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Review

Peppers: A "Hot" Natural Source for Antitumor Compounds

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Abstract: *Piper*, *Capsicum*, and *Pimenta* are the main genera of peppers consumed worldwide. The traditional use of peppers by either ancient civilizations or modern societies has raised interest in their biological applications, including cytotoxic and antiproliferative effects. Cellular responses upon treatment with isolated pepper-derived compounds involve mechanisms of cell death, especially through proapoptotic stimuli in tumorigenic cells. In this review, we highlight naturally occurring secondary metabolites of peppers with cytotoxic effects on cancer cell lines. Available mechanisms of cell death, as well as the development of analogues, are also discussed.

Keywords: peppers; *piper*; *capsicum*; secondary metabolites; antitumor activity; apoptosis

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4. Introduction

Antineoplastic chemotherapy remains a challenge nowadays since the current drugs affect both tumorigenic and healthy cells, causing undesirable adverse effects due to low selectivity and high toxicity [1]. Moreover, resistance against anticancer drugs may brutally impair the effectiveness of chemotherapy. These issues illustrate the need for new anticancer therapies and the development of more effective and safer antitumor agents [2].

Natural products play an important role in the discovery of new drugs and in addition, they are an important source of innovative molecular scaffolds for the treatment of various diseases, especially cancer. According to Newman and Cragg (2016) [3], among antitumor drugs approved worldwide between 1940 and 2014, 49% of the new molecular entities were natural products or directly derived compounds. Big pharmaceutical companies have retreated from their natural product-derived drug discovery projects, yet several authors have reported new methods and techniques that enhance exploration of the chemical diversity of natural products (e.g., mass spectrometry, genomics, proteomics, automated extract production, and phenotypic high-throughput screening) [3–8]. Of note is that these new techniques have allowed the identification of many active compounds in traditional medicines [9–15].

Primarily used as spices for foods due to the pungent flavor and aroma, peppers have an important position as excellent producers of secondary metabolites that have a wide range of pharmacological properties. For instance, the *Piper*, *Capsicum*, and *Pimenta* genera have been used by ancient civilizations (e.g., Chinese, Mayan, and Caribbean traditional medicines) in formulations for cancer treatment. However, their value as a natural source for cytotoxic compounds has only gained attention in the last decades [16–19]. Herein, we summarize the in vitro proapoptotic activity of secondary metabolites of peppers and discuss the current efforts to produce pepper-derived analogues with enhanced cytotoxic activity. We observed that most of the research in this field was done

by academic institutions. Although many compounds have a potent proapoptotic profile, high selectivity for cancer cells, and easy synthetic accessibility, none of them have progressed to the clinics so far.

2. Pepper Ethnopharmacology

Piperaceae, a promising natural source for new drugs, is a pantropical family of plants comprising approximately 4000 species that contain biologically active natural products, including amides, lignans, neolignans, benzopyrene, pyrones, flavonoids, and terpenoids. These compounds led peppers to be broadly used in folk medicine worldwide, especially in Asia and Latin America [16,20,21]. The Piperaceae family has five genera: *Macropiper*, *Zippelia*, *Peperomia*, *Manekia*, and *Piper*, which is the largest genus of this family (nearly 2000 species) [22]. Many *Piper* species are popularly used for the treatment of several disorders, such as rheumatism [23], cardiac arrhythmias [24], asthma [25], upset stomach [26], and many kinds of infections [21]. Further biological properties have been reported for secondary metabolites of *Piper*, such as antinociceptive [27], anti-inflammatory [28,29], antiplatelet aggregation [30], antioxidant [31], antiophidic [32], anxiolytic/antidepressant [33], antidiabetic [32], hepatoprotective [34], leishmanicidal [35], anti-secretory [36], and cytotoxic effects [37].

The Solanaceae family comprises 98 genera and nearly 2700 species [38]. Interestingly, common dietary ingredients appear in Solanaceae subfamilies, such as tomatoes and potatoes (*Solanum*), bell and chili peppers (*Capsicum*), and tobacco (*Nicotiana*) [39]. The biological aspects of this family are primarily related to their alkaloid content (e.g., tropanes, nicotine, capsaicinoids, and glycoalkaloids) [40–45]. Chili peppers that are found in the *Capsicum* genus are believed to have been part of the human diet since immemorial time. It is well established that Central and South American Indians grew these peppers before Christopher Columbus' arrival [46]. The *Capsicum* genus comprises ~27 species with a large number of varieties [47,48]. Among the related biological activities, chili peppers are believed to act as antioxidants [49,50] and hypoglycemic [51], antimicrobial [12], anti-inflammatory [52], thermoregulatory [53], and antitumor [54] agents.

According to several authors [55,56], the Myrtaceae family is composed of 5500 species that are clustered into 140 genera that are widely distributed in neotropical forests and savannas. This massive family is widely explored for the production of essential oils and spices (*Myrtus* sp. And *2eolignane*.) [57,58], in natura food [59], and wood-derived products (*Eucalyptus* sp.) [60]. The *Pimenta* genus comprises 16 species mainly found in the Caribbean region [55,61,62], and its essential oil and leaf extracts have several biological properties such as cytotoxicity [63], anti-nociceptive and anti-inflammatory [64,65], antioxidant [66,67], insecticidal [68], antimicrobial [69,70], and antifungal [71] effects.

3. The Apoptosis Pathways

Apoptosis, a programmed senescence process of cell death, naturally occurs (i) when cells lose their proliferative capacity after a certain number of cell divisions, (ii) in cellular defense events (e.g., immune reactions), and (iii) and after severe cellular damage (e.g., solar radiation) [72,73]. Nevertheless, apoptosis can be avoided due to deregulation of extrinsic and intrinsic key components that trigger its pathway, a very common characteristic in many cancers [74]. Advances in the understanding of these biochemical pathways have created opportunities to modulate defective processes through the proapoptotic activity induced by natural and synthetic compounds [75,76].

Most known proapoptotic effects act as upregulation of death receptors, leading to activation of caspases and cell death (via extrinsic pathway) [77,78]. On the other hand, the intrinsic pathway can be triggered by compounds that generally produce high levels of damaged DNA [79]. These compounds, natural or synthetic, can also stimulate proapoptotic regulators of the B-cell lymphoma 2 (BCL-2) family [80], promoting the

collapse of internal mitochondrial membrane potential ($\Delta\psi$) followed by an overflow of the mitochondrial content, such as cytochrome *c* (Cyt *c*), direct IAP binding protein with low pI), and HtrA2 (High temperature requirement protein A2 (DIABLO) [81,82]. In the cytosol, Cyt *c* forms the apoptosome, which promotes the activation of caspases, resulting in apoptosis [83,84].

Among the reviewed compounds, the secondary metabolites of peppers, some analogues, and their potency over cancer cell lines are described in Table 1 and Table S1. Moreover, as can be seen in the next items of this review, chemical constituents are described in detail and cell death mechanisms, when available, are also presented.

Table 1. Potency (IC_{50}; μM) of pepper-derived compounds against several cancer cell lines.[1.]

Compound	Cell Line and IC_{50} (μM)	Reference
Piperolactam A (**1**)	A549 (10.1); HCT15 (27.8); SK-MEL-2 (18.3); SK-OV-3 (18.3)	[85,86]
Piperolactam B (**2**)	A549 (21.7); HCT15 (21.3); SK-MEL-2 (11.6); SK-OV-3 (14.4); P-388 (46.1)	[85,86]
Piperolactam C (**3**)	A549 (>162.0); P-388 (78.0); HT-29 (69.0)	[85]
4	L1210 (1.6)	[87,88]
5	L1210 (2.6)	[87,88]
6	L1210 (2.3)	[87,88]
7	L1210 (1.6)	[87,88]
8	L1210 (1.8)	[87,88]
9	MCF-7 (2.0)	[89]
Piplartine or Piperlongumine (**10**)	518A2 (2.6); A2780 (0.5); A549 (1.9); CEM (4.4); GBM10 (3.8); HCT116 (6.0); HCT8 (2.2); HL60 (5.3); HT1080 (3.4); HT-29 (1.4); JURKAT (5.3); K-562 (5.7); KB (5.6); MCF-7 (5.0); MOLT-4 (1.7); MRC-5 (35.0); SF188 (3.9); SKBR3 (4.0); T98G (4.9); WI38 (26.8); ZR-75-30 (5.9)	[88,90–94]
11	A549 (4.1); MCF-7 (4.2)	[88]
12	A549 (4.7); MCF-7 (4.9)	[88]
13	A549 (1.8); MCF-7 (1.6)	[88]
14	A549 (2.0); MCF-7 (1.8)	[88]
15	A549 (3.8); MCF-7 (5.0)	[88]
16	A549 (24.0); MDA-MB-231 (11.7)	[93]
17	A549 (18.0); MDA-MB-231 (23.7)	[93]
18	A549 (19.8); MDA-MB-231 (6.7)	[93]
19	A549 (3.9); MDA-MB-231 (6.1)	[93]
20	A549 (4.1); MDA-MB-231 (7.3)	[93]
21	A549 (4.8); MDA-MB-231 (2.7)	[93]
22	A549 (2.7); MDA-MB-231 (2.5)	[93]
23	A549 (2.2); MDA-MB-231 (2.1)	[93]
Pipermethystine **24**	HepG2 (not reported)	[95]
Piperlonguminine **25**	MCF-7 (6.0); MCF-12A (50.8); MDA-MB-231 (261.7); MDA-MB-468 (8.0); SW-620 (16.9)	[96]
Pellitorine **26**	HL60 (58.0); MCF-7 (8.0)	[97,98]
Sarmetine **27**	P-388 (ED_{50} = 13.0)	[99]
Piperine **28**	A549 (427.5); COLO-205 (46.0); HeLa (95.0); Hep-G2 (70.0); IMR-32 (89.0); MCF-7 (99.0)	[100–102]
Piperninaline **29**	L5178Y (17.0)	[103]
Dehydropiperninaline **30**	L5178Y (8.9)	[103]
Aduncamide **31**	KB (ED_{50} = 18.0)	[104,105]
32	Not active	[106]

33	Not active	[106]
34	Not active	[106]
Piperarborenine A **35**	A549 (4.23); HT-29 (6.21); P-388 (0.21)	[85]
Piperarborenine B **36**	A549 (1.39); HT-29 (2.41); P-388 (0.13)	[85]
Piperarborenine C **37**	A549 (0.23); HT-29 (0.26); P-388 (0.18)	[85]
Piperarborenine D **38**	A549 (0.28); HT-29 (0.35); P-388 (0.20)	[85]
Piperarborenine E **39**	A549 (0.19); HT-29 (0.22); P-388 (0.02)	[85]
Piperarboresine **40**	A549 (5.01); HT-29 (5.69); P-388 (4.87)	[85]
Piplartine-dimer A **41**	P-388 (8.48)	[85]
Chabamide **42**	A549 (67.3); CNE (67.0); COLO-205 (5.4); DU-145 (16.0); HeLa (24.0; 189.8); HepG2 (60.8); K-562 (10.8); MCF-7 (39.1); SGC-7901 (12.0)	[107,108]
Chabamide F **43**	COLO-205 (181.7); HeLa (119.4); HepG2 (44.6); HT-29 (259.7); MCF-7 (49.9)	[107]
Chabamide G **44**	COLO-205 (0.0369); HeLa (85.3); HepG2 (108.0); MCF-7 (51.4)	[107]
Chabamide H **45**	COLO-205 (69.5); HepG2 (253.5); MCF-7 (319.4)	[107]
Chabamide I **46**	COLO-205 (80.5); HeLa (263.4)	[107]
Chabamide J **47**	HT-29 (450.4)	[107]
Chabamide K **48**	COLO-205 (379.4); Hela (191.0); HepG2 (437.2); HT-29 (397.8)	[107]
cis-Yangonin **49**	A2780 (2.9); K652 (1.6)	[109]
trans-Yangonin **50**	A2780 (9.3); K652 (5.5)	[109]
Demethoxyyangonin **51**	A2780 (16.6); K652 (12.6)	[109]
Kavain **52**	A2780 (11.0); K652 (23.2)	[109]
Methysticin **53**	A375 (65.0); HaCaT (29.0)	[110]
54	A375 (65.0); HaCaT (29.0)	[110]
Flavokavain A **55**	MCF-7 (25.0); MDA-MB-231 (17.5)	[111,112]
Flavokavain B **56**	A2058 (18.3); ACC-2 (4.7); CaCo-2 (9.9); Cal-27 (26.7); DU-145 (3.9); H460 (18.2); HaCaT (13.6); HCT116 (7.5); HuH7 (15.9); HSC-3 (17.2); LAPC4 (32.0); LNCaP (48.3); MCF-7 (38.4); MCF-7/HER2 (13.6); MDA-MB-231 (12.3/45.0); NCI-H727 (11.3); PC-3 (6.2); RL (8.2); SKBR3/HER2 (10.0); SK-LMS-1 (4.4)	[112–118]
Flavokavain C **57**	A549 (40.3); CaSKi (39.9); CCD-18Co (160.9); EJ (8.3); HCT116 (12.7); HepG2 (60.0); HT-29 (39.0); L-02 (57.0); MCF-7 (47.6); RT-4 (1.5)	[119,120]
58	CaCo-2 (10.0); HaCaT (10.9); HCT116 (9.2); MCF-7 (10.5); NCI-H727 (11.0); PC-3 (9.6); RL (10.1)	[112]
59	CaCo-2 (11.2); HaCaT (10.4); HCT116 (7.7); HuH7 (15.0); MCF-7 (10.3); MDA-MB-231 (13.2); NCI-H727 (14.8); PC-3 (7.3); RL (9.0)	[112]
60	CaCo-2 (9.6); HaCaT (10.5); HCT116 (10.0); HuH7 (16.6); MCF-7 (15.9); NCI-H727 (9.9); PC-3 (8.7); RL (8.9)	[112]
61	CaCo-2 (9.2); HCT116 (12.4); MCF-7 (8.8); PC-3 (13.2); RL (5.4)	[112]
62	HCT116 (54.1); MCF-7 (7.3);	[121]
63	CaCo-2 (5.8); HaCaT (7.2); HCT116 (6.9); HuH7 (15.5); MCF-7 (9.4); MDA-MB-231 (12.9); NCI-H727 (11.4); PC-3 (5.1); RL (6.9)	[112]
64	CaCo-2 (3.9); HaCaT (5.3); HCT116 (4.3); HuH7 (8.9); MCF-7 (9.4); MDA-MB-231 (8.7); NCI-H727 (8.2); PC-3 (3.1); RL (5.9)	[112]
65	CaCo-2 (4.5); HaCaT (8.7); HCT116 (4.2); HuH7 (9.8); MCF-7 (8.9); MDA-MB-231 (13.0); NCI-H727 (4.0); PC-3 (8.1); RL (9.0)	[112]
66	CaCo-2 (8.8); HaCaT (7.7); HCT116 (6.8); HuH7 (14.1); MCF-7 (9.3); MDA-MB-231 (9.9); NCI-H727 (8.7); PC-3 (7.6); RL (8.3)	[112]
67	CaCo-2 (5.5); HaCaT (7.6); HCT116 (6.2); HuH7 (14.6); MCF-7 (7.7); MDA-MB-231 (10.7); NCI-H727 (5.5); PC-3 (5.5); RL (6.4)	[112]
68	CaCo-2 (5.7); HaCaT (7.6); HCT116 (5.4); HuH7 (12.7); MCF-7 (7.5); MDA-MB-231 (8.2); NCI-H727 (6.0); PC-3 (5.8); RL (6.5)	[112]
69	CaCo-2 (6.8); HaCaT (9.0); HCT116 (6.2); HuH7 (13.9); MCF-7 (9.5); MDA-MB-231 (11.1); NCI-H727 (11.3); PC-3 (7.1); RL (8.3)	[112]
70	CaCo-2 (2.6); HaCaT (2.8); HCT116 (2.7); HuH7 (4.9); MCF-7 (5.0); MDA-MB-231 (3.3); NCI-H727 (4.1); PC-3 (2.5); RL (3.4)	[112]

Grandisin **71**	EAT (0.2); HL60 (60.0); U937 (30.0); V79 (174.0)	[122,123]
72	A549 (6.90); SK-MEL-2 (4.50); SK-OV-3 (9.40)	[86]
73	3T3-A31 (0.043)	[124]
Conocarpan **74**	A549 (11.2); HL60 (5.8); MCF-7 (7.8); SMMC-7721 (8.9); SW-480 (2.1)	[125]
Decurrenal **75**	MCF-7 (169.1)	[126]
Eupomatenoid-5 **76**	786-0 (TGI = 6.6); HT-29 (TGI = 48.5); K-562 (TGI = 338.5); MCF-7 (TGI = 21.2); NCI-H460 (TGI = 34.8); OVCAR-3 (TGI = 18.7); PC-3 (TGI = 21.0); UACC-62 (TGI = 27.9)	[127]
Capsaicin **77**	3T3 (83.0); A375 (6.0); A2058 (200.0); AsPC1 (150.0); B16F10 (117.0); BxPC3 (150.0); HepG2 (50.0); MCF-7 (53.0); MCF-10[a] H-*ras* (56.0); MDA-MB-231 (21.7); PC-3 (20.0); RT-4 (80.0)	[128–130]
78	B16F10 (87.0) ; MCF-7 (32.0)	[128–130]
79	B16F10 (38.0); MCF-7 (28.0); MDA-MB-231 (87.0)	[131]
80	B16F10 (75.0); MDA-MB-231 (109.0)	[132]
81	B16F10 (50.0); MCF-7 (32.0); MDA-MB-231 (14.2)	[129]
82	B16F10 (120.0); MDA-MB-231 (75.0)	[132]
83	MCF-7 (142.4); MDA-MB-231 (104.6)	[133]
84	MCF-7 (144.6); MDA-MB-231 (173.2)	[133]
85	B16F10 (130.0); SK-MEL-28 (85.0)	[130]
86	A2058 (55.2); SK-MEL-25 (67.2); U-87 (86.9)	[134]
Capsanthin **87**	DU-145 (ND); PC-3 (ND)	[135,136]
Capsorubin **88**	A549 (< 20.0)	[135,136]
Ericifolin **89**	LNCaP (< 5.0)	[137]
Nilocitin **90**	HCT116 (19.4); HepG2 (22.8); MCF-7 (40.8)	[63]
Pedunculagin **91**	HCT116 (4.4); HepG2 (6.4); MCF-7 (18.4)	[63]
Castalagin **92**	HCT116 (7.4); HepG2 (9.8); MCF-7 (26.2)	[63]
Grandinin **93**	HCT116 (13.8); HepG2 (18.4); MCF-7 (22.1)	[63]

[1] IC_{50} = half of maximal inhibitory concentration; ED_{50} = median of effective dose; TGI = total growth inhibition; ND = not determined.

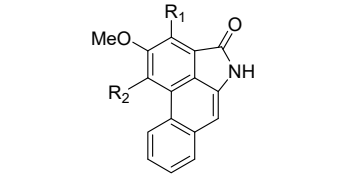
4. Literature-Related Cytotoxic Compounds

4.1. Piper *sp.*

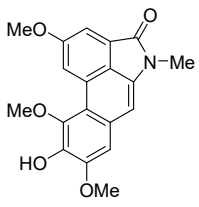
Piperolactams **1–3** (Figure 1) are present in several species of *Piper*, such as *P. caninum*, *P. marginatum*, and *P. kadsura* [98,138,139]. This class of compounds is metabolized in vitro and in vivo to a reactive cyclic *N*-acylnitrenium ion that forms DNA adducts with purine bases, leading to cancer cell death; however, genotoxic and carcinogenic effects in non-tumorigenic cells were observed, as well as shrimp and mice toxicity [140–142]. Compounds **1–2** demonstrated moderate (IC_{50} ~10.0 μM) cytotoxicity against A549 lung and SK-MEL-2 skin cancer cells [139,141], whereas **3** was weakly active against P-388 lymphoma and HT-29 adenocarcinoma cells [85]. Many analogues of **1–3**, based on different substitutions at the aristolactam and aporphine moieties, were also achieved. In 2002, Couture et al. (2002) observed that changes in the hydroxyl and methoxyl substituents conferred potent compounds against L1210 leukemia cells in the low μM range (**4–8**, Table 1) [87]. Hedge and coworkers (2010) evaluated the activity of semi-synthetic aristolactams against CDK2, a kinase protein involved in cell cycle regulation. The most potent analogue found (**9**) displayed strong CDK2 inhibition (IC_{50} = 35 nM) and cytotoxicity against MCF-7 breast cancer cells (IC_{50} = 2.0 μM) [89].

Piplartine or piperlongumine **10** is the major bioactive alkaloid extracted from the dried fruits of the *Piper* genus [143,144], of which the species *P. longum* L., *P. tuberculatum*, and *P. chaba* are the most prominent [145]. The literature correlates the observed cytotoxicity of **10** against tumorigenic and normal cell lines (Table 1) to an accumulation of Reactive Oxygen Species (ROS) due to the interaction with antioxidant proteins, activation of p38, and c-Jun *N*-terminal kinases (JNKs), thus leading to cell damage and apoptosis [146,147]. Many compounds derived from **10** were synthesized and evaluated against cancer cell lines. Curiously, the insertion of aryl and alkyl groups to the cinnamyl moiety (**11–23**) afforded potent compounds against A549 lung and MCF-7 and MDA-MB-231 breast

cancer cells. Replacement of the acidic proton from the di-hydropyridinone moiety by halogens (**18–23**) also generated cytotoxic compounds [88,93]. An interesting review regarding analogues of **10**, as well as their anticancer properties and molecular bases for their activity, was written by Piska and coworkers [148].



piperolactam A **1** R_1 = H R_2 = OH
piperolactam B **2** R_1 = OMe R_2 = OH
piperolactam C **3** R_1 = OMe R_2 = OMe



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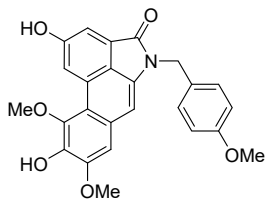

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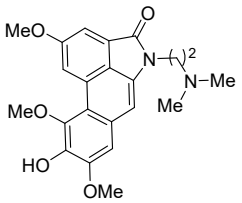

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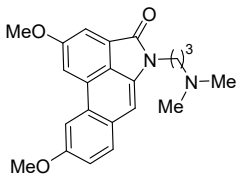

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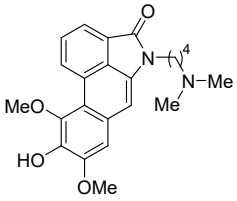

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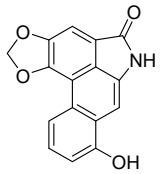

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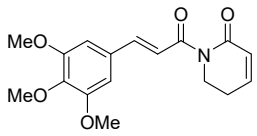
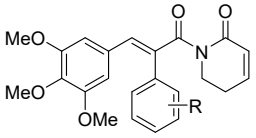
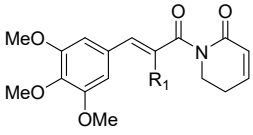


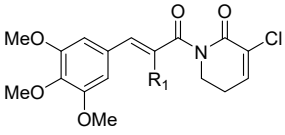
piplartine **10**



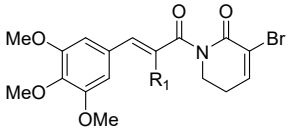
11 R = H
12 R = 4-Me
13 R = 4-OMe
14 R = 4-Et
15 R = 4-F



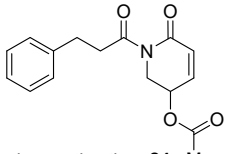
16 R_1 = Me
17 R_1 = Et



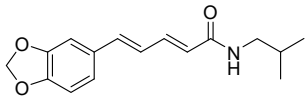
18 R_1 = H
19 R_1 = Me
20 R_1 = Et



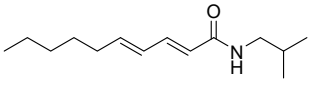
21 R_1 = H
22 R_1 = Me
23 R_1 = Et



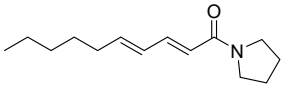
pipermethystine **24**



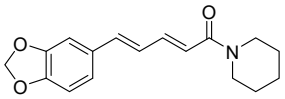
piperlonguminine **25**



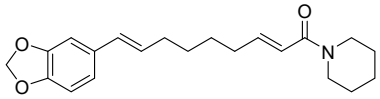
pellitorine **26**



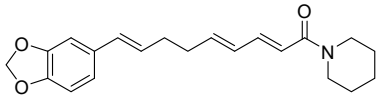
sarmentine **27**



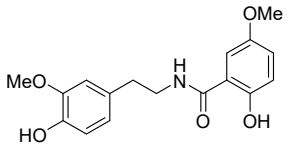
piperine **28**



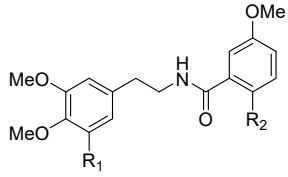
pipernonaline **29**



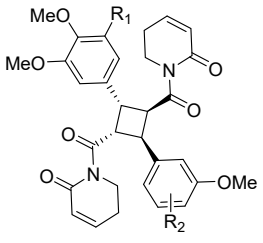
dehydropipernonaline **30**



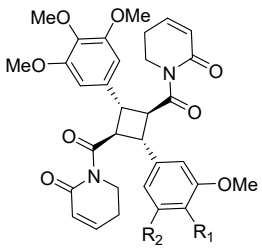
aduncamide **31**



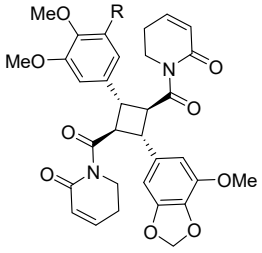
taiwanamide A **32** R_1 = H R_2 = OH
taiwanamide B **33** R_1 = H R_2 = OMe
taiwanamide C **34** R_1 = OMe R_2 = OMe



piperarborenine A **35** R_1 = H R_2 = 4-OMe
piperarborenine B **36** R_1 = OMe R_2 = 3-OMe



piperarborenine C **37** R_1 = R_2 = OMeO
piperarborenine D **38** R_1 = OMe R_2 = H



piperarborenine E **39** R = H
piperarboresine **40** R = OMe

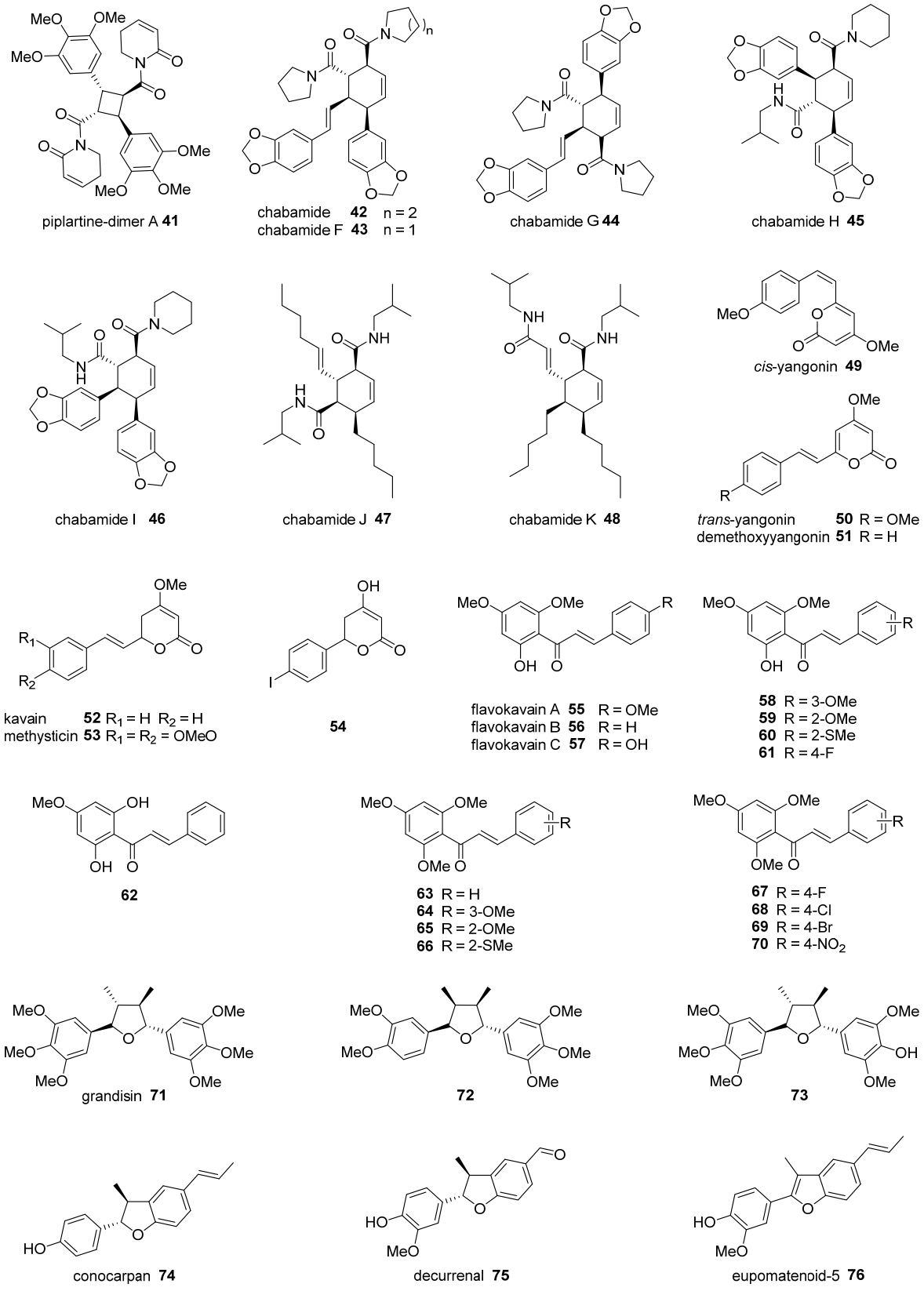


Figure 1. Chemical structures of the reported *Piper* sp. Cytotoxic compounds and analogues.

Pipermethystine **24** is another important alkaloid with antitumor activity, which was isolated from leaves of *P. methysticum* [149] and, subsequently, Nerurkarand et al. (2004) observed that **24** inhibited 90% of cellular viability in HepG2 liver carcinoma cells at 100 μM. It is interesting to note that the inhibitory effect of **24** caused a mitochondrial disruption, reduction of adenosine triphosphate (ATP) concentrations, and activation of caspase-3, leading to apoptosis [73,78,95].

Piperlonguminine **25**, found in *P. divaricatum*, *P. longum*, *P. ovatum*, and also in other *Piper* species, was recently patented due to its cytotoxic properties against cancer cells [150,151]. Compound **25** demonstrated potent proapoptotic activity against breast cancer cells by activation of caspases-3, -7, -8, the BAX protein, and the induction of cell cycle arrest at the G_2/M phase with a reduction in topoisomerase II expression, leading to DNA damage [96,152].

Pellitorine **26** and sarmentine **27** are found in several *Piper* species, such as *P. tuberculatum*, *P. nigrum*, *P. sintenense*, *P. sarmentosum*, *P. nigrum*, and *P. lolot* [21,99,153]. Compound **26** was found to be cytotoxic towards MCF-7 breast cancer cells (IC_{50} = 8.0 μM) and HL60 human leukemia (IC_{50} = 58.0 μM), whereas **27** was only found to be active against P-388 leukemia cells (ED_{50} = 13 μM) [98].

Piperine **28** is the major alkaloid found in *P. nigrum*, the most common pepper species used as a spice in almost every culture worldwide [154]. The cytotoxic activity of **28** was evaluated against several cancer cells and caused the induction of cell cycle arrest at the G_2/M phase, the activation of caspase-3 and -9, an increase in BAX, and a concomitant reduction in BCL-2 (mediated by p53). Additionally, **28** caused upregulation on the expression of TRPV1 receptors, MMP-2, and MMP-13 [102]. An interesting review about the structure–activity relationship regarding analogues of **28** was reported by Qu et al. [155].

Pipernonaline **29** and dehydropipernonaline **30** were isolated from fruit extracts of *P. retrofractum* [103,156] and *P. longum* L. [157,158]. Both **29** and **30** revealed promising cytotoxic activity against L5178Y mouse lymphoma and PC-3 human prostate cancer cells by inducing cell cycle arrest at the G_0/G_1 phase, caspase-3 activation, ROS production, and mitochondrial membrane disruption [103,159].

Aduncamide **31** was first isolated from the leaves of *P. aduncum* as part of a Swiss research program interested in the isolation of biologically active metabolites found in the traditional medicine of Papua New Guinea [104,105]. Even though **31** presented cytotoxicity against KB cells (HeLa-derived tumorigenic cells, ED_{50} = 18.0 μM), no further research was conducted with this compound. Although three natural analogues of **31** were found in *P. taiwanense* (**32–34**), no cytotoxicity has been observed for this set of compounds so far [106].

Piperarborenines **35–41** were isolated from *P. arborescens* [160] and demonstrated potent cytotoxic activity against human cancer cells, reaching submicromolar activity [85]. Notably, a remarkable potent activity was found for **39** against P-388 leukemia (IC_{50} = 0.02 μM), HT-29 colon, and A549 lung cells (IC_{50} = 0.20 μM for both cell lines). The chemical complexity of this class of compounds and its promising anticancer activity is highlighted by the number of publications focusing on the synthesis of **39–40** and related analogues [94,161–164].

Chabamides **42–48** have been isolated from *P. chaba* [165] and are naturally produced by the condensation of **28** with further secondary metabolites [166] via the Diels–Alder reaction [107]. Compound **42** presented proapoptotic effects in cancer cell lines, inducing cell cycle arrest at the G_0/G_1 phase, increased p21 and BAX, and decreased BCL-2 antiapoptotic proteins [108,167]. Compounds **43–48** were found to be less active than **42**, in which remarkable proapoptotic activity was found towards COLO-205 colon cancer cells (IC_{50} = 36.9 nM) [107].

The cytotoxic compounds **49–53** were discovered on *P. methysticum*, a largely consumed spice in Pacific cultures [168,169]. Curiously, the cis-pyranone **49** was threefold more cytotoxic towards K652 leukemia cells than the trans isomer **50** (IC_{50} = 1.6 and 5.5 μM, respectively) [109]. The mechanism of apoptosis was studied in HepG2 liver cancer

cells in which chromatin condensation and nuclear fragmentation were observed [170]. Further derivatives of **52** have been evaluated against tumorigenic cells. The most active compound of the series (**54**), however, presented twofold higher cytotoxicity for human normal keratinocytes than for melanoma cells, impairing further studies in vivo [110]. Moreover, compounds **49–53** were also reported to be potent cytochrome P450 inhibitors and hepatotoxic [171].

Chalcones **55–56** were found in *P. methysticum*, *P. dilatatum*, and *P. rusbyi* [109,172,173]. Even though these compounds were strongly associated with death receptor upregulation [115,116], further studies suggested that along with **57**, they might modulate the BLC-2 family, inducing mitochondrial disruption and downregulation of X-linked inhibitor of apoptosis protein (XIAP) [119,174,175]. Western blot analysis also indicated the cleavage of Poly (ADP-ribose) polymerase (PARP) mediated by JNK [117], Akt/MAP-kinase inactivation, and a reduction in the levels of cyclin A and B1, Cdc2, and Cdc25C [176,177]. Curiously, **56** was highly cytotoxic against HCT116 colon carcinoma and PC-3 prostate cancer cells (IC_{50} = 7.5 and 6.2 μM, respectively), whereas **55** remained inactive [112,113,119,120,178]. Moreover, **56** presented in vivo antitumor activity against DU-145 human prostate cancer and KB cancer cells in tumor xenograft models [113,176]. Analogues **58–70** were evaluated against the liver, colon, breast, prostate, lung, and lymphoma cancer cell lines [112]. Interestingly, the most active compounds were found to be para-substituted by halogens (**67–69**) and nitro (**70**). This set of compounds induced cell cycle arrest at the G_1/S and M phases, and apoptosis via the PI3K/AKT/mTOR pathway [119,178].

Tetrahydrofuran neolignans such as **71–73** have been isolated from *P. solmsianum,* but they also can be found in species of the Lauraceae, Myristicaceae, and Schisandraceae families [179,180]. Studies have demonstrated that compound **71** has cytotoxic and antitumor activities, suggesting its potential to be used as an anticancer agent [181,182]. Upon treatment with **71**, cancer cells underwent cell cycle arrest at the G_1 phase, chromatin condensation, phosphatidylserine externalization, DNA fragmentation, upregulation on caspase activity, and apoptosis [122,183]. The poor aqueous solubility of **71** was ameliorated through nanoencapsulation, which presented almost 16-fold higher cytotoxicity against Balb/c 3T3-A31 fibroblasts (IC_{50} = 5.0 nM) [184]. The natural analogue **72** and the demethylated metabolite **73** were also found to be cytotoxic against several cancer cell types [124].

Compounds **74–76** can be found in several species of *Piper*, such as *P. regnellii*, *P. solmsianum*, *P. decurrens*, *P. abutiloides*, *P. kadsurai*, and *P. rivinoides* [185–190]. Although **74** was a potent cytotoxic compound over a panel of cancer cells, **75** was slightly active only in MCF-7 breast cancer cells (IC_{50} = 169.1 μM) [125,191]. Moreover, cancer cells treated with 9eolignane **76** displayed a high apoptosis rate through phosphatidylserine externalization, caspase activation, a loss of cell membrane integrity, and an increase in ROS. Upon treatment with **76**, MCF-7 revealed apoptosis-like alterations such as pyknosis, blebbing, and evagination of plasma membrane; on the other hand, 786-0 cells displayed cytoplasmic content release associated with the necrotic process [192]. Remarkably, in vivo experiments using an Ehrlich solid tumor mice model demonstrated that treatment with **76** reduced the tumor volume by 30% with no observation of adverse effects in mice [127].

4.2. Capsicum *sp.*

Capsaicinoids are the most studied compounds related to red peppers of the *Capsicum* genus. Jalapeño pepper *(C. annuum*), habanero (*C. chinense*), and tabasco (*C. frutescens*) have a high capsaicinoid concentration, ranging from 0.2% to 4.2% [193–196], depending on environmental conditions and quantification methods [47]. Capsaicin **77** (Figure 2), is the main capsaicinoid metabolite found in red peppers and can be isolated mainly from fruits of the *Capsicum* species [197]. The analgesic, pungent, and pro-apoptotic effects of **77** are related to their interaction with Transient Receptor Potential Vanilloid (TRPV) receptors at the sensory neurons [198]. This family of transmembrane receptors (TRPV1 to

TRPV6) is found in several tissues and mediates the influx of Ca^{2+} into the cytosol [199]. The TRPV receptors can be activated by many stimuli such as proton (H^+), heat, and natural substances such as **28**, **77,** and resiferatoxin [200–202]. In sensory neuronal fibers, the activation of TRPV1 by **77** triggers a rapid increase in Ca^{2+} flux, causing neuronal depolarization and the characteristic burning sensation [203–206]. Compound **77** is also supposed to interact with other TRP receptors involved in cancer progression, such as TRPV6 [207] and TRPM8 [208]. Chow et al. (2007) [209] suggested that **77** induces apoptosis preferentially via TRPV6, with selectivity for tumor cells. Recently, however, the activity of **77** against TRPV6 was evaluated in a Ca^{2+} flux assay [134,210]. The authors observed that in this assay, the compound was not able to change the channel transport. Despite the mode of action of **77** still being inconclusive, further studies indicated that the modulation of TRP channels and enhancement on Ca^{2+} influx may trigger apoptosis by calpain activation and effector caspases as well [211]. This compound has been investigated against more than 40 types of tumors, attracting the attention of many researchers as a promising drug candidate for cancer treatment [128]. Upon treatment with **77**, tumor cells undergo disruption of the mitochondrial membrane, increasing ROS generation and caspase-3 and -9 activity [212]. In vivo mice models revealed that administration of **77** significantly reduced tumor growth (>50%) in breast and leukemia cancers [76,213]. As the inherent pungency of **77** greatly limits its application in therapeutics, it has led several research groups to design analogues lacking pungency of **77** [129,131–133,210,214,215].

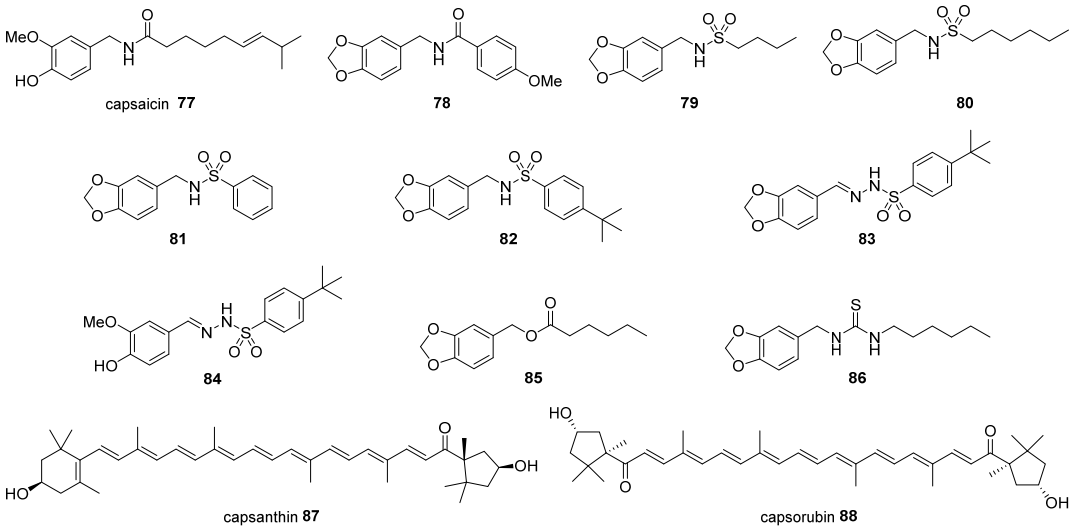


Figure 2. Chemical structures of the reported *Capsicum* sp. cytotoxic compounds and some analogues.

Compound **78** inhibited MCF-7 breast cancer cells at 32.0 μM, showing a better effect when compared to **77** (53.0 μM). Additionally, common changes typically associated with apoptosis were observed, such as cell shrinkage, pyknosis, mitochondrial depolarization, the formation of apoptotic vesicles, and DNA fragmentation [129]. Furthermore, it was observed that cells treated with **78** exhibited a reduced number of mitoses, disruption of mitotic spindles, and cell cycle arrest at the G_2/M phase [129]. Compounds **79–82** presented proapoptotic activity against B16F10 murine melanoma and MDA-MB-231 and MCF-7 human breast cancer cells with no pungency in vivo. Moreover, these compounds induced cell cycle arrest and downregulation of BCL-2 expression [129,131]. Noteworthy, **79** significantly reduced tumor volume in a breast tumor model in vivo [129,131]. Further bioisosteric analogues **83–86** exhibited weaker activity over breast cancer cells [130,133,134]**.**

Carotenoids such as **87** and **88** are abundant in red peppers such as *C. annuum*, *C. baccatum*, *C. chinense*, and *C. pubescens* [216]. Compound **87**, in a concentration-independent way, partially reduced prostate cancer cell proliferation, inducing cell cycle arrest and apoptosis, but the effect was less pronounced in vivo using F344 rats [135,217]. On the other hand, compound **88** presented potent cytotoxicity against A549 lung cancer cells, with an $IC_{50} < 20.0$ μM [136].

4.3. Pimenta *sp.*

Amongst the other reviewed genus, *Pimenta* sp. is less explored and possesses fewer representatives (16 species). The cytotoxic compounds related to *Pimenta* sp. reported in the literature came from treatments with extracts of *Pimenta dioica* berries and leaves [19]. Curiously, breast cancer cells underwent autophagy, whereas prostate cancer cells underwent cycle arrest at the G_1/S phase and also apoptosis. The proapoptotic activity of the extract was linked to the presence of glycopyranoside **89** (Figure 3), which induced apoptosis in LNCaP human prostate adenocarcinoma cells ($IC_{50} < 5.0$ μM) by reducing cyclin-D1, CDK4, and androgen receptor transcription [15,137]. However, the purified **89** has no activity against MCF-7 and MDA-MB-231 breast cancer cells [137]. Several cytotoxic polyphenols (**90–93**) isolated from *P. dioica* leaves were evaluated in further studies. These compounds were tested against MCF-7 breast, HepG2 liver, and HCT116 colon cancer cells (Table 1)[63]. Compound **91** was the most cytotoxic (IC_{50} = 18.4, 6.4, and 4.4 μM, respectively), presenting the most protective activity against ROS and nitric oxide (NO) release.

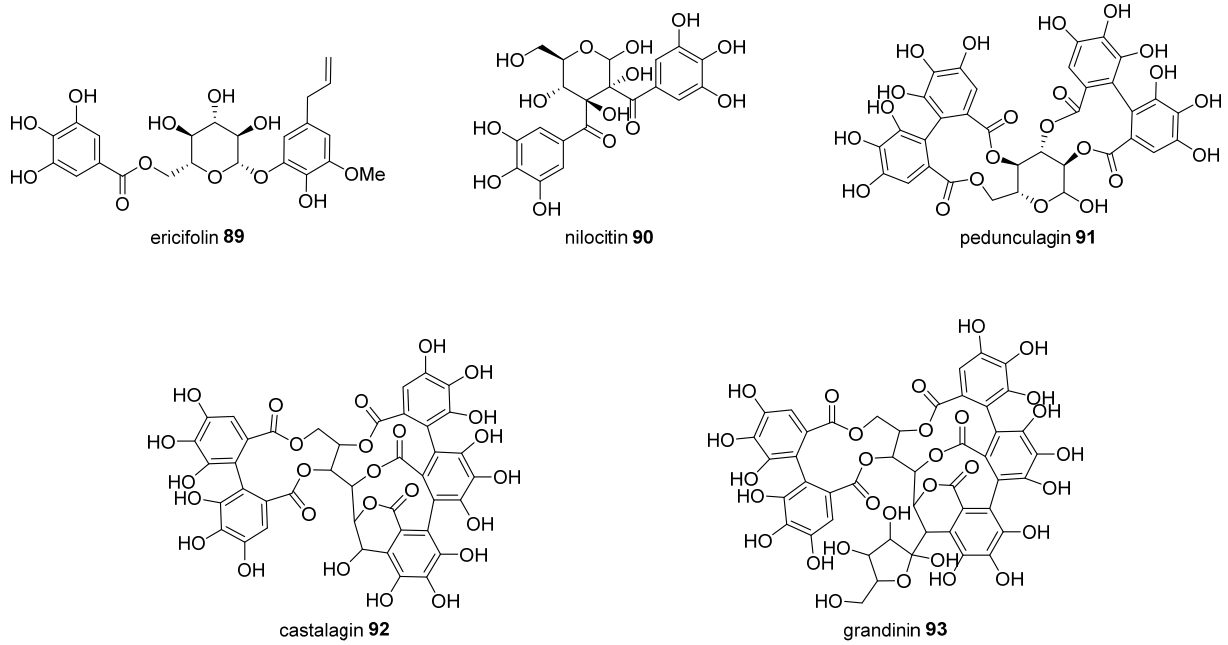


Figure 3. Chemical structures of the reported *Pimenta dioica* cytotoxic compounds.

5. Conclusions

Peppers produced by the *Piper*, *Capsicum*, and *Pimenta* genera are consumed worldwide and represent a significant natural source of secondary metabolites with high chemical diversity. In the last two decades, natural pepper compounds have been inspiring academic and industry researchers due to their cytotoxic effects on many tumorigenic cell lines. This fact highlights the potential of peppers to be used as a natural source of new molecular entities with anticancer activity. However, despite all efforts, antitumor therapy still does not have pepper-derived representatives. We can observe from the literature that

compounds such as piperolactams (**1–3**), grandisin (**71**), and capsaicin (**77**) present physical–chemical properties, PK-PD profiles, and/or adverse effects that may impair clinical trials to treat malignancies. Nevertheless, this review has shown several derivatives and analogues with enhanced biological data, with some of them still undergoing preclinical trials and translational research. Of note is that some pepper-derived compounds, for instance, piperarborenines (**35–40**), methysticin (**53**), conocarpan (**74**), and ericifolin (**89**), have an intriguing proapoptotic mechanism but there is still a lack of information on their detailed mechanisms of cell death. This fact shows a promising area of research in *Piper*, *Capsicum*, and *Pimenta* metabolites that can contribute to the design of new chemical entities based on natural scaffolds.

Supplementary Materials: The following are available online: Table S1: Description of cancer cell lines from table 1.

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