 **102.** Glalignin C
Sigesbeckia glabrescens		
 **103.** Glalignin E	 **104.** Glaneolignin A	 **105.** Dihydrodehydrodiconiferyl alcohol

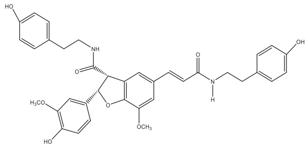
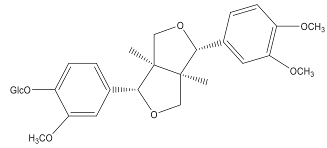
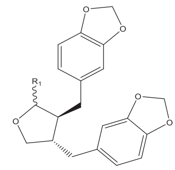
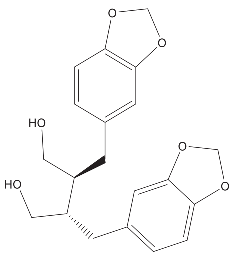
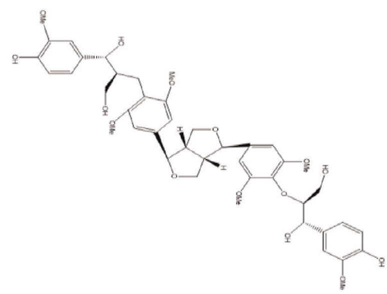
Wikstroemia scytophylla		
Sigesbeckia glabrescens	*Jurinea macrocephala*	*Piper cubeba*
		 **108**. R_1 = MeO **109**. R_1 = OH **110**. R_1 = EtO
106. Tribulusamide A	**107.** Pinoresinol monomethyl ether-b-D-glucoside (PMG)	**108.** Methylcubebin (MB) **109.** Cubebin (CB) **110.** Ethylcubebin (EB)
P. cubeba	*Solanum violaceum*	
 **111.** Dyhydrocubebin (DB)	 **112.** (1S,2S)-1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-[(2S,3R, 4R)-tetrahydro-4-[(4-hydroxy-3-methoxyphenyl)methyl]-3-(hydroxymethyl)- 2-furanyl] phenoxy]-1,3-propanediol (MFP)	

Table 2.
Lignans and neolignans structures.

among others, but the comparability of these studies depends on the type of assay with which the findings are reported. Therefore, the assay selection is of great importance in understanding the toxicity profile of lignans, as an approximation of their cytotoxic potential if used in humans.

The aim of this research was to present an overview of the anticancer activity of lignans *in vitro* and *in vivo* studies (**Table 1**), with the type of assay described in the international literature in the last 5 years, as well as their structures (**Table 2**).

2. Discussion

Lignans act as antioxidants and play an important role in protection against herbivores, pathogenic fungi, and bacteria [59]. These lignans have positive effects on different diseases, such as cancer and type 2 diabetes.

The lignans present in the feed diet might be metabolized by the gut microbiota through deglycosylations, p-dehydroxylations, and m-demethylations, but there is no enantiomeric inversion, producing phytoestrogens (molecules with an estrogen-like effect), but there is not enantiomeric inversion; these metabolites are called “mammalian lignans or enterolignans” [60], for example, aglycones of enterolactone and enterodiol, formed from matairesinol and secoisolariciresinol, respectively. Both of these aglycones have antitumor effects against breast, colon, and lung cancer [61].

In this review, we found 112 lignans and norlignans with cytotoxic activity, isolated from plants of 34 families, such as Magnolicea, Lauraceae, and Sauracea, among others. We found that 13 of these lignans have a high activity on several human cancer cell lines.

Only cytotoxicity activity was determined in 92 of these lignans and this effect was evaluated by MTT assay. The antitumor effect of sesamine and honokiol was determined on tumors induced with lymphoma cells and squamous cells carcinoma respectively.

In the treatment of cancer, there are used compounds that produce cell death in two ways: apoptosis and direct toxicity, then the new therapies are focused on substances to induce apoptotic cancer cell death [62]. In this review, we found 16 lignans that promote cell death by apoptosis.

The apoptotic cell death could occur by the disruption of the mitochondrial membrane, which is a crucial signaling pathway in the induction of apoptosis diminishing the levels of ATP, inhibiting ERK and p38 MAPK signaling. Bcl-2 (antiapoptotic protein) protein family control apoptosis by regulating mitochondrial membrane permeability while Bax is an inducer of apoptosis. Caspase-9 is activated, promoting the cleavage of caspase-3 and PARP, which contributes to apoptosis and ultimately cell death. Lignans 23 y 35 induced apoptosis by this route [29, 20].

MMP-9 is an overexpressed proteolytic enzyme in cancer cells that acts as a precursor to the action of other endopeptidases. This enzyme is a new target for cancer therapy owing to its pivotal role in metastatic tumors. Compounds 41, 42, and 43 inhibit the overexpression of MMP-9 [32].

In vitro test flow cytometry is used for the investigation and diagnosis of diseases such as cancer. In the different studies reported in this review, this technique was used to find out: the percentage of viable cancer cells, the characteristics of the cells such as size and shape, tumor markers, cell cycle analysis, and type of cell death [63]. In **Table 1**, it is shown that compounds 35, 47, 51, 61, and 112 induced apoptotic death of cancer cells by this technique.

Tubulin and its assembly product, microtubules, are among the most successful targets in cancer chemotherapy. It is currently known that podophyllotoxin and its commercial derivatives Etoposide and Teniposide exert their mechanism of action in cancer cells by altering Topoisomerase II and tubulin [64]. Williams et al. (2017) found that Bifidenone lignan also acts at the microtubule level of NCI-H460 cells, causing the inhibition of tubulin polymerization and therefore the arrest of the G2 / M phase of the cell cycle [32].

Arctigenin (ATN) is a dibenzylbutirolactone lignan isolated from the fruit of Arctium lappa and exhibited a cytotoxic effect on different breast cancer cell lines (MDA-MB-231, MDA-MB-435S, MDA-MB-453, and MDA-MB-468). In ER-positive MCF-7 cells, ATN inhibited downstream effector molecules of the target of rapamycin (TOR), decreasing the expression of estrogen receptor-α (Erα) and inducing autophagy.

Another way for cell death: Autophagy is a self-degradative process, which involves the enzymatic breakdown of different cytoplasmatic components. This process promotes the elimination of damaged or harmful components [65].

In vitro, this lignan inhibited the migration and invasion of MDA-MB-231 by downregulation of MMP-2, MMP-9, and heparinase expression [66].

(−)-Trachelogenin (TA) belongs to the dibenzylbutyrolactone lignan class and has been isolated from different plants, such as Trachelospermi caulis, *T. asiaticum, T.*

Jasminoides, and Combretum fruticosum. This lignan has different pharmacological activities, such as anti-inflammatory [67], antidepressant, and anticancer effects [68]. TA did not induce apoptosis but induced autophagic death, mediated by increased LC3; its possible mechanism of induced autophagic cell death involves cytoplasmic vacuolization and formation of autophagosomes mediated by increasing LC3 activation, promoting changes in the expression of Beclin-1 levels [24].

4-O-methylhonokiol (MH) is a neolignan, a type of phenolic compound. It is found in the bark of *Magnolia grandiflora*, *Magnolia virginiana* flowers, and *Magnolia officinalis*. MH induced cytotoxicity on human oral carcinoma cells (OSCC PE/CA-PJ41). Its anticancer activity is due to its capacity to induce ROS-mediated alteration of MMP, mitochondrial apoptosis, and cell cycle arrest [25], and to inhibit neuroinflammation, amyloidogenesis, and memory impairment [69]. MH protected against diabetic cardiomyopathy in type 2 diabetic mice [70]. It also inhibited NkKB activity on human colon cancer cells and cell cycle arrest, and induced apoptosis [71]. Additionally, MH induced apoptosis on oral squamous cancer cells (OSCC) via Sp1 [72].

Deoxypodophyllotoxin (DPT) was isolated from plants of the genus Podophyllum and has also been obtained from other species, such as *Athriscus sylvestris*, *Juniperus oblonga,* and *Cupressus macrocarpa*. DPT presented high toxicity and some side effects, so its use is limited [73]. In vitro, DPT reduced the cell proliferation of NB cells, MDA-MB-231, and A549 lines, induced apoptosis and cell cycle arrest, reduced the expression of pCNA, and increased intracellular free calcium levels that promoted NB cell death.

Matairesinol (MT) was isolated from *Juniperus oblonga* and exhibited anti-inflammatory [74] and cytotoxic activity against neuroblastoma cell lines, with and without tetracycline-inducible MYCN over-expression, and induced apoptosis and cell cycle arrest [39]. MT ameliorated experimental autoimmune uveitis [75] and showed angiogenic activity in vivo and in vitro. This compound also inhibited the proliferation of human umbilical vein endothelial cells (HUVECs) [76].

Other lignans with significant anticancer activity are: methoxypinoresinol, which is a furanoid lignan isolated from the leaves of *Calotropis gigantea*; honokiol was isolated from *Magnolia officinalis*; trachelogenin isolated from *Combretum fruticosum*; bifidenone, which is isolated from *Beilschmiedia* sp.; hedyotol-B, which was isolated from the stems of *Herpetospermum pedunculosum*; bejolghotin G, H, and I, which were isolated from the leaves and twigs of *Cinnamomum bejolghota*. These compounds have been isolated recently, and they are the subject of few pharmacological studies.

The most studied cancer cell lines were lung, hepatocellular carcinoma, colon, and breast. The cell lines diversity was colon cancer, breast cancer, human melanoma, and pancreatic cancer. These cell lines had the highest number of reports.

The lignans and neolignans with middle activity in lung cancer cells were: 12—20, 63—68, 112, colon cancer cells: 12—20, 63—68, 80—85,112, hepatocellular carcinoma cells: 12—20, 69, 70, 80—85, 112, and breast cancer cells: 11, 51, 63–68, 107,112.

In this review, we found that the less studied cancer cells were ovarian, gastric, endocervical adenocarcinoma cells, cholangiocarcinoma, laryngeal, leukemia, neuroblastoma, pancreatic cancer, prostate cancer, renal cancer, and osteosarcoma.

This review shows that various lignans and neolignans could be promising candidates for the treatment of different types of cancer.

Conflict of interest

The authors declare that they have no competing interests.

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