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The Potential of Chinese Herbal Medicines in the Treatment of Cervical Cancer

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Abstract

Cervical cancer is a global health issue and places a considerable economic and medical burden on society. Thus, a concerted effort to improve the treatment of cervical cancer is warranted. Although several treatment options are currently available for treating patients with cervical cancer, such as chemoradiation and neoadjuvant or adjuvant chemotherapy, more aggressive systemic therapies and newer therapeutic agents are under investigation. Medicinal herbs have long been used to treat diseases. In this review, we summarize studies analyzing the antitumor effects and underlying mechanisms of Chinese herbal medicines, including the effects of crude extracts and compounds in vitro or in animal models for inducing apoptosis and inhibiting invasion or metastasis. Chinese herbal medicines with therapeutic targeting, such as those that interfere with tumor growth and progression in cervical cancer, have been widely investigated. To apply Chinese herbal medicine in the treatment of cervical cancer, adequate clinical studies are required to confirm its clinical safety and efficiency. Further investigations focused on the purification, pharmacokinetics, and identification of compounds from Chinese herbal medicines in cervical cancer treatment are necessary to achieve the aforementioned treatment goals.

Keywords

cervical cancer, medicinal herb, Chinese herbal medicine, cancer treatment, apoptosis

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Introduction

Cervical cancer is a pertinent global health issue as it is the fourth most common cancer in women worldwide and causes more than one quarter of a million deaths per year.[1] Such cancer confers an economic and medical burden on society. Thus, a concerted global effort to improve the treatment of cervical cancer is warranted. The treatment of cervical cancer is based on the International Federation of Gynecology and Obstetrics staging system.[2] Cervical cancer stages range from I to IV. Patients with locally advanced or early-stage cervical cancer have access to conventional treatments, including surgery, chemotherapy, and radiotherapy. However, no standard therapy is available for patients with metastatic cervical cancer.[3] Treatment options might be insufficient and have associated side effects. In addition to several treatment options being available to treat cervical cancer, such as chemoradiation and neoadjuvant or adjuvant chemotherapy, more aggressive systemic therapies and newer therapeutic agents are under investigation.[4]

Cancer is characterized by a multistep development of considerable complexity, including uncontrolled cell proliferation, invasion, migration, and metastasis.[5] Antitumor therapies for human cancer tend to be based on administering apoptosis-inducing drugs that inhibit proliferation, invasion, and metastasis. Medicinal herbs

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have long been used to treat many diseases, including cancer.[6]

In this review, we summarize studies analyzing the antitumor effects and underlying mechanisms of Chinese herbal medicines, including the effects of crude extracts and compounds in vitro or in animal models for inducing apoptosis and inhibiting invasion or metastasis.

Effects of Chinese Herbal Medicines on Cervical Cancer Cells

Crude Extracts of Chinese Herbal Medicines With Anti-Cervical Cancer Effects

Antrodia cinnamomea. *Antrodia cinnamomea*, also called *Antrodia camphorata*, is a food source used in traditional Chinese medicine.[7] Crude extracts of *A camphorata* exhibit a wide range of biological activities, with several studies having focused on its anticancer effects. The hepatoprotective activities[8] and activities against liver injury[9] of *A camphorata* have also been reported. By using the lyophilized powder of *A camphorata* mycelium with distilled water, *A camphorata* was revealed to be nontoxic. Furthermore, the researchers involved in that study demonstrated the effects of *A camphorata* extracts, including its dose-dependent antioxidant and antimutagenic effects on 4NQNO and its DNA-protective activities against hydroxyl radical–induced damage.[10] Pharmacological studies of *A camphorata* have mostly been in vitro or in vivo experiments on animals.[11] Few clinical trials analyzing the effects of *A camphorata* extracts on humans have been reported. Clinical studies are required to confirm the therapeutic effects of such extracts. The effects of ethyl acetate extract from *A camphorata* fruiting bodies on hepatocellular carcinoma cell lines Hep G2 and PLC/PRF/5 have been investigated,[12] finding that cell growth decreased and apoptosis was induced in both Hep G2 and PLC/PRF/5.[12] The antiproliferative effects of methanol extracts from *A camphorata* mycelia were investigated, with the findings suggesting that apoptosis of human hepatoma HepG2 cells could be achieved through regulation of the Fas pathway.[13] The effect of a fermented culture broth of *A camphorata* was shown to inhibit growth and have antiproliferative effects on MCF-7 cells through apoptosis induction.[14] Furthermore, the induction of phase G(2)M arrest and the antimetastatic effects of *A camphorata* extracts on urinary bladder cancer have been demonstrated.[15] A study also found that a fermented culture broth of *A camphorata* induced cell cycle arrest of MDA-MB-231 cells and apoptosis in an in vivo breast cancer model involving athymic nude mice.[16] Extracts of *A camphorata* fruiting bodies induced leukemia HL 60 cell apoptosis and could be a potential chemotherapeutic adjuvant.[17]

The apoptotic effect of the crude extract of *A camphorata* on cervical cancer cells, HeLa and C-33A, has been reported.[18] *A camphorata* extract increased the activity of caspase-3, -8, and -9 as well as the cytosolic level of cytochrome c in HeLa and C-33A cell lines. The expressions of Bad, Bak, and Bim were increased, and the expressions of Bcl-2 family proteins were decreased. The expressions of inhibitor of apoptosis proteins (IAPs) and X-linked IAP protein also decreased, as did cell survival. Thus, the cytotoxic effect of *A camphorata* extract on cervical cancer cells through both extrinsic and intrinsic apoptotic pathways was demonstrated.[18]

Terminalia catappa. Various phytoconstituents from the leaves, fruits, and seeds of *Terminalia catappa* have been identified.[19] The antimicrobial, anti-inflammation, hepatoprotective, and anticancer activities of *T catappa* leaf extracts (TCEs) have been recognized.[19] TCEs exhibited hepatoprotective effects on liver damage induced by D-galactosamine[20] and liver mitochondria damaged by carbon tetrachloride.[21] Furthermore, the inhibitory effect of TCEs on lung cancer metastasis in vitro and in vivo was proven.[22] The underlying molecular mechanisms of the antimetastatic effects of TCEs on hepatocellular carcinoma were demonstrated by a recent study.[23] The researchers found that TCEs exert antimetastatic effects through inhibiting the activities and expression of matrix metalloproteinase-9 (MMP-9) in hepatocellular carcinoma Huh7 cells.[23]

The antitumor effect of TCEs against Ehrlich ascites carcinoma in an animal model has been reported.[24] Tumor-bearing animals, namely Swiss albino mice, were treated with ethanol extract of *T catappa* leaves. Decreasing levels of lipid peroxidation and glutathione and increasing levels of superoxide dismutase and catalase activity were detected. The researchers demonstrated the antitumor effect of TCEs by modulating lipid peroxidation and augmenting antioxidant defense systems.[24] The antimetastatic effect of ethanol extracts of *T catappa* on cervical cancer cells after treatment with 12-O-tetradecanoylphorbol-13-acetate was reported.[25] The results of that study revealed that TCE exerted antimetastatic effects on cervical cancer cells by inhibiting the expression of MMP-9 and mitogen-activated protein kinase (MAPK) pathways on such cells.[25]

Chelidonium majus. *Chelidonium majus*, commonly known as greater celandine, has been shown to contain several isoquinoline alkaloids, such as sanguinarine, chelidonine, chelerythrine, berberine, and coptisisine, in the crude extract of its roots, shoots, and leaves.[26] Both *C majus* and its main alkaloid chelidonine have cytotoxic effects against cancer cells, such as leukemia,[27] PANC-1 (pancreatic cancer), and HT-29 (colon cancer) cells.[28] The effects of chelidonine isolated from the ethanolic extract of *C majus* on HeLa cells were demonstrated by Paul et al.[26] Chelidonine, isolated from the ethanolic extract of *C majus*, was reported to inhibit proliferation and induce apoptosis in HeLa cells through

Table 1. Functions of the Crude Extracts of Chinese Herbal Medicines in Uterine Cervical Cancer.

	Chinese Herbal Medicine	Cell Lines/Animal Models	Action	References
1	*Antrodia camphorata*	HeLa and C-33A cells	Cytotoxic to cervical cancer cells through both extrinsic and intrinsic apoptotic mechanisms	Yang et al[18]
2	*Terminalia catappa*	HeLa and SiHa cells	Antimetastatic effects through the inhibition of matrix metalloprotein-9 and MAPK pathway	Lee et al[25]
3	*Chelidonium majus*	HeLa cells	Promoting apoptosis in HeLa cells through p38-p53 and PI3K/AKT signaling pathways	Paul et al[26]
4	*Lycopodium clavatum*	HeLa cells	Inhibiting proliferation of HeLa cells through induction of apoptosis via caspase-3 activation	Mandal et al[29]
5	*Myrica cerifera*	HeLa and PC3 cells	Inducing apoptosis in cancer cells by triggering caspase activation	Paul et al[32]

upregulating the expression of p38 and p53 and downregulating the expression of AKT, PI3K, JAK3, STAT3, E6, and E7.[26] The researchers of that study posited that these effects of chelidonine on cervical cancer cells were through the p38-p53 and AKT/PI3 kinase signaling pathways.[26]

Lycopodium clavatum. The ethanolic extract of *Lycopodium clavatum* has been used as an alternative medicine for treating Alzheimer's disease and liver ailments.[29] The protective potential of *L clavatum* extract on mice chronically fed hepatocarcinogens has also been shown.[30] The anticancer effects of lycopodine on cervical cancer were investigated by an in vitro study using HeLa cells.[29] Numerous activities of lycopodine were detected, including the induction of chromatin condensation, the enhancement of cell populations in the sub-G1 region, the fragmentation of internucleosomal DNA, and the activation of caspase-3.[29] The antiproliferative effect of lycopodine on HeLa cells was achieved through the induction of apoptosis via caspase-3 activation.[29]

Diarylheptanoid-Myricanone. *Myrica cerifera* extract has been used as an anticancer drug, with hepatoprotective and apoptosis-promoting abilities also reported.[31] The mechanism has been investigated by applying myricanone from the crude ethanolic extract of *M cerifera* in human hepatocellular carcinoma (HepG2) and normal liver (WRL-68) cell lines.[31] The extract of *M cerifera* exhibited anticancer potential for inducing apoptosis in HepG2 cells through the generation of reactive oxygen species (ROS) and the depolarization of the mitochondrial membrane.[31] Myricanone triggered apoptotic effects through ROS generation and mitochondrial membrane depolarization, elevating mitochondria-dependent caspase activity to induce apoptosis in HepG2 cells. The anticancer effect of diarylheptanoid-myricanone isolated from the ethanolic extract of *M cerifera* on HeLa cells has been investigated and was found to have a greater cytotoxic effect and promote G0/G1 arrest.[32] The researchers demonstrated that myricanone induced apoptosis by triggering caspase activation and downregulating NF-κB and STAT3 signaling cascades[32] (Table 1).

Bioactive Compounds From Chinese Herbal Medicines in Uterine Cervical Cancer

Butein. Butein can be isolated from various plants, including *Semecarpus anacardium, Toxicodendron vernicifluum*, and *Dalbergia odorifera*, and it exhibits anti-allergic anti-inflammatory activities,[33] selectively inhibits NF-κB in activated human mast cells,[34] and suppresses MMP-9 expression and vascular endothelial growth factor in prostate cancer cells.[35] The effects of butein on cervical cancer cell growth, apoptosis, migration, and invasion have been investigated, with researchers finding that butein induced HeLa cell cycle at the G2/M stage and cell apoptosis through the PI3K/AKT/mTOR pathway.[36] Induction of apoptosis of human cervical cancer cells by butein has been reported recently.[37] The researchers found that butein disturbed mitochondrial transmembrane potential and caspase activities in C-33A and SiHa cells; moreover, they demonstrated butein's proapoptotic effect, including inhibition of IAPs and activation of both extrinsic and intrinsic proapoptotic pathways.[37]

Nujiangexathone A. Many traditional Chinese herbal medicines contain active compounds and exhibit anticancer effects.[38] Nujiangexathone A (NJXA), a compound isolated from the leaves of *Garcinia nujiangensis*, exhibits cytotoxic effects against tumor cell lines.[39] NJXA has been proposed to inhibit the proliferation of several human cancer cell lines,[40] the mechanism of which has been previously investigated.[39,40]

Ubiquitin proteasome–dependent degradation of hnRNPK accelerated the cell cycle arrest of cervical tumor cell growth delayed in a HeLa xenograft model.[39] The tumor-inhibitory effect of NJXA was achieved through downregulation of hnRNPK.[39] The apoptosis-inducing activities of NJXA on HeLa and SiHa cells and in vitro have been studied.[40] NJXA induced caspase-dependent apoptosis. Changes in the levels of Bcl-2 family proteins, caspase-3 activation, cytochrome c release, and chromosome fragmentation have been identified.[40] NJXA induced apoptosis by activating the ROS-mediated JNK signaling pathway.[40]

APS-1d. APS-1d is a novel polysaccharide isolated from *Angelica sinensis*. The root of *A sinensis* is a well-studied Chinese herbal medicine and has been used as an anti-inflammatory and hematopoietic agent for thousands of years.[41] Recent advances in phytochemistry indicate that the crude extracts and pure compounds of *A sinensis* have numerous pharmacological activities, including antispasmodic, antioxidant, cardiovascular, and cerebrovascular effects and neuroprotective action.[42] *A sinensis* polysaccharides have various important biological activities.[41] The proapoptotic effects of APS-1d in HeLa cells both in vitro and in vivo have been investigated,[43] with findings revealing that APS-1d inhibited the growth of HeLa cells, induced the apoptosis of such cells in vitro, and promoted the apoptosis of these cells in vivo.[43] Furthermore, increasing the levels of proapoptotic proteins Bax and Bak and decreased the levels of antiapoptotic proteins Bcl-2 and Bcl-XL in APS-1d–treated cells.[43] APS-1d can inhibit HeLa cell proliferation and induce apoptosis via the intrinsic mitochondrial pathway.[43]

Lappaol F. The antitumor activity of lappaol F, extracted from *Arctium lappa* L, was investigated in vitro and in vivo.[44] The researchers demonstrated that lappaol F strongly inhibited HeLa cell growth in xenograft tumors in nude mice. In HeLa cells, lappaol F suppressed cell growth and induced G1 and G2 cell cycle arrest and cell death. Lappaol F suppressed tumor growth in nude mice bearing the xenograft tumors of HeLa cervical cancer cells. From these results, the researchers posited that p21 may play a crucial role in lappaol F–mediated regulation of cyclin B1 and CDK1 and G2 cell cycle arrest and upregulate p21 at the transcriptional level in a p53-independent model.[44]

Elephantopus mollis 23. *Elephantopus mollis* 23 (EM23), a natural sesquiterpene lactone from *E mollis*, is a traditional herbal medicine with multiple pharmacological activities, such as apoptotic activity in myeloid leukemia cells K562 and HL-60[45] and cytotoxic activities against mouse neuroblastoma B104 cells.[46] The apoptotic effect of EM23 has been investigated in CaSki and SiHa human cervical cancer cell lines. EM23 exerts growth inhibitory effects and results in caspase 3 activation, mitochondrial dysfunction, ASK1/JNK signaling activation, and inhibition of the expression levels of Trx/TrxR. A study demonstrated that EM23 inhibits activity of TrxR in cell-free systems and can induce downregulation of Trx and TrxR in CaSki and SiHa cells.[47]

Eupafolin. Eupafolin is a flavone isolated from *Artemisia princeps* Pampanini. Eupafolin has several biological effects, such as anti-inflammatory activity against TNF-α–induced lung inflammation,[48] antitumor and antiangiogenic activity in hepatocellular carcinoma,[49] and enhancement of TRAIL-mediated apoptosis in renal carcinoma Caki cells.[50] The proapoptotic and molecular activity involving eupafolin in cervical adenocarcinoma HeLa cells was investigated,[51] with the researchers finding that eupafolin triggered the activation of caspases 3, 6, 7, 8, and 9, as well as induced apoptosis dependent on caspase activation. Eupafolin induced mitochondrial membrane depolarization, modulated the expression of Bcl-2 family proteins, and induced caspase-8 activation by eupafolin via a Bcl-2–dependent pathway. The apoptotic effect of eupafolin on HeLa cells was through caspase-dependent pathways, involving caspases 3, 9, and 8.[51]

Baicalein. Baicalein is the active ingredient extracted from the root of *Scutellaria baicalensis*, which is used in traditional Chinese medicine. It has multiple effects, such as anti-inflammatory, anti-allergic, antioxidative, and antitumorigenic activities.[52] Baicalein is involved in inhibiting various cancers, such as breast, bladder, and ovarian cancers.[53]

Recent studies have reported that baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway[54] and inhibits hepatocellular carcinoma cells through suppressing the expression of CD24.[55] Furthermore, the restraining effect of baicalein on human cervical cancer cell line HeLa has been demonstrated.[52] Baicalein induced HeLa cell apoptosis and significantly inhibited HeLa cell migration.[52] Baicalein markedly downregulated extracellular signal–regulated kinase 1/2, MMP-2, and MMP-9 levels both in mRNA and protein.[52]

Arctiin. Arctiin is a major lignan constituent of *Arctium lappa*. Its anti-inflammatory and antitumor effects have been widely explored.[56] The anticancer effects of arctiin regarding in vitro or in vivo animal models were investigated, revealing findings such as remarkable antitumor effects on mouse skin tumors,[57] protective effects on heterocyclic amino-induced mammary carcinogenesis in rats,[58] and growth inhibition in prostate cancer PC-3 cells via the upregulation of the antiadhesion mucin MUC-1 gene.[59] The inhibitory mechanism of arctiin in cervical cancer cells was through the downregulation of cyclin D1 expression.[60] The growth inhibition induced by arctiin was correlated with the downregulation of cyclin D1.[60]

Corosolic Acid. The biological activities of corosolic acid (CRA), which can be obtained from various herbs, have been investigated.[57,61,62] CRA, extracted from *Lagerstroemia speciosa* L, lowered postchallenge plasma glucose levels in vivo in humans.[61] CRA, a constituent of banaba leaves, has been reported to prevent oxidative stress, inflammation, and hypertension in vivo in SHR/NDmcr-cp rats.[62] CRA, isolated from the fruit of *Crategus pinnatifida* var psilosa, exhibited antagonistic activity against the phorbol ester–induced morphological modification of leukemic cells via the suppression of protein kinase C activity.[57] The

antitumor effect of CRA isolated from *Actinidia valvata* Dunn on human cervix adenocarcinoma HeLa cells was investigated,[63] finding that CRA induced apoptosis through increasing Bax/Bcl-2 ratios by upregulating Bax expression, disrupting mitochondrial membrane potential, and triggering the activation of caspases 8, 9, and 3 in HeLa cells.[63] Based on these results, the researchers posited that the apoptotic effect of CRA on HeLa cells is achieved through the activation of caspases via a mitochondrial pathway.[63]

Praeruptorin A. Praeruptorin A, from the dried root of *Peucedanum praeruptorum* Dunn, was revealed to have antimicrobial activity in a previous study.[64] The anti-inflammatory[65] and anticancer effects[66] of praeruptorin A have been reported. The activity of praeruptorin A against cervical cancer cells was investigated in a recent study.[67] In that study, praeruptorin A inhibited cervical cancer HeLa and SiHa cell proliferation and migration and invasion.[67] The expression of MMP-2 was reduced, the tissue-inhibiting expression of metalloproteinase-2 (TIMP-2) increased, and ERK1/2 activation was suppressed in the cervical cancer cells treated with praeruptorin A; moreover, praeruptorin A suppressed MMP-2 expression and ERK1/2 signaling in cervical cancer cells.[67]

Fisetin. Fisetin, a naturally occurring flavonoid, is present in fruits and vegetables. Fisetin has been described as a health-promoting dietary supplement.[68] Its effect on the antimetastatic potential of cervical cancer cells was previously investigated.[69] Fisetin suppressed the tetradecanoylphorbol-13-acetate (TPA)–induced activation of p38 MAPK and uPA and inhibited TPA-enhanced migration and invasion. The involved mechanism was the downregulation of urokinase plasminogen activator expression through suppressing the p38 MAPK-dependent NF-κB signaling pathway.[69] Furthermore, the therapeutic molecular mechanism of inducing apoptosis was through the ERK1/2-mediated activation of the caspase-8/caspase-3–dependent pathways.[70]

Deoxyelephantopin. Deoxyelephantopin, extracted and purified from *Elephantopus scaber*, inhibited the growth of SiHa cells and triggered apoptosis through multiple molecular signaling pathways.[71] The molecular mechanisms of the antiproliferative and apoptosis-inducing properties of deoxyelephantopin were investigated.[71] An increase in p53 and p21 levels and a decrease in the phosphosignal transducer and activator of transcription 3 (pSTAT3-Tyr705), cyclin-dependent kinase 1 (cdc2), and cyclin B1 were detected. Downregulation of antiapoptotic proteins (Bcl2 and Bcl-xL) and upregulation of apoptotic protein (Bax) was also identified.[71]

Beta-Elemene. Beta-elemene is an active component of the traditional Chinese medicinal herb *Curcuma zedoaria*. Beta-elemene exhibits antitumor effects in various cancer cell lines, including hepatoma,[72] MCF-7 human breast cancer,[73] and non–small cell lung cancer[74] cell lines. The antitumor effect of β-elemene on cervical cancer SiHa cells has been investigated.[75] Beta-elemene may inhibit cell proliferation and invasion and induce apoptosis. The expression levels of p53 and Bax were enhanced, and the expression of Bcl2 was suppressed. Downregulation of MMP-2 and MMP-9 expression levels was also detected.[75] The therapeutic molecular mechanism was through attenuation of the Wnt/β-catenin signaling pathway.[75]

Polydatin. Polydatin, also known as piceid, is a stilbene compound that can be extracted from *Polygonum cuspidatum*.[76] Studies have demonstrated the various effects of polydatin, including its cardioprotective effects against ischemia or reperfusion injury,[77] its beneficial effects on attenuating ventricular remodeling in pressure-overload rat models,[78] its inhibition of lung cancer cell growth by inducing apoptosis and causing cell cycle arrest,[79] and its promotion of apoptosis and inhibition of proliferation in osteosarcoma cells.[80] Polydatin inhibits cell proliferation and induces apoptosis in Hep-2 and laryngeal cancer cell AMC-HN-8 through the suppression of the PDGF/AKT signaling pathway.[76] A proliferation-inhibiting effect and the induction of the apoptosis of polydatin were also noted in cervical cancer HeLa cells.[81] In the same study, researchers showed that the growth-inhibiting effect caused S-phase arrest for HeLa cells, decreased the mRNA and protein expression levels of PI3K, AKT, mTOR, and P70S6K, and promoted cell apoptosis.[81] Polydatin induces human cervical cancer cell apoptosis via the PI3K/AKT/mTOR signaling pathway.

Matrine. Matrine, an alkaloid isolated from *Sophora flavescens*, has been widely studied for its bioactivities and pharmacological effects, including anti-inflammatory, antimicrobial, antiviral, insecticidal, and anticancer activity.[82,83] Matrine has been shown to have antitumor effects for numerous types of cancer, such as breast,[84] lung,[85] and prostate[86] cancer. The molecular mechanisms of matrine in terms of its antitumor effects implicate the regulation of oncogene expression, the blockade of cell cycle progression, the inhibition of cytokine production, the induction of apoptosis, and the modulation of signaling pathways.[82,83] The antitumor effects of matrine on cervical cancer cells were evaluated in a recent study.[87] Matrine inhibited the cell growth and invasive and metastatic ability of HeLa and C33A cervical cancer cells in vitro; moreover, matrine inhibited tumor growth in vivo in a xenograft nude mouse model. Concerning the mechanism of matrine, induction of apoptosis, suppression of MMP-2 and MMP-9 expression, and inhibition of cervical cancer cell invasion were all achieved through the suppression of the p38 signaling pathway.[87]

Table 2. Effects of Bioactive Compounds From Chinese Herbal Medicines on Uterine Cervical Cancer.

	Active Compound	Cell Lines/Animal Models	Function or Action	References
1	Butein	C33A and SiHa cells	Inducing apoptosis through activation of both extrinsic and intrinsic pathways	Yang et al[37]
2	Nujiangex-athone A	HeLa and SiHa cells	Suppresses cervical cancer growth by targeting hnRNPK	Zhang et al[39]
3	APS-1d	HeLa cells/BALB/c nude mice	Inducing apoptosis through an intrinsic apoptotic pathway	Cao et al[43]
4	Lappaol F	HeLa cells/BALB/c nude mice	Growth suppression through inducing G1 and G2 cell cycle arrest	Sun et al[44]
5	*Elephantopus mollis* 23	CaSki and SiHa cells	Induced cell apoptosis and cell cycle arrest	Shao et al[47]
6	Eupafolin	HeLa cells	Induced apoptosis mediated by caspase-dependent pathways	Chung et al[51]
7	Baicalein	HeLa cells	Downregulated MMP-2 and MMP-9 levels	Ye et al[52]
8	Arctiin	HeLa cells	Anti-proliferative effect downregulation of cyclin D1 expression	Matsuzaki et al[60]
9	Corosolic acid	HeLa cells	Apoptosis through mitochondrial pathway and caspase activation	Xu et al[63]
10	Praeruptorin A	HeLa and SiHa cells	Inhibits cell growth and invasion by suppressing MMP-2 expression	Wu et al[67]
11	Fisetin	SiHa and CaSki cells/	Antimetastatic by downregulating urokinase plasminogen activator	Chou et al[69]
		HeLa cells	Apoptosis through caspase 8/3–dependent pathway	Ying et al[70]
12	Deoxyelephantopin	SiHa cells	Impairs growth of cervical carcinoma SiHa cells and induces apoptosis	Farha et al[71]
13	β-elemene	SiHa cells	Induced apoptosis by enhancing the expression of p53 and Bax, and suppressing the expression of Bcl-2	Wang et al[75]
14	Polydatin	HeLa cells	Inhibits cell proliferation and induces apoptosis via suppression of the PDGF/AKT signaling pathway	Li et al[76]
15	Matrine	HeLa and C33A cells	Antimetastasis via downregulating the p38 signaling pathway	Wu et al[87]

Conclusion and Future Prospects

Cervical cancer is a pertinent health concern for women worldwide. We reviewed the literature regarding the use of Chinese herbal medicines in the treatment of cervical cancer. These studies revealed that Chinese herbal medicines may be beneficial for treating patients with cervical cancer. The crude extracts or bioactive compounds from Chinese herbal medicines exhibit antiproliferative, apoptosis-inducing, anti-invasive, and static effects in uterine cervical cancer cell lines (HeLa, SiHa, or C33A cell lines) or animal models (BALB/c nude mice; Tables 1 and 2). These investigated drugs, with different molecular targets and modes of action, hold promising therapeutic potential and exhibited growth inhibition of xenograft tumors in nude mice. Cancer development and metastasis involve complex processes. Considerable advances in our understanding of invasion and metastasis have been achieved in recent years. The development of novel drugs with antitumor effects or for improving the quality of life of patients with cancer has been widely explored, with promising results.[88,89]

Prospects

Chinese herbal medicines with therapeutic targeting, such as interference with tumor growth and progression in cervical cancer cells and in nude mice, have been widely investigated. However, the effectiveness of Chinese herbal medicines in the treatment of cervical cancer is still unconfirmed. To apply Chinese herbal medicine in the treatment of cervical cancer, adequate clinical studies are required to confirm its clinical safety and efficiency. Further investigations focused on the purification, pharmacokinetics, and identification of compounds from Chinese herbal medicines in cervical cancer treatment are necessary to achieve this goal.

Authors' Note

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