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

1. 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], antithrombosis aggregation [30], antioxidant [31], antiplatelet aggregation [32], antiplatelet aggregation [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 Pimenta sp.) [57,58], in natura food [39], 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) 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 (Δψ) followed by an overflow of the mitochondrial content, such as cytochrome c (Cyt c), direct IAP binding protein with low pl), 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 (IC₅₀; µM) of pepper-derived compounds against several cancer cell lines.

| Compound | Cell Line and IC₅₀ (µM) | References |
|----------|-------------------------|------------|
| 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] |
| Pipartine or Piperlongumine (10) | 518A2 (2.6); A2780 (0.5); A549 (1.9); CEM (4.4); GBM10 (3.8); HCT116 (6.0); HCTS (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 (ED₅₀ = 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 (ED₅₀ = 18.0) | [104,105] |
| Compound                  | Cell Line and IC\textsubscript{50} (µM)                                                                 | References |
|--------------------------|---------------------------------------------------------------------------------------------------------|------------|
|                          |                                                                                                         |            |
| 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]       |
| Piperarboreines 40       | A549 (5.01); HT-29 (5.69); P-388 (4.87)                                                                 | [85]       |
| Pipiltarine-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); 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]      |
| \textit{cis}-Yangonin 49 | A2780 (2.9); K652 (1.6)                                                                                 | [109]      |
| \textit{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); CaSk (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]      |
Table 1. Cont.

| Compound            | Cell Line and IC\textsubscript{50} (µM)                                                                 | References |
|---------------------|----------------------------------------------------------------------------------------------------------|------------|
| 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); SMCC-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-10A 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\textsubscript{50} = half of maximal inhibitory concentration; ED\textsubscript{50} = median of effective dose; TGI = total growth inhibition; ND = not determined.
4. Literature-Related Cytotoxic Compounds

4.1. Piper sp.

Piperlongumine 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*-acrylnitrilium 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 ary1 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 (18–25) 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].

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].

Piperlongumine 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 G2/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 G2/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].
Figure 1. Cont.
Figure 1. Chemical structures of the reported Piper sp. cytotoxic compounds and analogues.
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 LS174Y mouse lymphoma and PC-3 human prostate cancer cells by inducing cell cycle arrest at the G0/G1 phase, caspase-3 activation, ROS production, and mitochondrial membrane disruption [103,159].

Aduncamid 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, ED50 = 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 (IC50 = 0.02 μM), HT-29 colon, and A549 lung cells (IC50 = 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 G0/G1 phase, increased p21 and BAX, and decreased BCL-2 anti-apoptotic 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 (IC50 = 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 (IC50 = 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 cytchrome 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 (IC50 = 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 G1/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 G1 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 (IC₅₀ = 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 (IC₅₀ = 169.1 µM) [125,191]. Moreover, cancer cells treated with neolignan 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 evaporation 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 Ca²⁺ 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 Ca²⁺ 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 Ca²⁺ 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 Ca²⁺ 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].

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 G2/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 \textit{C. annuum}, \textit{C. baccatum}, \textit{C. chinense}, and \textit{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. \textit{Pimenta} sp.

Amongst the other reviewed genus, \textit{Pimenta} sp. is less explored and possesses fewer representatives (16 species). The cytotoxic compounds related to \textit{Pimenta} sp. reported in the literature came from treatments with extracts of \textit{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 \textit{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.
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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