Natural Products and Cervical Cancer

Subjects: Oncology

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Cervical cancer is the fourth most common cancer among women worldwide. Though several natural products have been reported regarding their efficacies against cervical cancer, there has been no review article that categorized them according to their anti-cancer mechanisms. In this study, anti-cancerous natural products against cervical cancer were collected using Pubmed (including Medline) and google scholar, published within three years. Their mechanisms were categorized as induction of apoptosis, inhibition of angiogenesis, inhibition of metastasis, reduction of resistance, and regulation of miRNAs. A total of 64 natural products suppressed cervical cancer. Among them, *Penicillium sclerotiorum* extracts from *Cassia fistula* L., ethanol extracts from *Bauhinia variegate candida*, thymoquinone obtained from *Nigella sativa*, lipid-soluble extracts of *Pinellia pedatisecta* Schott., and 1′S-1′-acetoxychavicol extracted from *Alpinia conchigera* have been shown to have multi-effects against cervical cancer. In conclusion, natural products could be attractive candidates for novel anti-cancer drugs.

cervical cancer | dietary natural products | apoptosis | angiogenesis | metastasis | resistance | microRNA

1. Introduction

Cervical cancer, which is a cancer arising from the cervix, is characterized by abnormal vaginal bleeding, vaginal discharge, pelvic pain, or pain during sexual intercourse [1]. Currently, cervical cancer is the fourth most common cancer among women in the world [2]. According to Globocan 2018, the prevalence rate of cervical cancer is 3.2% of all cancers. The main treatments for cervical cancer are surgery such as pelvic lymphadenectomy and radical hysterectomy, radiotherapy, and chemotherapy [3]. Another therapy is targeted therapy, which regulates epidermal growth factor receptor (EGFR) [4][5] and cyclooxygenase-2 (COX-2) [6][7] for treating cervical carcinoma. However, these treatments showed possible side effects and complications: Surgery could cause bleeding, damage to the organs around the surgery, and a risk of clots in the deep veins of the legs, radiotherapy could yield menopause, infertility, discomfort, or pain with intercourse, and the side effects of chemotherapy may affect not only cancer cells but also rapidly dividing cells in systems of the whole body [8][9]. Moreover, the drugs that are usually prescribed for cervical cancer showed several side effects and drug resistance [10]. Cisplatin, which is one of the most effective anticancer drugs, has resistance capacity by a self-defense mechanism [11]. 5-fluorouracil (5-FU) is also reported for resistance and side effects when it comes to cervical cancer patients [12]. Thus, we have focused on discovering a new potent treatment for cervical cancer from natural products.

Natural products extracted from living organisms including plants and animals have several active ingredients, which are reported to be attractive alternatives to chemotherapeutic drugs or suitable for combined use with chemotherapeutic drugs [13][14]. For example, purified flaxseed hydrolysate (PFH), extracted from Lignan, induces apoptosis and inhibits angiogenesis and metastasis on HeLa cells [15]. Thymoquinone from *Nigella sativa* also showed apoptotic effect and anti-proliferation in SiHa and CaSki cells. Such natural products include *Bauhinia variegate candida* ethanol extracts, Praeruptorin-B, and well-known tea.

MicroRNA (miRNA, miR) are involved in the pathological development and metastasis of cancer [16][17]. Several natural products showed an anti-cancer effect by regulation of cancer-related miRNAs. Our team reported that *Spatholobus suberectus* Dunn extract induces apoptosis by regulation of miR-657/activating transcription factor 2 (ATF2) in U266, U937 cells [18]. Another natural product, *Salvia miltiorrhiza*, showed an anti-cancer effect via regulation of miR-216b [19]. 1′S-1′-acetoxychavicol acetate (ACA) from *Alpinia conchigera* has been reported to induce apoptosis on SiHa and CaSki cells by targeting SMAD4 and miR-210. Targeting miRNAs with natural products could be a promising strategy for cervical cancer [20]. However, there have been no studies that organize the mechanisms, efficacy, and concentration of natural products for cervical cancer in last five years. In this present study, we aim to review the nonclinical studies about the anti-cancer mechanisms of natural products. The natural products were organized by their mechanisms including apoptosis, anti-metastasis, anti-angiogenesis, resistance, and microRNA regulation.

2. Results

2.1. Apoptosis

Apoptosis is a unique form of cell death and is an important process that regulates the homeostasis of cell survival [21]. Apoptosis eliminates potentially cancerous cells and this process is caused by atrophy of cells, synthesis of new proteins, and cell suicide genes; also, it has a great influence on the malignant phenotype [22]. For this reason, apoptosis is used as an anticancer mechanism for cancer research. A total of 47 studies have been performed to elucidate apoptosis-mediated anti-cancer pathway of natural products in Hela and SiHa cells. A total of 54 natural products were reviewed.

2.1.1. Compounds

Among the natural products, 35 compounds showed an apoptotic effect against cervical cancer (Table 1). The chemical structures of the compounds are shown in Figure 1.

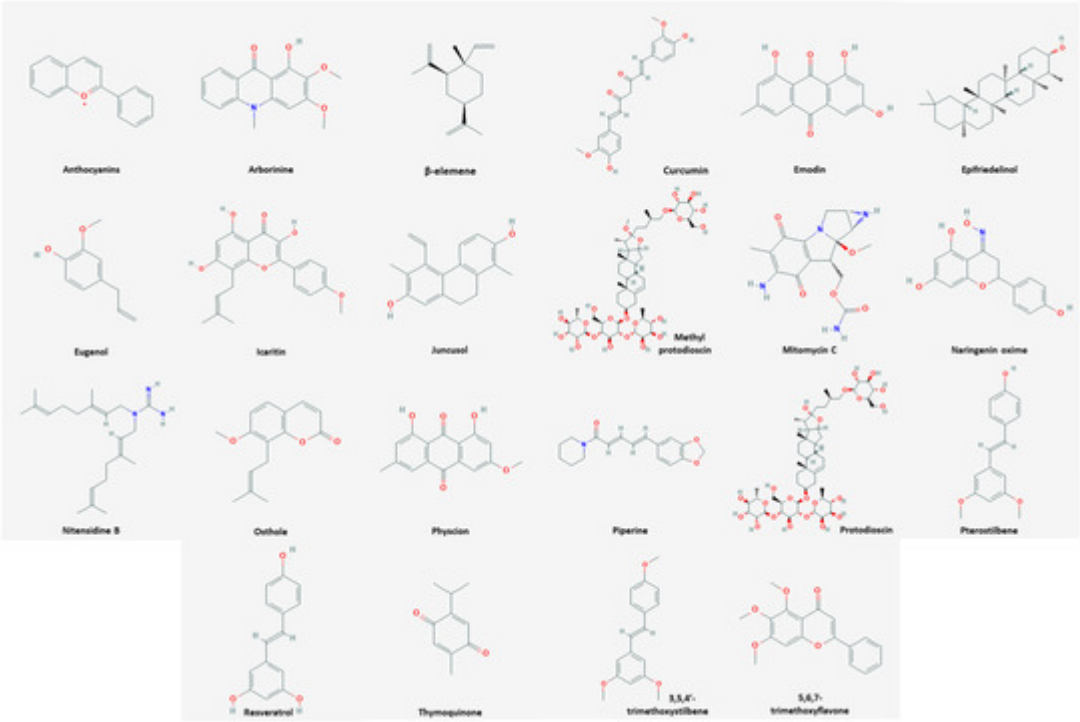

Figure 1. Chemical structures of compounds derived from natural products inducing apoptosis.

Table 1. Apoptosis inducing natural products-compounds.

Classification	Compound	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Etc.	Acylhydrazone		HeLa	2.21 μM; 48 h	Inhibition of cancer activity		[23]
Plant	Anthocyanins	Root tubers and leaves of *Ipomoea batatas*	HeLa	100, 200 μg/mL; 48 h	Induction of apoptosis, cell cycle arrest	↑CFP/YFP	[24]
Plant	Arborinine	*Glycosmis parva*	HeLa	110 μg/mL; 24 h	Induction of apoptosis Inhibition of migration	↑caspase-3, -7 ↓Bcl2-L1	[25]
Plant	β-elemene	*Curcuma zedoaria*	SiHa	30, 40, 50 μg/mL; 24, 48, 72 h	Inhibition of proliferation and migration Induction of cell cycle	↑p15, p53, Bax ↓cyclin D1, Bcl-2, MMP-2, -9, β-catenin, TCF7, c-Myc	[26]

Classification	Compound	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
					arrest and apoptosis		
Plant	Copper oxide nanoparticles	*Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera, Tamarindus indica*	HeLa	2, 5, 10, 25, 50, 100 μg/mL; 48 h	Inhibition of oxidative stress Induction of apoptosis		[27]
Plant	Curcumin	*Curcuma longa*	HeLa, C57BL/6, BALB/c	In vitro: 2 μg/mL; 48 h In vivo: 25 mg/kg	Induction of apoptosis and cell cycle arrest	↑p53, cytochrome c, PARP, caspase-3, -7, -9 ↓Bcl-2, NF-κB	[28]
Plant	Emodin	*Rhamnus sphaerosperma* var. *pubescens*	SiHa, C33A	46.3, 92.8, 185 μg/mL; 6, 12, 24 h	Induction of, apoptosis	↓NO-, O_2-, HOCl/OCl-, p-Akt	[29]
Plant	Epifriedelinol	*Aster tataricus*, *Vitex peduncularis* Wall.	HeLa	50, 100, 250, 500, 1000 μg/mL; 72 h	Induction of apoptosis	↑caspase-3, -8, -9 ↓Bcl-2, -xL, survivin	[30]
Plant	Eugenol	*Syzygium aromaticum*	HeLa, SiHa	12.5, 25 μM; 24, 48 h	Induction of apoptosis	↑Bax, PARP, caspase-3, ROS ↓Bcl-2, XIAP	[31]
Plant	Icaritin	*Epimedium*	HeLa, SiHa	HeLa: 12.5, 25 μM; 24, 48, 72 h SiHa: 17, 34 μM; 24, 48, 72 h	Induction of apoptosis Inhibition of proliferation	↑ROS, Bax, c-caspase-3, -9 ↓Bcl-2, XIAP	[32]
Plant	Juncusol	*Juncus inflexu*	HeLa, SiHa, CaSki	1, 3, 10, 30 μM; 24, 48, 72 h	Induction of apoptosis Inhibition of proliferation	↑caspase-3, -8, -9 ↓EGFR, tubulin polymerization	[33]

Classification	Compound	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Methyl protodioscin	Rhizoma of *Polygonatum sibiricum*	HeLa	18.31, 40, 49 μM; 24 h	Induction of apoptosis and cell cycle arrest Inhibition of proliferation	↑ ROS	[34]
Plant	Mitomycin C	Ginger, Frankincense	HeLa	10 μg/mL; 24 h	Induction of apoptosis Inhibition of proliferation		[35]
Etc.	Naringenin oxime Naringenin oxime ether		HeLa, SiHa	HeLa: 12, 24 μM; 24 h SiHa: 18, 36 μM; 24 h	Induction of apoptosis Inhibition of proliferation	↑caspase-3	[36]
Plant	Nitensidine B	Leaves of *Pterogyne nitens* Tul.	HPV16, SiHa	30, 60, 120 μM; 6, 12, 24 h	Induction of apoptosis	↑caspase-3, -7 ↓aldolase A, alpha-enolase, pyruvate kinase, glyceraldehyde 3-p-dehydrogenase	[37]
Plant	Notoginsenoside R7	*Panax notoginseng*	HeLa, BALB/c	In vitro: 5, 10, 20, 40 μM; 24, 36, 48 h In vivo: 5, 10 mg/kg	Induction of apoptosis Inhibition of proliferation	↑Bax, p-PTEN, Akt ↓Bcl-2, -xL, caspase-3, -9, raptor	[38]
Plant	Osthole	*Cnidiummonnieri* (L.) Cusson	HeLa, SiHa, C-33A, CaSki	40, 80, 120, 160, 200, 240 μM; 24, 48 h	Induction of apoptosis Inhibition of proliferation	↑Bax, c-caspase-3, -9 proteins, E-cadherin, H2AX ↓Bcl-2, MMP-2, -9, β-catenin, vimentin, N-cadherin, IKKα, p-IKKα, p65, p-	[39]

Classification	Compound	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
						p65, p50, NF-κB	
Plant	Physcion	*Rhamnus sphaerosperma* var. *pubescens*	SiHa, C33A	43.8, 87.5, 175 μg/mL; 6, 12, 24 h	Induction of apoptosis	↓HOCl/OCl-, p-Akt	[29]
Plant	Phyto-synthesis of silver nanoparticles	Garlic, Green tea, Turmeric	HeLa	2, 5, 10, 25, 50, 100 μg/mL; 48 h	Induction of apoptosis	↓free radical	[40]
Plant	Piperine	*Piper nigrum* L.	HeLa, PTX	50 μM; 6, 24, 72 h with paclitaxel	Induction of apoptosis	↑Bax, Bcl-2, c-PARP, caspase-3 ↓p-Akt, Mcl-1	[41]
Plant	Prenylflavonoids C1	*Mallotus conspurcatus*	HeLa	30 μM; 24 h	Induction of apoptosis	↑EGFP, ROS, Bcl-2, cytochrome c, Apaf-1, caspase-3, -9 ↓c-Myc, hTERT	[42]
	Prenylflavonoids C5			10 μM; 24 h			50
Plant	Protodioscin	*Dioscoreae rhizome*	HeLa, C33A	4 μM; 24, 48 h	Induction of apoptosis and mitochondrial dysfunction	↑JNK, p38, PERK, ATF4, Bax, caspase-3, -8, -9, PARP ↓Bcl-2	[43]
Etc.	Pterostilbene	[53]	HPV E6, TC1, C57Bl/6	In vitro: 30 μM; 48 h In vivo: 1 mM; 5 days	Induction of cell cycle arrest	↑caspase-3 ↓PCNA, VEGF	[44]
	Resveratrol						
Plant	Tf-CT-ME	*Tripterygium wilfordii*	HeLa	[54] 0.5, 1, 2 μg/mL; 24 h	Induction of cell cycle arrest and apoptosis Inhibition of proliferation	↑c-caspase-3 ↓Bcl-2/Bax	[45]

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R1 were increased and MMP-2 and 9 were decreased in HeLa cells by treatment of ethanol extracts from *Bauhinia variegate candida* at dose of 15 μg/mL for an incubation time of 24 h [55]. Controlling mechanisms, it could reduce cell viability and inhibit migration and induct apoptosis. In conclusion, it contained components with potential tumor-selective cytotoxic action. Ethanol extracts isolated from *Botryidiopsidaceae* species induced apoptosis and inhibited oxidant, proliferation, migration, and invasion in HeLa cells [56]. It upregulated p53 and c-caspase-3 and downregulated Bcl-2 at doses of 6.25 μg/mL, 12.5 μg/mL, 25 μg/mL, and 50 μg/mL for an incubation time of 24 h. In conclusion, inhibitory effects of ethanol extracts on migration and invasion might occur via the modulation of genes related to the processes of cellular invasion and migration. Ethanol extracts from *Chloromonas* species upregulated c-caspase-3 and p53 and downregulated Bcl-2 in HeLa cells at dose of 12.5 μg/mL and 25 μg/mL for an incubation time of 24 h and 72 h [57]. The result meant that ethanol extracts dealt with cancer cells by increasing the pro-apoptotic protein and reducing the anti-apoptotic protein. It suggested that induction of apoptosis through the modulation of apoptosis associated genes and inhibition of proliferation and oxidant were involved in the

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Classification	Compound	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy [58]	Mechanism	Reference
Seed	Thymoquinone	*Nigella sativa*	SiHa, CaSki	10, 20, 40 µM; 24, 36, 48 h	Inhibition of migration and invasion	↑Bax, E-cadherin ↓Bcl-2, Twist1, vimentin	[46]
Plant	Triphala	*Terminalia chebula* Retz., *Terminalia bellerica* (Gaertn) Roxb., *Phyllanthus emblica* Linn.	HeLa	25-150 µg/mL; 48 h	Induction of apoptosis [29]	↑ERK, p53 ↓c-Myc, cyclin D1, p-Akt, p-NF-κB, p56, p-p44/42, MAPK	[47]
Plant	1′S-1′-acetoxychavicol acetate	*Alpinia conchigera*	CaSki, SiHa	20, 30 µM; 6, 12, 48 h	Induction of apoptosis [59]	↑RSU1, GAPDH	[48]
Plant	2D of oleanolic acid and glycyrrhetinic acid	*Ligustri Lucidi Fructus, Glycyrrhiza uralensis*	HeLa	2, 4 µM; 24, 48 h	Induction of apoptosis Inhibition of proliferation	↑ROS	[49]
	3O of oleanolic acid and glycyrrhetinic acid [60]			1, 2 µM; 48 h			
Etc.	3,5,4′-trimethoxystilbene		HeLa	10 µM; 48 h	Induction of apoptosis		[50]
	5,6,7-trimethoxyflavone						
Plant	5′-*epi*-SPA-6952A	*Streptomyces diastatochromogenes*	HeLa	2, 4, 8, 16 µg/mL; 24 h	Induction of apoptosis and cell cycle arrest Inhibition of proliferation	↑Bax/Bcl-2, cytochrome c, caspase-3, -9, c-PARP, p53 ↓MMP	[51]

extracts at the density of 50 mg/mL for an incubation time of 24 h with 4 Gy radiotherapy [62]. Through the mechanisms, it enhanced radiotherapy. Lipid-soluble extracts from *Pinellia pedatisecta* Schott. upregulated β-catenin, c-Myc, cyclin D1, PPAR1, and downregulated Th2 and Th17 in HPV and TC-1 cells at a dose of 500 µg/mL dealing with 72 h [63]. This result suggested that induction of apoptosis and cell cycle arrest were involved in the pathway. The subset proportion of Th1 cells increased significantly and both Th2 cells and Th17 cells decreased profoundly. In vivo, T lymphocyte infiltration in tumor-burdened mice was enhanced with treatment. Methanol extracts from *Allium atroviolaceum* upregulated caspase-3, -5, and -9 and downregulated Bcl-2, CDK1, and p53 in HeLa cells at concentrations of 20 µg/mL, 40 µg/mL, 60 µg/mL, 80 µg/mL, and 100 µg/mL for 24 h, 48 h, and 72 h [64]. The efficacy was the best at 72 h. Controlling the mechanisms, it inhibited cell growth and proliferation, induced cell cycle arrest, and reduced cell viability. The level of cleaved caspase-3 was increased and the level of PARP-1 was decreased by methanol extracts from *Carduus crispus* in HeLa cells at doses of 250 µg/mL and 500 µg/mL for 24 h [65]. The expression of cleaved forms of caspase-3 and PARP-1 suggested that the extract induced apoptosis through caspase-3 activation in HeLa cells. In conclusion, this result suggested that reduction of cell viability, induction of apoptosis, inhibition of oxidant and proliferation were involved in the pathway. Methanol extracts isolated from *Cyperus rotundus* induced apoptosis and DNA fragmentation and inhibited migration in HeLa cells at doses of 25 µg/mL, 50 µg/mL, and 100 µg/mL for an incubation time of 24 h and 48 h [66]. Cytotoxic effects of methanol extracts on the tested cancer cell lines ranged from 4.52 ± 0.57 µg/mL−1 to 9.85 ± 0.68 µg/mL−1

cyan fluorescent protein (CFP); yellow fluorescent protein (YFP); B-cell lymphoma 2 (Bcl-2); Bcl-2-associated X protein (Bax); B-cell lymphoma 2 (Bcl-2); matrix metalloproteinase (MMP); transcription factor (TCF); c-myelocytomatosis oncogene (c-Myc); cytochrome complex (cytochrome c); poly ADP-ribose polymerase (PARP); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); phospho-Akt (p-Akt); B-cell lymphoma-extra large (Bcl-xL); reactive oxygen species (ROS); X-linked inhibitor of apoptosis protein (XIAP); cleaved caspase (c-caspase); epidermal growth factor receptor (EGFR); 3-phosphate dehydrogenase (3-p-dehydrogenase); phospho-phosphatase and tensin homolog (p-PTEN); epithelial cadherin (E-cadherin); H2A histone family member X (H2AX); neural cadherin (N-cadherin); inhibitor of NF-κB kinase α (IKKα); phospho-IKKα (p-IKKα); phospho-p65

[illegible] [67] [illegible] [68] [illegible] IC_{50} [illegible] 26.25 μg/mL. Meanwhile, *Pyrrosia piloselloides* water extracts were without influence. Panicker et al. reported that methanol extracts from *Teucrium mascatense* were shown to activate caspases and PARP on HeLa cells, following treatment with 25 μg/mL, 50 μg/mL, 125 μg/mL, and 250 μg/mL, for 72 h [69]. In addition, cell rounding, shrinkage, and detachment from other cells were shown by methanol extracts. This result suggested apoptosis and alteration of cell morphology were related to the pathway.

Table 2. Apoptosis inducing natural products-extracts.

Classification	Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Aqueous extract	*Anemone nemorosa*	HeLa	20.33 ± 2.480 μg/mL; 24, 48 h	Induction of apoptosis Inhibition of proliferation	↑PS translocation, c-caspase-3, -8, ROS (24 h) ↓MMP, ROS (48 h)	[52]
Plant	Aril extract	*Strelitzia nicolai*	HeLa	250 μg/mL; 24, 48, 72 h	Inhibition of oxidative stress Induction of apoptosis		[53]
Plant	Ethanol extract	*Astragalus membranaceus*, *Angelica gigas*, *Trichosanthes kirilowii* Maximowicz.	HeLa	100, 200, 400 μg/mL; 24, 48 h	Induction of apoptosis and cell cycle arrest Inhibition of cell viability	↑c-caspase-3, -8, PARP-1 ↓Bax, cyclin D, CDK2, CDK4, CDK6, p27	[54]
Plant	Ethanol extract	*Bauhinia variegate candida*	HeLa	15 μg/mL; 24 h	Inhibition of cell viability and migration Induction of apoptosis	↑c-caspase-3, -8, RIP, TNF-R1 ↓MMP-2, MMP-9	[55]
Plant	Ethanol extract	*Botryidiopsidaceae* species	HeLa	6.25, 12.5, 25, 50 μg/mL; 24 h	Inhibition of oxidative stress and	↑p53, c-caspase-3 ↓Bcl-2	[56]

Classification	Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
					migration Induction of apoptosis		
Plant	Ethanol extract	*Chloromonas* species	HeLa	12.5, 25 μg/mL; 24, 72 h	Inhibition of oxidative stress Induction of apoptosis	↑c-caspase-3, p53 ↓Bcl-2	[57]
Plant	Ethanol extract	*Dendrobium chrysanthum*	HeLa, Swiss albino mice	In vitro: 450 μg/mL; 24 h In vivo: 50, 100 mg/kg	Induction of apoptosis	↑Bax, p53 ↓Bcl-2	[58]
Plant	Ethanol extract	*Rhamnus sphaerosperma* var. *pubescens*	SiHa, C33A	25, 50, 100 μg/mL; 6, 12, 24 h	Induction of apoptosis	↓HOCl/OCl-, p-Akt	[29]
Plant	Ethyl acetate extract	*Gynura formosana* Kitam.	HeLa	30 μg/mL; 72 h	Inhibition of proliferation	↑ LC3-II/LC3-I, ↓P62/GAPDH, MCM7/GAPDH	[59]
Fungus	Ethyl acetate extract	*Penicillium sclerotiorum*	HeLa	5, 25, 50 μg/mL; 24 h	Induction of apoptosis and cell cycle arrest	↑Bax, p53, Apaf-1 ↓Bcl-2	[60]
Plant	Ethyl acetate extract	*Streptomyces* species	SiHa	20, 40, 60 μg/mL; 24 h	Induction of apoptosis and autophagy	↑caspase-3, -9, Bax, LC3-Ⅱ ↓PARP, LC3-I, Beclin1, p62	[61]
Plant	Extract	Blueberry	SiHa	50 mg/mL; 24 h with 4 Gy radiotherapy	Enhancement of radiotherapy	↑p53 ↓cyclin D, E, p21, survivin	[62]
Plant	Lipid-soluble extract	*Pinellia pedatisecta* Schott.	$HPV^{+}TC$-1, C57BL/6	In vitro: 500 μg/mL; 72, 120 h In vivo: 10, 20 mg/kg	Induction of cell cycle arrest and apoptosis	↑ β-catenin, c-Myc, cyclin D1, PPAR1 ↓Th2, Th17	[63]
Plant	Methanol extract	*Allium atroviolaceum*	HeLa	20, 40, 60, 80, 100 μg/mL; 24, 48, 72 h	Induction of cell cycle arrest	↑caspase-3, -5, -9 ↓Bcl-2, CDK1, p53	[64]

2.2. Anti-angiogenesis

Angiogenesis is a major cause in the development and metastasis of a variety of tumor types [70]. Local angiogenesis provides oxygen and essential nutrients to the growing tumor, supports tumor expansion and invasion into nearby normal tissue, and is essential for distant metastasis [71]. To be specific, in cervical cancer,

Classification	Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy [72]	Mechanism	Reference
Plant	Methanol extract	*Corylus avellane* L.	HeLa	250, 500 µg/mL; 24 h	Inhibition of oxidative stress Induction of apoptosis	↑caspase-3 ↓PARP-1	[65]
Plant	Methanol extract	[73] *Cyperus rotundus*	HeLa	25, 50, 100 µg/mL; 24, 48 h	Induction of apoptosis		[66]
Plant	Methanol extract	*Polyalthia longifolia*	HeLa [15]	22 µg/mL; 6, 12, 24, 36 h	Induction of apoptosis	↑Bax, BAD, caspase-3, p21, p53 ↓Bcl-2	[67]
Plant	Methanol extract	*Pyrrosia piloselloides*	HeLa,	16.25 µg/mL; 24, 48, 72 h	Inhibition of proliferation		[68]
Plant	Methanol extract	*Teucrium mascatense*	HeLa	25, 50, 125, 250 µg/mL; 72 h	Induction of apoptosis Inhibition of proliferation	[60] ↑c-caspase-7, -8, -9, PARP	[69]

p53 and could be Ski cells own and poptosis In vivo, after the e study. d inhibit e-3 and n. These akose et cells by cid, oleic it could induce cell cycle arrest and inhibit angiogenesis at a dose of 7.75 µg/mL. Seifaddinipour et al. reported that ethyl acetate extracts isolated from *Pistacia vera* L. downregulated TNF, Bcl-2, IAP, and TRAF in CaSki cells [74]. Through the mechanisms, it induced apoptosis and inhibited angiogenesis. The efficient dose was 81.17 ± 2.87 µg/mL, dealing with a timeframe of 72 h.

Table 3. Angiogenesis inhibiting natural products.

Phosphatidylserine (PS); cyclin-dependant kinase (CDK); receptor-interacting protein (RIP); tumor necrosis factor roxisome

Classification	Compound/ Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Fruit	PfLP	*Praecitrullus fistulosus*	HeLa Swiss Albino mice	In vitro: 50 µg/mL; 24 h In vivo: 10 mg/kg	Induction of apoptosis Inhibition of angiogenesis	↓ MMP-2, -9	[73]
Plant	Purified flaxseed hydrolysate	Lignan	HeLa	17.4 µg/mL; 48 h	Induction of apoptosis Inhibition of angiogenesis and metastasis	↑ caspase-3 ↓ MMP-2, VEGF	[15]
Fungus	Ethyl acetate extract	*Penicillium sclerotiorum*	HeLa	7.75 µg/mL; 24 h	Induction of cell cycle arrest and apoptosis	↑ Bax, p53, Apaf-1 ↓ Bcl-2	[60]

Classification	Compound/ Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
					Inhibition of angiogenesis		
Plant	Ethyl acetate extract	*Pistacia vera* L.	CaSki	81.17 ± 2.87 μg/mL; 72 h	Induction of apoptosis Inhibition of angiogenesis	↓ TNF, Bcl-2, IAP, TRAF	[74]

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substance (7.75 μg/mL) was significantly lower than that of other anti-angiogenesis studies [60]. By increasing the expression of Bax, p53, and Apaf-1 and inhibiting Bcl-2, it was shown to induce not only anti-angiogenesis, but also cell cycle arrest and apoptosis at doses of 5 μg/mL, 25 μg/mL, and 50 μg/mL.

Praecitrullus fistulosus lectin protein (PfLP); inhibitor of apoptosis protein (IAP); TNF receptor-associated factor (TRAF).

2.3. Anti-Metastasis

Metastasis is the propagation of transformed cells from the organ of origin to other parts of the body and the successive proliferation of tumor colonies [76]. The mechanism includes complicated processes, such as cancer cell detachment from extracellular matrix, migration, invasion, and extravasation to the circulation, and most cancer patients die from metastasis rather than primary tumors [77]. Six natural products including EGCG inhibited metastasis (Table 4). The chemical structures of compounds are shown in Figure 2.

Figure 2. Chemical structures of compounds derived from natural products inhibiting metastasis.

Table 4. Metastasis inhibiting natural products.

Classification	Compound/ Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Astragaloside IV	Radix Astragali	SiHa	200 μg/mL; 24 h	Inhibition of cell metastasis	↑ E-cadherin ↓ p38, PI3K	[78]

Classification	Compound/ Extract	Source	Cell Line/ Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Epigallocatechingallate	Green tea	HeLa	50 µg/mL; 48 h	Inhibition of cell metastasis and proliferation Induction of apoptosis	↓ MMP-2, -9, VEGF	[79]
Plant	Praeruptorin B	*Peucedanum praeruptorum* Dunn.	HeLa, SiHa	40, 60 µM; 24 h	Inhibition of cell metastasis	↓ NF-κB, MMP-2, -9	[80]
Seed	Thymoquinone	*Nigella sativa*	CaSki, HeLa	5 µM; 24 h	Induction of apoptosis, migration and invasion	↑ E-cadherin ↓ Twist1, Zeb1	[46]
Plant	Ethanol extract	*Bauhinia variegata candida* [78]	HeLa	25 µg/mL; 24 h	Inhibition of cell viability, migration and invasion	↓ MMP-2, -9	[55]
Plant	Ethanol extract	*Terminalia catappa*	HeLa, SiHa	25, 50, 75 µg/mL; 24 h	Inhibition of cell metastasis	↓ MMP-9, ERK1/2	[81]

tment of etastasis MP-2, -9, [79]. Thus, ration in cervical cancer cells by reducing VEGF, CDK2, and ERK1/2. Praeruptorin-B isolated from *Peucedanum praeruptorum* Dunn. downregulated NF-κB, MMP-2, and -9 in HeLa and SiHa cells [80]. Inhibition of cell metastasis could be observed following the treatment of praeruptorin-B at doses of 40 µg and 60 µg over 24 h. Moreover, it blocked Akt phosphorylation without affecting the MAPK pathway. These results suggested that praeruptorin-B could be good at anticancer activity, especially in cervical cancer cells. Thymoquinone from *Nigella sativa* was shown to induce apoptosis, migration, and invasion on CaSki and HeLa cells [46]. It was efficient when CaSki cells and HeLa cells were treated at a concentration of 5 µM for 24 h. Furthermore, it included the mechanism of increasing E-cadherin level and decreasing the level of Twist1 and Zeb1. Ethanol extracts from *Bauhinia variegata candida* decreased the level of MMP-2 and -9 on HeLa cells [55]. This mechanism was caused when HeLa cells were treated at a concentration of 25 µg/mL for 24 h. Subsequently, it reduced cell viability, migration, and invasion. Lee et al. reported that the decline of MMP-9 and ERK1/2 was observed after the exposure of *Terminalia catappa* ethanol extracts on HeLa and SiHa cells [81]. This process was efficient when the dose was 25 µg/mL, 50 µg/mL, and 75 µg/mL, dealing with a timeframe of 24 h and it led to inhibition of cell metastasis. In conclusion, ethanol extracts blocked the MMP-9 through ERK1/2 pathway by anti-metastatic effects.

Phosphoinositide 3-kinase (PI3K); Zinc finger E-box-binding homeobox 1 (Zeb1)[46].

A total of six substances derived from natural products inhibited the metastasis of cervical cancer, and MMP control was the most important mechanism. Four substances regulated MMP, MMP-2 was inhibited in three substances, and MMP-9 was inhibited in four substances. E-cadherin is a protein remarkably related to tumor invasion,

metastatic transmission, and poor patient prognosis [82]. It was derived from two substances, and in addition, it showed anti-metastasis action through inhibitory mechanisms such as p38, VEGF, and Twist1. In particular, ethanol extracts from *Bauhinia variegate candida* exhibited multi-effect, inhibited migration and invasion at 25 µg/mL, and also induced apoptosis at 15 µg/mL [55]. However, the concentration of the natural product was so high (200 µg/mL) that there was a study involving cytotoxicity concerns [78].

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