Peppers Ethnopharmacology

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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.

Keywords: peppers ; Piper ; Capsicum ; secondary metabolites ; antitumor activity

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][4][5][6][7][8]. Of note is that these new techniques have allowed the identification of many active compounds in traditional medicines [9][10][11][12][13][14][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][17][18][19].

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][41][42][43][44][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 [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 (Δψ) 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. 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)	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]
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][91][92][93][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]

Compound	Cell Line and IC_{50} (μM)	References
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][101][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]

Compound	Cell Line and IC_{50} (μM)	References
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][113][114][115] [116][117][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-10A H-*ras* (56.0); MDA-MB-231 (21.7); PC-3 (20.0); RT-4 (80.0)	[128][129][130]
78	B16F10 (87.0); MCF-7 (32.0)	[128][129][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]

Compound	Cell Line and IC_{50} (μM)	References
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.

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