Plants and cervical cancer: An overview

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EXPERT OPINION

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Plants and cervical cancer: an overview

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Introduction: Cervical cancer, the second most common gynecological malignant tumor seriously harmful to the health of women, remains a leading cause of cancer-related death for women in developing countries. Although a large amount of scientific research has been reported on plants as a natural source of treatment agents for cervical cancer, it is currently scattered across various publications. A systematic summary and knowledge of future prospects are necessary to facilitate further plant studies for anti-cervical cancer agents.

Areas covered: This review generalizes and analyzes the current knowledge on the anti-cervical cancer properties and mechanisms involved for plants, and discusses the future prospects for the application of these plants.

Expert opinion: This review mainly focuses on the plants which have been scientifically tested *in vitro* and/or *in vivo* and proved as potential agents for the treatment of cervical cancer. The failure of conventional chemotherapy to reduce mortality as well as serious side effects involved makes natural products ideal candidates for exerting synergism and attenuation effects on anticancer drugs. Although the chemical components and mechanisms of action of natural plants with anti-cervical cancer potential have been investigated, many others remain unknown. More investigations and clinical trials are necessary to make use of these medical plants reasonably.

Keywords: cervical cancer, human papillomavirus, plant, therapy

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1. Introduction

In recent years, there has been a global trend toward the use of natural substances present in fruits, vegetables, oilseeds and herbs as anti-oxidants and functional foods [1]. Plant kingdom, therefore, holds a great promise for the discovery of new and effective anti-cervical cancer agents.

Cervical cancer is the second most common cause of cancer in women worldwide, with approximately 510,000 new cases and 288,000 deaths reported annually [2]. Although overall survival in patients with cervical cancer has been improved through widespread implementation of screening programs with increased proportions of patients being diagnosed with early lesions, prognosis for advanced cancer remains poor despite several efforts to improve treatment outcomes [3]. An agent that can selectively induce cell death in transformed cells without affecting normal cells will be an ideal chemotherapeutic agent against cancer [4]. The problems of unacceptable adverse effects such as dose-related toxicity, low specificity and the recurrence of patient tumors due to propagation of drug-resistant cells remain an inevitable obstacle to the achievement in anticancer chemotherapy [5,6]. Therefore, in addition to widespread use of the Papanicolaou smear and HPV (human papillomavirus) vaccine, there is a great need for the development of new therapeutic drugs more efficient than or synergizing with the existing ones.

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Article highlights.

- The therapeutic effects of plants on cervical cancer have been demonstrated by *in vitro* and *in vivo* assays.
- The underlying molecular mechanisms of action of many natural compounds with anti-cervical cancer effects have not been elucidated in detail.
- Although numerous natural compounds with anti-cervical cancer potential have been discovered from plants, there remains a significant untapped resource in herbal medicines.
- Some bioactive components from diets have been identified for their anti-cervical cancer potential, but many others remain unknown or untested.
- Many traditional medical formulations display the favorable anticancer effects clinically, but only a few have been studied for their anti-cervical cancer activities *in vitro* or *in vivo*.
- The plant-derived extracts (PDE) and compounds have been reported on preclinical investigations involved. However, there are no cervical cancer-related clinical trials reported.
- The signaling pathways by which plant medicines inhibit migration/invasion in cervical cancer cells remain unclear.

This box summarizes key points contained in the article.

One of the strategies is to consider natural products. In the modern system of medicine, about 25% of prescriptions contain active principle(s) derived from plants [7]. Plant-derived drugs play dominant roles in the treatment of cervical cancer [8], such as camptothecin, taxol and combretastatins [9]. Herbal plants have made important contributions to the development of anticancer drugs. Among 155 small molecule-based anticancer drugs approved by the US Food and Drug Administration (FDA) from 1940 to 2006, 47% were derived or isolated from natural sources [10]. Numerous natural substances are recognized to be anti-oxidants, cancer-preventive agents or even antitumor agents such as paclitaxel [11]. In addition, natural products are suitable alternatives used in control of cervical cancer instead of platinum-based drugs, which show some harmful side effects [12]. Nowadays, a great deal of effort is being expended to find effective plant-derived components for the treatment or prevention of cervical cancer. Therefore, all literature available was reviewed.

2. Plants for treating cervical cancer

Plants have always been a very good source of drugs and many beneficial uses of medicinal plants are extensively documented in traditional system of medicine of many cultures. Traditional medicines from plants offer great potential for the discovery of novel anti-cervical cancer drugs. Meanwhile, dietary phytochemicals that can selectively perturb cellular pathways to induce apoptosis in tumor cells have attracted research interest of scientists in novel apoptosis-inducing therapies in recent years. Various dietary agents including curcumin, resveratrol, tea polyphenols and flavonoids have been reported to induce apoptosis in a wide range of tumors [13]. This review mainly focuses on the plants which have been scientifically tested *in vitro* and/or *in vivo* and proved as potential anti-cervical cancer agents. Peer-reviewed articles in the last 10 years were gathered by consulting the databases PubMed, Elsevier, Springer and Scholar. The extracts and chemical constituents (CC) from plants with anti-cervical cancer potential are presented in **Tables 1** and **2**, respectively. Some phytochemicals widely distributed in various plants, vegetables and fruits are listed in **Table 3**. Also, there are five traditional Chinese medical formulations reporting their anti-cervical caner effects, that is, Guizhi-Fuling-decoction (GZFLD), Ge-Jee-Bok-Ryung-Hwan (GJBRH), Tien-Hsien Liquid, compound matrine capsule and Erhuangsan, which are composed of different medicinal plants.

There are several sources of anti-cervical cancer drugs: plants, vegetables, herbs and spices used in folk medicine. Traditional medicines have been accepted as one of the main sources of preventive drugs. The plant standardized extracts listed in **Table 1** are complex mixtures needed further to clarify the effective constituents and to elucidate the roles that these different components play in cytotoxicity observed when used alone or in combination. In addition, the synergistic effect of the individual active components of these extracts and molecular mechanisms involved need further investigation in order to evaluate the potential of these compounds as anticancer agents. The phytochemicals shown in **Table 2** are pure compounds. Although some bioactive components with anti-cervical cancer potential have been identified, many others remain unknown and/or untested. The protective effects of natural products have been related to the presence of phytochemicals, bioactive non-nutrient plant compounds, which commonly have complementary and overlapping mechanisms of action, including free radical scavenging, antimutagenesis, induction of apoptosis in cancer cell lines, among others. **Table 3** displays the phytochemicals widely distributed in various plants, vegetables and fruits and having anti-cervical cancer activity. The dietary plants can be used as dietary supplements. Food-based cancer prevention entities, such as black raspberries and their derivatives, have demonstrated a marked ability to inhibit preclinical models of epithelial cancer cell growth and tumor formation. As readily accessible source of natural anti-oxidants and anticancer, these plants generally contain various classes of polyphenols, flavonoids, carotenoids and vitamins with different health-promoting properties. Flavonoids are ubiquitous in plants and the common human diet. The high intake of foods and beverages rich in flavonoids have been associated with decreased risk of neoplasm [14]. Overall, diet plants and their bioactive components represent promising candidates for food-based chemoprevention strategies for cervical cancer. It has been observed that a diet rich in plant-based nutrients is important in reducing the risk of cervical cancer, such as black raspberries (*Rubus occidentalis*), *Cassia tora* Linn, Mango

Table 1. The extracts from different plants with anti-cervical cancer activity.

Extract	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Ethanol extract	*Rubus occidentalis*	Rosaceae	Fruit	HeLa, SiHa, C-33A	*In vitro*	Antiproliferation	Not investigated	[47]
Methanol extract	*Croton lechleri*	Euphorbiaceae	Leaf	HeLa	*In vitro/ in vivo*	Cytotoxicity Decrease of body weight	Not investigated	[48]
Ether extract	*Cremanthodium humile*	Compositae	Flower	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Release of cytochrome *c*, activation of caspase-3, -7 and -9, and generation of ROS	[22]
Aqueous extract	*Zingiber officinale*	Zingiberaceae	Rhizome	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Inhibition of microtubule structure and functions and increase of cell population in sub-G_0/G_1 phase	[49]
Butanol extract	*Cordyceps pruinosa*	Clavicipitaceae	Fruiting body	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Decrease of Bcl-2 protein, increase of Bax protein, release of cytochrome *c* and AIF and activation of caspases -3 and -9	[3]
Aqueous, ethyl acetate and butyl alcohol extracts	*Ficus hirta*	Moraceae	Root	HeLa	*In vitro*	Antiproliferation	Inhibition of cell viability, induction of morphology changes and increase of sub-G_1 phase	[50]
Methanol extract	*Scutellaria lindbergii*	Labiatae	Root	HeLa	*In vitro*	Antiproliferation	Induction of the sub-G_1 peak	[51]
Lipid-soluble extract	*Pinellia pedatisecta*	Araceae	Rhizome	CaSki, HeLa, HBL-100	*In vitro*	Induction of apoptosis Antiproliferation	Decrease of HPV E6 mRNA and protein expression, increase of caspase-8, caspase-3, Bax, p53 and p21 mRNAs as well as proteins, decrease of Bcl-2 mRNA and protein	[52]
Ethanol extract	*Mangifera indica*	Anacardiaceae	Peel	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Downregulation of anti-apoptotic Bcl-2 expression, increase of cell population in the sub-G_1 phase, activation of caspase-3, 7, 8, and 9 and degradation of PARP protein	[53]
Methanol, *n*-hexane and chloroform extracts	*Nigella sativa*	Ranunculaceae	Seed	HeLa	*In vitro*	Immune-modulatory AntiproliferationInduction of apoptosis	Regulation of the expression of pro- and anti-apoptotic genes	[29]
Ethanol extract	*Corallina pilulifera*	Briareidae	Seaweed	HeLa	*In vitro*			[54]

AIF: Apoptosis-inducing factor; HPV: Human papillomavirus; MMP: Matrix metalloproteinase; PARP: Poly(ADP-ribose) polymerase; PCNA: Proliferative cell nuclear antigen; ROS: Reactive oxygen species.

Table 1. The extracts from different plants with anti-cervical cancer activity (continued).

Extract	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
						Induction of apoptosis Antiproliferation	Induction of apoptosis through the mitochondria -dependent pathway and downregulation of DNA topoisomerase IIa gene expression	
Chloroform extract	*Citrus grandis*	Rutaceae	Leaf	HeLa	*In vitro*	Induction of apoptosis	Downregulation of Bcl-2 expression, activation of caspases and degradation of PARP protein	[55]
Methanol extract	*Cassia tora*	Leguminosae	Leaf	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Reduction of DNA content and caspase -3 activity	[56]
Methanol extract	*Pterocarpus santalinus*	Faboideae	Stem	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Release of cytochrome *c*, activation of caspases-9 and -3 and degradation of PARP	[57]
Ethanol extract	*Crocus sativus*	Iridaceae	Stigma	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Induction of a sub-G_1 peak and ROS production	[58]
Aqueous extract	*Pinus massoniana*	Pinaceae	Bark	HeLa	*In vitro*	Antiproliferation	Decrease of the migration rate of HeLa cells	[59]
Methanolic extract	*Phaseolus vulgaris*	Leguminosae	Seed	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Increase of Bax and caspase-3 expression	[60]
Aqueous extract	*Pinus massoniana*	Pinaceae	Bark	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of cell cycle arrest, increase of Bax expression, downregulation of Bcl-2 expression and activation of caspase-9 and -3	[61]
Phenolic extract	*Duchesnea indica*	Rosaceae	Whole plant	HeLa C-33A U_{14}	*In vitro/ in vivo*	Induction of apoptosis Antiproliferation Increase of survival of tumor-bearing mice and reduction of tumor weight	Upregulation of Bax, downregulation of Bcl-2, promotion of translocation of Bax to mitochondria, release of cytochrome *c*, provocation of S phase arrest, and decrease of PCNA and ki67 expression	[62]
Aqueous extract	*Solanum nigrum*	Solanaceae	Whole plant	U_{14}	*In vitro/ in vivo*	AntiproliferationInduction of apoptosis	Modulated immune response of tumor-bearing mice, caused G_0/G_1 phase cell	[1]

AIF: Apoptosis-inducing factor; HPV: Human papillomavirus; MMP: Matrix metalloproteinase; PARP: Poly(ADP-ribose) polymerase; PCNA: Proliferative cell nuclear antigen; ROS: Reactive oxygen species.

Table 1. The extracts from different plants with anti-cervical cancer activity (continued).

Extract	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
						Inhibition of tumor growth	cycle arrest and induced apoptosis	
Hydroalcoholic extract	*Triticum aestivum*	Gramineae	Wheat sprout	HeLa	*In vitro*	Induction of apoptosis	Induction of all proteasome activities gradual inhibition	[63]
Ethanol extract	*Livistona chinensis*	Arecaceae	Seed	HeLa	*In vitro*	Induction of apoptosis	Not investigated	[64]
Abrus agglutinin peptide fraction	*Abrus precatorius*	Leguminosae	Seed	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induced ROS generation and decreased Bcl-2/Bax ratio to elicit mitochondrial permeability transition and activate caspase-3, finally leading to DNA fragmentation and cell apoptosis	[65]
Aqueous extract	*Cinnamomum cassia*	Lauraceae	Bark	SiHa	*In vitro*	Induction of apoptosis	Increase of intracellular calcium signaling as well as loss of mitochondrial membrane potential, and downregulation of MMP-2 expression to reduce migration potential	[43]
Ethanol extract	*Phryma leptostachya*	Phrymaceae	Whole plant	HeLa	*In vitro*	Induction of apoptosis	Downregulation of Bcl-2 and caspase-3 protein expression	[66]
Ethanol extract	*Artemisia afra*	Compositae	Leaf	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of caspase activation and cell cycle arrest in the G_2/M phase	[67]
Aqueous and methanol extracts	*Agrimonia eupatoria*	Rosaceae	Leaf, stem and flower	HeLa	*In vitro*	Antiproliferation	Not investigated	[68]

AIF: Apoptosis-inducing factor; HPV: Human papillomavirus; MMP: Matrix metalloproteinase; PARP: Poly(ADP-ribose) polymerase; PCNA: Proliferative cell nuclear antigen; ROS: Reactive oxygen species.

Table 2. The CC isolated from different plants with anti-cervical cancer activity.

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Isoliquiritigenin (4,20,40-trihydroxychalcone)	Flavonoids	*Licorice*	Leguminosae	Rootrhizome	HeLa	*In vitro*	Antiproliferation	Induction of cell cycle arrest in both the G_2 and M phases via inhibition of topoisomerase II activity and regulation of DSB-mediated ATM/Chk2 signaling pathway in HeLa cells	[69]
Lycopodine	Alkaloids	*Lycopodium clavatum*	Lycopodiaceae	Whole plant	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of chromatin condensation and internucleosomal DNA fragmentation, enhancement of cell population in sub-G_1 region, increase of ROS generation and mitochondrial membrane potential depolarization, release of cytochrome c and activation of caspase-3	[70]
Marchantin C	Phenolics	*Dumortiera angust*	Marchantiaceae	Whole plant	HeLa	*In vitro/ in vivo*	Antiproliferation Induction of apoptosis Decrease of the size of tumors	Induction of cell cycle arrest at G_2/M phase, decrease of microtubules and Bcl-2, and increase of cyclin B1, Bax and caspase-3. Inhibition of the growth of human cervical tumor xenografts through down-modulating Bcl-2 expression and decrease of the amount of microtubules in tumor tissue	[24]
Nebrodeolysin	Hemolysins(a monomeric protein)	*Pleurotus nebrodensis*	Gramineae	Fruiting body	HeLa	*In vitro*	Induction of apoptosis	Exhibited remarkable hemolytic activity toward rabbit erythrocytes, caused efflux of potassium ions from erythrocytes and induced apoptosis in HeLa cells	[71]
SS-II (the second fraction of soyasaponins)	Flavonoids	*Glycine max*	Papilionaceae	Seed	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis through the mitochondrial pathway	[72]
Tan IIA	Quinines	*Salvia miltiorrhiza*	Labiatae	Rootrhizome	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of mitotic arrest and apoptosis through the JNK-mediated mitochondrial pathway	[35]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Trichosanthin	Proteins	*Trichosanthes kirilowii*	Cucurbitaceae	Root tuber	HeLa	*In vitro*	Antiproliferation	Decrease of the amount of γ-actin mRNA, downregulation of α- and β-tubulin mRNAs	[73]
23-Hydroxyursolic acid	Pentacyclic triterpenes	*Cussonia bancoensis*	Araliaceae	Stem bark	HeLa	*In vitro*	Induction of apoptosis	Decrease of Bcl-XL and Bcl-2 expression and NF-κB p65 protein level	[74]
3α, 23-Isopropylidenedioxyolean-12-en-27-oic acid	Triterpenes	*Aceriphyllum rossii*	Saxifragaceae	Leaflet stem	HeLa	*In vitro*	Induction of apoptosis	Release of cytochrome *c*, activation of caspase-9, increase of ER stress, GPR78 and GADD153 activation, Ca^{2+} release and activation of calpain	[11]
Astragalus mongholicus lectin	Lectins	*Astragalus mongholicus*	Leguminosae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of S-phase arrest, upregulation of p21 and p27 and reduction of active complex cyclin E/CDK2 kinase formation	[75]
Peptides	Peptides	*Triticum aestivum*	Gramineae	Bud	HeLa	*In vitro*	Antiproliferation	Induction of DNA damage and G_2 arrest, inactivation of the CDK1-cyclin B1 complex and increase of active chk1 kinase expression	[76]
Oblongifolin C	Lignans	*Garcinia yunnanensis*	Guttiferae	Whole plant	HeLa	*In vitro/ in vivo*	Induction of apoptosis Antiproliferation Inhibit the growth of xenografted tumors	Induction of Bax translocation, cytochrome *c* release, mitochondrial fission and swelling and reduction of mitochondrial membrane potential	[10]
(-)-Anonaine	Alkaloids	*Michelia alba*	Magnoliaceae	Leaf	HeLa	*In vitro*	Induction of apoptosis	Upregulation of Bax and p53 proteins expression, increase of intracellular NO, ROS, glutathione depletion and disruptive mitochondrial transmembrane potential	[77]
18-Hydroxyferruginol, Hinokiol, kayadiol	Diterpenoids	*Torreya nucifera*	Taxaceae	Pulp	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Increase of Bax/Bcl-2 ratio and depolarization of mitochondrial membrane potential	[78]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Berberine	Alkaloids	*Coptis chinensis*	Ranunculaceae	Rhizome	HeLa	*In vitro*	Induction of apoptosis	Induction of DNA topoisomerase poisoning, downregulation of Bcl-2 and Bcl-XL, upregulation of Bax and increase of ROS generation. Enhancement of the cytotoxic effect of cisplatin	[79]
Eupafolin	Flavonoids	*Artemisia princeps*	Compositae	Leaf	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis through the caspase-dependent pathway	[80]
Ganoderic acid Mf and ganoderic acid S	Triterpenes	*Ganoderma lucidum*	Polyporaceae	Mycelia	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis through the mitochondria-dependent pathway	[81]
Heterofucan SF-1.5v	Sulfated polysaccharides	*Sargassum filipendula*	Sargassaceae	Seaweed	HeLa	*In vitro*	Induction of apoptosis Antiproliferation	Release of mitochondrial AIF into cytosol, decrease of Bcl-2 expression and increase of Bax expression	[82]
HY253 (7,8a-divinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1H-fluorene-2,4a,4b,9a-tetraol)	Terpenoids	*Aralia continentalis*	Araliaceae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Release of cytochrome c, upregulation of Bcl-2 protein, activation of caspase-8, -9 and -3 and cleavage of PARP	[83]
Zerumbone	Monosesquiterpines	*Zingiber zerumbet*	Zingiberaceae	Rhizome	HeLa	*In vitro*	Cytoselective toxicity Antiproliferation	Increase of the level of caspase-3, induction of G_2/M phase cell cycle arrest and inhibition of the level of IL-6 in cancer cells	[12,84]
Kaempferol-7-*O*-β-D-glucoside	Flavonoids	*Smilax china*	Liliaceae	Rhizome	HeLa	*In vitro*	Antiproliferation	Induction of G_2/M phase growth arrest, decrease of cyclin B1 and CDK1, inhibition of NF-κB nuclear translocation, upregulation of Bax and downregulation of Bcl-2	[85]
Liquiritigenin	Flavonoids	*Glycyrrhizae*	Papilionaceae	Rootrhizome	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Upregulation of p53, release of cytochrome *c* and elevation of caspase-9 and -3 activities	[86]
Lycopodine	Alkaloids	*Lycopodium clavatum*	Huperziaceae	Spore	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Enhancement of cell population in sub-G_1 region and ROS generation, and depolarization of mitochondrial membrane potential	[87]

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Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Nucleases CMN1 and CMN2	Proteins	*Chelidonium majus*	Papaveraceae	Stalk	HeLa	*In vitro*	Induction of apoptosis	Induction of expression of proteins responsible for apoptosis execution	[88]
Oridonin	Diterpenoids	*Rabdosia rubescens*	Labiatae	Aerial parts	HeLa	*In vitro*	Antiproliferation	Downregulation of the protein kinase B (Akt) activation, expression of FOXO transcription factor and GSK3	[89]
Curcumin	Phenolic acids	*Curcuma longa*	Zingiberaceae	Rhizome	HeLa SiHa CaSki	*In vitro*	Antiproliferation Induction of apoptosis	Upregulation of Bax, AIF, release of cytochrome c and downregulation of Bcl-2, Bcl-XL, COX-2, iNOS and cyclin D1	[90]
Saikosaponin-a and -d	Triterpene saponins	*Bupleurum falcatum*	Umbelliferae	Root	HeLa SiHa	*In vitro*	Induction of apoptosis	Induction of cellular ROS accumulation mediates synergistic cytotoxicity in saikosaponins and cisplatin co-treated cancer cells	[45]
Thymoquinone	Benzoquinones	*Nigella sativa*	Ranunculaceae	Seed	SiHa	*In vitro*	Induction of apoptosis	Elevation of p53 and downregulation of the Bcl-2 protein	[41]
Mannose-binding lectin	Lectins	*Sophora flavescens*	Leguminosae	Root	HeLa	*In vitro*	Induction of apoptosis	Typical caspase-dependent apoptotic mechanism	[91]
Parviflorene F (1)	Sesquiterpenoids	*Curcuma parviflora*	Zingiberaceae	Whole plant	HeLa	*In vitro*	Induction of apoptosis	Enhancement of mRNA and protein expression of TRAIL-R_2, and activation of caspase-8, -9 and -3	[92]
APS-1d (a novel polysaccharide)	Polysaccharides	*Angelica sinensis*	Umbelliferae	Root	HeLa	*In vitro/in vivo*	Antiproliferation Induction of apoptosis	Regulation of Bcl-2 family protein expression, decrease of the mitochondrial membrane potential and increase of the cytosolic cytochrome c level and caspase-9, -3 and PARP activities	[93]
Clitocine	Nucleosides	*Leucopaxillus giganteus*	Tricholomataceae	Fruiting body	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Downregulation of Bcl-2 and upregulation of Bax, release of cytochrome c and activation of caspase-3	[27]
DPPT	Lignans	*Anthriscus sylvestris*	Umbelliferae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Inhibition of tubulin polymerization and regulation of cyclin A and cyclin B1 expression, and activation of caspases-3 and -7	[94]

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Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
HMBBJ	Quinones	*Juglans mandshurica*	Juglandaceae	Leaf	HeLa	*In vitro*	Antiproliferation	Downregulation of Bcl-2 expression, upregulating Ba x expression and increase of sub-G_1 group	[95]
A novel mannose-binding lectin (designated CML)	Lectins	*Clematis montana*	Ranunculaceae	Stem	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Typical caspase-dependent apoptosis	[96]
AgNPs	Others	*Melia azedarach*	Meliaceae	Leaf	HeLa	*In vitro/ in vivo*	Induction of apoptosis Increase of life span	Disruption of the mitochondrial respiratory chain, increase of ROS production and interruption of ATP synthesis and causing DNA damage	[97]
Essential oil	Essential oils	*Amomum tsao-ko*	Zingiberaceae	Fruit	HeLa	*In vitro*	Cytotoxicity	Not investigated	[98]
Decursin and decursinol angelate	Coumarins	*Angelica gigas*	Umbelliferae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Activation of caspases, cleavage of PARP, increase of TRAIL and TRAIL receptors expression, regulation of the Bcl-2, Bcl-XL, survivin, cIAP-1, -2 and XIAP expression	[99]
Enhydrin (1), uvedalin (2), sonchifolin (3)	Sesquiterpene lactones	*Smallanthus sonchifolius*	Compositae	Leaf	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Increase of the caspase-3/7 activation. Inhibition of the NF-κB binding protein activation	[100]
Rhodoxanthin	Carotenoids	*Potamogeton crispus*	Potamogetonaceae	Whole plant	HeLa	*In vitro*	Antiproliferation	Reduction of the mitochondria transmembrane potential, increase of the intracellular Ca^{2+} concentration and accumulation of cells in the S phase	[101]
Oroxylin A	Flavonoids	*Scutellaria baicalensis*	Labiatae	Root	HeLa	*In vitro/ in vivo*	Induction of apoptosis	Decrease of Bcl-2 protein expression and degradation of PARP	[102]
Paucinervins A – D (1 – 4), and 15 known ones	Benzophenones and xanthones	*Garcinia paucinervis*	Guttiferae	Leaf	HeLa-C3	*In vitro*	Induction of apoptosis	All of them activated caspase-3, paucinervin B exhibited the strongest inhibitory effect against HeLa cell growth among four newly identified paucinervins, and eight compounds reduced YFP/CFP emission ratio	[103]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
ATA	Triterpenoids	*Astilbe chinensis*	Saxifragaceae	Rhizome	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Downregulation of Bcl-2 expression, upregulation of Bax expression, decrease of $\Delta\Psi$m and activation of the caspase-3 pathway	[104]
Astilbotriterpenic acid (1)	Triterpenoids	*Astilbe chinensis*	Saxiffagaceae	Rhizome	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of caspase activation, release of ROS, downregulation of Bcl-2 and upregulation of Bax	[16]
Abrus agglutinin peptide fractions	Peptides	*Abrus precatorius*	Papilionaceae	Seed	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Generation of ROS, decrease of Bcl-2/Bax ratio and induction of mitochondrial permeability transition	[105]
Coumarin A/AA	Coumarins	*Mammea americana*	Mammea	Fruit	HeLa	*In vitro*	Induction of apoptosis	Activation of an apoptosis-like cell death program, release of the pro-apoptotic protein AIF, without disturbance of cell cycle	[106]
(+)-40 -Decanoyl-*cis*-khellactone and (+)-30 -decanoyl-*cis*-khellactone	Khellactones	*Angelica purpuraefolia*	Umbelliferae	Rhizome	HeLa SiHa C-33A	*In vitro*	Antiproliferation Induction of apoptosis	(+)-40-Decanoyl-*cis*-khellactone elicited apoptosis via both extrinsic and intrinsic pathways but (+)-30-decanoyl-*cis*-khellactone induced apoptosis only by the intrinsic pathway. Both of them acted as an anticancer supplement by inducing cell cycle arrest in the S/G_2 phase and caspase-dependent apoptosis	[107]
Actinoporin RTX-A	Actinoporins	*Heteractis crispa*	Actiniidae		HeLa	*In vitro*	Induction of apoptosis	Induction of p53-independent apoptosis and inhibition of activation of the oncogenic AP-1 and NF-κB nuclear transcriptional factors	[108]
Coumarins (CU-1 to CU-4), phenylpropanoids (PE-1 and PE-2), polyacetylene(PA-1), daucane esters (DE-1 to DE-16)	Sesquiterpenes	*Ferula communis, Ferula glauca, Ferulago campestris*	Umbelliferae	Aerial part	HeLa	*In vitro*	Antiproliferation	Not investigated	[109]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
AMDT	Sesquiterpenes	*Artemisia annua*	Compositae	Hairy root	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis through the mitochondria-dependent pathway and activation of caspase cascade	[110]
Caffeic acid (3,4-dihydroxycinnamic acid)	Phenolic acids	*Ocimum gratissimum*	Labiatae	Whole plant	HeLa	*In vitro*	Antiproliferation	Not investigated	[111]
Indirubin-30-monoxime	Alkaloids	*Angelica sinensis* (Danggui-Long-Hui-Wan)	Umbelliferae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis through the extrinsic pathway with type II response mediated by the pro-apoptotic Bcl-2 family members (Bid and Bax)	[112]
SNL-P1a (fraction 1a of SNL-P)	Polysaccharides	*Solanum nigrum*	Solanaceae	Whole plant	U_{14}	*In vitro/in vivo*	Antiproliferation Induction of apoptosis Inhibition of tumor growth	Protected thymus tissue against the onslaught of tumor by inhibiting thymus lymphocyte apoptosis, and decreased Bcl-2/Bax ratio in thymus lymphocytes of tumor-bearer. Protective effect on thymus tissue of tumor-bearing mice	[113]
Xanthone V1	Xanthones	*Cratoxylum formosum, Vismia laurentii*	Guttiferae	Root Leaf Seed	HeLa CaSki	*In vitro*	Antiproliferation Induction of apoptosis	Induction of cell cycle arrest in S-phase and activation of caspase -3 and -7	[114]
2-Acetylfuro-1,4-naphthoquinone	Quinones	*Newbouldia laevis*	Bignoniaceae	Root	HeLa CaSki	*In vitro*	Antiproliferation	Induction of cell cycle arrest in S-phase	[114]
Silibinin	Flavonolignans	*Silybum marianum*	Compositae	Milk thistle	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of G_2 arrest and the decrease in CDKs involved in both G_1 and G_2 progression, elicitation of apoptosis in HeLa cells via both the mitochondrial and death receptor-mediated pathways	[115]
CRA	Triterpenoids	*Actinidia valvata*	Actinidiaceae	Root	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis via activation of the caspase-dependent mitochondrial pathway	[116]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 2. The CC isolated from different plants with anti-cervical cancer activity (continued).

Chemical constituent	Sort	Botanical name	Family	Medicinal part	Cell type	Observation	Activity	Mechanism of action	Refs.
Stigmasterol, beccamarin	Phytosterols	*Mesua beccariana*	Clusiaceae	Stem bark	HeLa	*In vitro*	Antiproliferation	Not investigated	[117]
3β,21α-Dihydroxyisohopane	Triterpenes	*Carissa carandas*	Apocynaceae	Leaf	HeLa	*In vitro*	Cytotoxicity	Not investigated	[118]
30-Hydroxy-11a-methoxy-18b-olean-12-en-3-one	Triterpenes	*Maytenus procumbens*	Celastraceae	Leaf	HeLa	*In vitro*	Induction of apoptosis	Served as a mediator of the ROS scavenging system	[119]
MCPT	Camptothecinoids	*Nothapodytes foetida*	Icacinaceae	Stem bark	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis in HeLa cells via extrinsic and intrinsic apoptotic pathways	[120]
Celastrol	Triterpenes	*Trypterygium wilfordii Hook*	Celastraceae	Whole plant	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Depolarization of $\Delta\Psi$m and increase of caspase activity	[121]
KM	Flavonoids	*Justicia spicigera*	Acanthaceae	Whole plant	HeLa	*In vitro/in vivo*	Induction of apoptosis Decrease of body weight and increase of the survival	Induction of cell cycle arrest in G_1 phase and apoptosis via the caspase-dependent intrinsic pathway.	[19]
Salvialeriol (1), 6-hydroxysalvinolone (2), deacetylnemorone (3), 2-acetoxylupeol (4), lupine-2,3-diol (5)	Diterpenes (1), diterpenoids (2, 3)	*Salvia leriifolia*	Labiatae	Whole plant	HeLa	*In vitro*	Antiproliferation	Compounds 1, 3, 4, 5 inhibited α-chymotrypsin and compound 2 competitively suppressed this enzyme	[122]
Green synthesis of AgNPs	Others	*Podophyllum hexandrum*	Berberidaceae	Leaf	HeLa	*In vitro*	Induction of apoptosis	Induction of cell death in HeLa cells through a ROS-mediated apoptotic process.	[123]
Biosynthesis of AgNPs	Others	*Morinda citrifolia*	Rubiaceae	Root	HeLa	*In vitro*	Cytotoxicity	Not investigated	[124]

AgNPs: Silver nanoparticles; AIF: Apoptosis-inducing factor; AMDT: (*Z*)-7-acetoxy-methyl-11-methyl-3-methylene-dodeca-1,6,10-triene; AP-1: Activator protein 1; ATA: 3β-hydroxy-12-oleanen-27-oic acid; CC: Chemical constituent; CDK: Cyclin-dependent kinase; COX: Cyclooxygenase; CRA: Corosolic acid; DPPT: Deoxypodophyllotoxin; ER: Endoplasmic reticulum; FOXO: Forkhead box class O; GSK3: Glycogen synthase kinase 3; HMBBJ: *P*-hydroxymethoxybenzobijuglone; KM: Kaempferitrin; iNOS: Inducible nitric oxide synthase; MCPT: 9-methoxycamptothecin; NF-κB: Nuclear factor-kappaB; NO: Nitric oxide; PARP: Poly(ADP-ribose) polymerase; ROS: Reactive oxygen species; Tan IIA: Tanshinone IIA.

Table 3. Anti-cervical cancer phytochemicals widely distributed in various plants, vegetables and fruits.

Phytochemicals	Sort	Cell type	Observation	Activity	Mechanism of action	Refs.
Quercetin	Flavonoids	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of G_2/M phase cell cycle arrest, upregulation of proapoptotic Bcl-2 family proteins, cytochrome *c*, Apaf-1 and caspases and downregulation of anti-apoptotic Bcl-2 proteins and survivin	[13]
Cannabidiol	Cannabinoids	HeLa, C-33A	*In vitro*	Anti-invasion	The decrease of invasion by upregulation of TIMP-1. Knockdown of cannabidiol-induced TIMP-1 expression by siRNA led to a reversal of the cannabidiol-elicited decrease in tumor cell invasiveness	[125]
Fisetin	Flavonoids	HeLa	*In vitro/in vivo*	Antiproliferation Induction of apoptosis Significantly reduced tumor growth	Activation of the phosphorylation ERK1/2, inhibition of ERK1/2 by PD98059, activation of caspase-8/-3 pathway	[126]
Gallic acid	Phenols	HeLa	*In vitro*	Induction of apoptosis	Induction of cell death via apoptosis and/or necrosis was accompanied by ROS increase and GSH depletion	[127]
Isoliquiritigenin	Flavonoids	HeLa	*In vitro*	Antiproliferation	Induction of G_2/M phase cell cycle arrest, increase of p21 expression in a p53-dependent manner and decrease of cdc2, cdc25C and cyclin B expression, regulation of the Bcl-2 family protein expression, phosphorylates Chk2 and subsequently increases the accumulation of inactive cdc25C and cdc2	[128]
Isoflavone	Flavonoids	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis through the mitochondrial pathway	[129]
Catechin hydrate	Polyphenols	SiHa	*In vitro*	Induction of apoptosis	Regulation of the expression of p53 and caspase-3, -8 and -9	[130]
Methyl jasmonate	Plant stress hormones	CaSki, SiHa, HeLa, C-33A	*In vitro*	Antiproliferation	Upregulation of Bax level, reduction of p53 and p21 levels	[131]
Resveratrol	Polyphenols	SiHa, HeLa, C-33A	*In vitro*	Antiproliferation	Suppression of C-33A, SiHa and HeLa cells growth through induction of cell apoptosis	[132]
Oxidized lutein	Carotenoids	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis through scavenging of free radicals	[133]
Luteolin	Flavonoids	HeLa	*In vivo*	Induction of apoptosis Inhibition of tumor growth	Luteolin sensitized HeLa cells to TRAIL-induced apoptosis by both extrinsic and intrinsic apoptotic pathways	[134]
EGCG and RA	Polyphenols, retinoids	HeLa	*In vitro*	Antiproliferation	Combination of EGCG with RA induced apoptosis and inhibited telomerase activity	[135]
Naringin	Flavonoids	SiHa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of apoptosis through both death-receptor and mitochondrial pathways	[136]

Apaf-1: Apoptotic protease activating factor-1; EGCG: (-)-epigallocatechin gallate; ERK1/2: Extracellular regulated kinases 1/2; GSH: Glutathione; RA: Retinoic acid; ROS: Reactive oxygen species; TIMP: Tissue inhibitor of metalloproteinase.

Table 4. Anti-cervical cancer derivatives of natural compounds from plants.

Chemotherapeutic drug	Derivative	Cell type	Observation	Activity	Mechanism of action	Refs.
Diethyl 5,7,40 -trihydroxy flavanone *N*-phenyl hydrazone (N101-2)	Naringenin derivative	SiHa, CaSki	*In vitro*	Antiproliferation	Induction of apoptosis by arresting cell cycle at sub-G_1 phase, activation of mitochondria-emanated intrinsic and Fas-mediated extrinsic signaling pathways, and inhibition of the PI3K/AKT pathway in CaSki and SiHa human cervical cancer cells	[137]
3- and 10-bromofascaplysins	Fascaplysin derivative	HeLa	*In vitro*	Induction of apoptosis	Induction of caspase-8, -9, -3-dependent apoptosis	[138]
2′-Nitroflavone	Nitroflavone derivative	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis through both death receptor and mitochondria-dependent pathways	[139]
Diethyl chysin-7-yl phosphate (CPE: C19H19O7P) and tetraethyl *bis*-phosphoric ester of chrysin (CP: C23H28O10P2)	CR derivative	HeLa	*In vitro*	Antiproliferation	Induction of tumor cell apoptosis and downregulation of PCNA expression (tumor malignancy)	[140]
BHA	Fat-soluble phenolic derivative	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Induction of caspase-dependent apoptosis and increase of GSH depletion and O^{2-} level	[141]
PG (3,4,5-trihydroxybenzoic acid propyl ester)	Gallate derivative	HeLa	*In vitro*	Antiproliferation Induction of apoptosis	Inhibition of HeLa cells growth via caspase-dependent apoptosis as well as cell cycle arrest	[142]

BHA: Butylated hydroxyanisole; CR: Chrysin; GSH: Glutathione; PCNA: Proliferative cell nuclear antigen; PG: Propyl gallate; PI3K: Phosphatidylinositol 3-kinase.

(*Mangifera indica*) and Yacon (*Smallanthus sonchifolius*). In addition to these extracts and phytochemicals, some synthesized derivatives (SD) compounds (mentioned in **Table 4**) have also been reported to possess anti-cervical cancer effects. These chemotherapeutic drugs are synthesized based on phytochemicals separated from vegetables or herbs. All of them exhibit significant growth inhibition, antiproliferation or cytotoxicity in cervical cancer.

Although numerous *in vitro* studies have substantiated the anti-cervical cancer activity of plant extracts and phytochemicals, the evidence of clinical trials is absent. The majority of the plants (mentioned in **Tables 1**, **2**, **3** and **5**) traditionally used as anti-cervical cancer agents have not been studied thoroughly in animals. The phytochemicals with *in vitro* activity may actually be inactive *in vivo* due to too high doses. Moreover, many of them have not been tested for their cytotoxicitiy to normal cells, which seriously limits their *in vivo* experiment. A few formulations studied are shown in **Table 5**. GZFLD, a traditional Chinese medical (Kampo) formulation, has been observed to exert the stronger anticancer effects not only *in vitro* but also *in vivo*. The effects are not the simple addition of five plants involved. A single component of the formulation probably has a few or even no anticancer effects. To the contrary, the mixture can exert the strong activity of anticancer when these five plants are combined in an appropriate proportion. Numerous traditional formulations effectively and extensively used in clinic have not been investigated.

3. Suggested mechanisms and targets of action of compounds isolated from plants

Disruption of cellular homeostasis between cell death and cell proliferation can elicit cancer [15]. Inhibition of cell growth and induction of cell death are two major means of antitumor growth [16]. Several studies have demonstrated that cell cycle arrest, enhancement of gap junctional communication and induction of apoptosis have been proposed as possible mechanisms for growth inhibition of cancer cells by natural compounds and dietary agents. Cell cycle progression and apoptosis are two pivotal signaling mechanisms of homeostasis maintenance in healthy tissues and normal cells [17,18]. *Justicia spicigera* is used for the empirical treatment of cervical cancer in Mexico. Kaempferitrin (KM) is the major component of this extract exerting cytotoxic and antitumor effects.

Table 5. Traditional medical formulations with anti-cervical cancer activity.

Medical formulation	Composition	Cell type	Observation	Activity	Mechanism of action	Refs.
GZFLD	*Cinnamomum cassia* Blume, *Paeonia lactiflora* Pall, *Paeonia suffruticosa* Andrews, *Prunus persica* Batsch, *Poria cocos* Wolf.	HeLa	*In vitro*	Anti-invasion	Enhancement of TIMPs expression and activation, downregulation of MMPs expression and activation	[143]
GJBRH	*Cinnamomi* Ramulus, *Pachyma hoelen* Rumphius, *Moutan Cortex* Radicis	HeLa	*In vitro*	Induction of apoptosis	Induction of apoptosis in HeLa cells via ER stress-pathway associated mitochondria-dependent pathway	[144]
Tien-Hsien Liquid	*Cordyceps sinensis, Oldenlandia diffusa, Indigo pulverata* levis, *Polyporus umbellatus, Panax ginseng, Solanum nigrum, Pogostemon cablin, Atractylodis macrocephalae*	C-33A	*In vitro*	Cytotoxicity	Not investigated	[145]
Compound matrine capsule	*Sophora flavescens* Ait., *Rhodiola rosea, Acanthopanax senticosus*	HeLa	*In vitro*	Antiproliferation	Induction of sub-G_1 peak and S arrest	[146]
Erhuangsan	*Coptis chinensis*	HeLa	*In vitro*	Antiproliferation	Downregulation of Bcl-2 protein expression	[147]

ER: Endoplasmic reticulum; GJBRH: Ge-Jee-Bok-Ryung-Hwan; GZFLD: Guizhi-Fuling-decoction; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase.

KM induces high cytotoxic effects *in vitro* and *in vivo* against HeLa cells. The general mechanisms involved include: arrest of cell cycle in G_1 phase and induction of apoptosis via the caspase-dependent intrinsic pathway. Also, KM has preventive effects on tumor [19]. Apart from induction of apoptosis through death receptor and mitochondrial pathways, numerous plants also inhibit the proliferation of human cancer cells. Meanwhile, anti-migration and/or inhibition of invasion are important ways to the cervical cancer treatment, such as GZFLD and cannabidiol.

3.1 Apoptosis

Apoptosis, also named programmed cell death, plays a crucial role in the homeostasis of organisms under both physiological and pathological conditions, and targeting the malignant cells for apoptosis has always been an aim that various anticancer therapies try to achieve [20]. Apoptosis is the most convenient manner of tumor cell elimination, as this type of cell death is a final state that does not cause any possible future danger [21]. There exist two major pathways leading to apoptosis in cells: the extrinsic pathway involving activation of the TNF/Fas death receptor family and the intrinsic pathway involving mitochondria [22]. The mitochondrial (intrinsic) pathway is controlled at the level of mitochondrial membrane by the Bcl-2 superfamily of proteins [23]. Biochemically, apoptotic cells are characterized by the reduction of mitochondrial transmembrane potential, intracellular acidification, excessive production of reactive oxygen species (ROS), externalization of phosphatidylserine residues in membrane bilayers, selective proteolysis of cellular proteins and degradation of DNA into internucleosomal fragments.

Although many targets of action by which apoptosis can be induced in tumor cells have been experimentally studied or postulated, few are well known or defined for induction of apoptosis by plant-derived compounds in cervical cancer cells. In **Tables 1 – 3**, the part of suggested mechanisms and targets of action for some natural compounds are: i) Telomerase. Most human cancers have short telomeres and express high levels of telomerase activity when compared with normal tissue. Therefore, telomerase has emerged as an attractive target for arresting cancer cell growth in various cancers. ii) Tubulin and microtubule. Tubulin polymerizes to form dynamic structure microtubule, which is involved in a number of important cellular functions such as segregation of the chromosomes during mitosis and meiosis and maintenance of the cellular cytoskeleton structure. Especially, microtubules constitute the mitotic spindle apparatus during cell division, which is critical for cellular proliferation [24]. Drugs suppress microtubule dynamics by binding to different sites of tubulin heterodimer, disturb the assembly of the mitotic spindle apparatus and arrest cell cycle progression through M-phase, leading to eventual cell apoptosis. iii) DNA topoisomerase. Topoisomerase I is essential for DNA replication [25]. Topoisomerase II-mediated DNA damage activates cell cycle arrest and apoptotic pathways, and subsequently causes cell

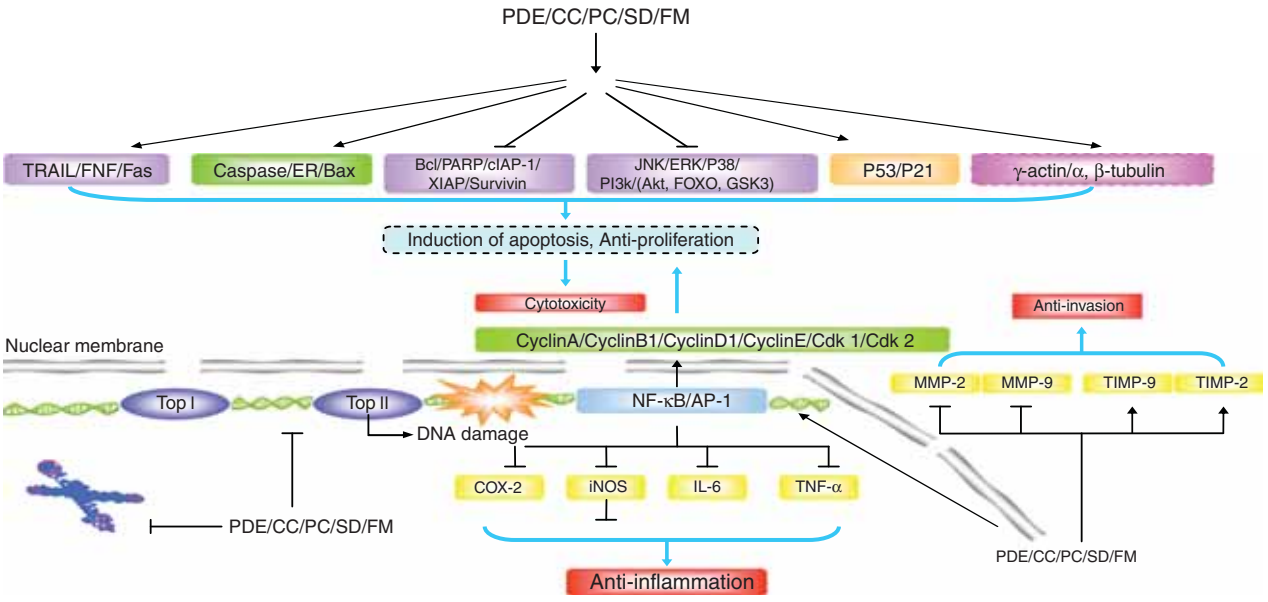

Figure 1. The schematic diagram of the anti-cervical cancer effects of PDE/CC/PC/SD/FM.
↑: Hints activation or upregulation; ↓: Hints inhibition or downregulation.

death [26]. iv) p53 and nuclear factor-kappaB (NF-κB). Wild-type p53 can downregulate Bcl-2 expression and upregulate Bax expression, altering the balance of couple genes in favor of apoptosis [27]. NF-κB, a prosurvival transcription factor, inhibits cell apoptosis by influencing the expression of anti-apoptotic Bcl-2 members and inhibitor of apoptosis (IAPs) [28]. v) TNF-related apoptosis-inducing ligand (TRAIL). TRAIL is a promising candidate for cancer therapeutics due to its ability to selectively induce apoptosis in malignant tumor cells with no toxicity against normal tissue. Agents that suppress the proliferation of malignant cells by inducing apoptosis may represent a useful mechanistic approach to both cancer chemoprevention and chemotherapy [29]. Therefore, induction of apoptosis in cancer cells is one of the useful strategies for anticancer drug development [30]. Nowadays, this strategy still remains an essential route to new pharmaceutical research.

Caspases, a family of cysteinyl aspartate-specific proteases, play an essential role in the regulation and execution of programmed cell death [31,32]. Activation of the executioner caspases is often referred to as the apoptotic commitment point in the signaling cascade where the cell commits to die [33]. It is well established that activation of a caspase cascade occurs in apoptosis via activation of either the mitochondrial (intrinsic) pathway or death receptor (extrinsic) pathway [34].

3.2 Cell cycle arrest

Many anticancer and DNA-damaging agents arrest the cell cycle at G_0/G_1, S or G_2/M phase and then induce cell apoptosis. The majority of human solid tumors is genetically unstable and has defects in the cell-cycle checkpoint control mechanism. Such tumors frequently contain mutations that disrupt G_1 components of the cell cycle, which affects the abilities of chemotherapeutic drugs to inhibit cell proliferation and induce apoptosis [16]. A basic requirement for anticancer drugs is that they should have a strong preference in killing cancer cells over non-cancer cells. Since cancer cells usually undergo active cell division (mitosis), a useful approach to finding anticancer drugs is to test whether a compound can selectively kill mitotic cells [35]. Therefore, cell cycle arrest is one of the targets for many anticancer drugs. Among them, taxanes, colchicines and vinca alkaloids are well-known examples that induce G_2/M phase arrest leading to subsequent apoptosis [36].

3.3 Anti-migration and/or anti-invasion

Metastasis, one of the most malignant features for invasive cancer cells, is extremely difficult to be overcome with current cancer therapeutic strategies, and modulation of cancer cell invasion has recently emerged as a topic of increasing interest. The levels of tumor invasiveness and malignancy are mainly determined by a sensitive balance between collagen- and proteoglycan-degrading matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors of MMPs (TIMPs). Among four distinct members of the TIMP family, elevated TIMP-1 mediates the anti-invasive effects of several anti-carcinogenic drugs. Furthermore, decreased TIMP-1 level is demonstrated to correlate with high cancer invasiveness [37].

4. Etiology, clinical treatment and prospects

HPV infection is considered to be the necessary cause for cervical cancer [38]. Persistent infection with high-risk human

papillomavirus (HR-HPV), most types 16 and 18, is an essential prerequisite for the development of cervical cancer [39]. Two inspiring landmarks have occurred in the fight against cervical cancer. First, the Pap test (Papanicolaou smear established in 1943) makes it possible to screen and detect this disease early. Second, a study established the efficacy of the HPV vaccine in preventing cervical dysplasia, and the HPV vaccine was approved by the US FDA in 2006 [40]. The identification of HPV as the etiological factor for cervical cancer provides an opportunity to prevent HPV infection through preventive HPV vaccine and to control through effective therapeutic vaccines against HPV. Two preventive vaccines have recently been licensed for use: Gardasil and Cervarix. However, the vaccines will reduce only, but not eliminate, the risk of cervical cancer, as they presently target only HPV-6, -11, -16 and -18 oncogenic genital types. World Health Organization revealed that HPV vaccines do not cure cancers; they can prevent some, but not all, HPV-related cancers, and 30% are not covered by the vaccines [41]. However, the therapeutic vaccines can compensate for the shortcomings of the preventive vaccines that do not generate therapeutic effects against established HPV infection. Therefore, immunotherapy is possibly a very important therapeutic approach to cervical cancer in future.

It is generally accepted that radical surgery or radiotherapy can be curative for the majority of patients with early stage cervical cancer, while chemotherapy or neoadjuvant chemotherapy are always the first choice for those with advanced cervical cancer, where the prognosis remains very poor [42]. Cervical carcinoma in patients with poor prognosis is characterized by rapid cellular proliferation and strong expression of anti-apoptotic genes. These features may be due to incomplete cell cycle arrest and apoptosis resistance to conventional therapies. The failure of conventional chemotherapy to reduce mortality invites attention toward new alternative approaches that can reduce morbidity as well as side effects conferred by conventional chemotherapy [43]. Therefore, the development of new therapeutic strategies through identifying potential targets is warranted. Finding better candidates through activity-guided isolation of bioactive fractions and compounds from natural products using kinds of *in vitro* and *in vivo* bioassay systems is an efficient way to discover leading matters of new drugs from plants [44]. Famous examples of plant-based anticancer drugs include camptothecin, etoposide, paclitaxel and vincristine [10]. In addition, combination with agents that sensitize cancer cells to chemotherapeutics has been recognized as an effective strategy to overcome chemoresistance. For example, saikosaponins significantly sensitize cancer cells to cisplatin, which improves the anticancer value of cisplatin [45].

5. Conclusion

This review analyzed 26 plant extracts, 66 CCs isolated from different plants, 14 phytochemicals widely distributed in various plants, vegetables and fruits, 6 derivatives of natural compounds from plants and 5 traditional medical formulations (detailed in **Tables 1 – 5**, respectively). There are 92 plants enumerated in this article. The action targets involved (**Figure 1**) for natural plants with anti-cervical cancer potential include telomerase, tubulin and microtubule, DNA topoisomerase, p53 and NF-κB and TRAIL. The mechanisms of action are associated with induction of apoptosis, cell cycle arrest and anti-migration and/or anti-invasion (**Figure 1**).

6. Expert opinion

This paper has presented the lists of the extracts, constituents and formulations from various medicinal plants, vegetables and fruits used in the treatment of cervical cancer. Although many drugs of natural origin have been discovered, it is still necessary to search for novel anticancer agents with more effectivity and less toxicity. Also the failure of conventional chemotherapy to reduce mortality as well as serious side effects involved makes natural products ideal candidates for exerting synergism and attenuation effects on anticancer drugs. Some novel natural compounds sometimes have more potent anti-cervical cancer activity than known agents. For example, tanshinone IIA (Tan IIA), a compound isolated from *Salvia miltiorrhiza* Bunge (Danshen), could trigger the mitotic arrested cells to enter apoptosis faster than vincristine or taxol [35]. However, the underlying molecular mechanisms of action of many compounds with anti-cervical cancer activity have not been studied or elucidated in detail. Although some common molecular signal pathways and several distinct targets have been disclosed, the responses of molecular targets to compounds with anti-cervical cancer effects remain unclear.

Recent studies focusing on molecular targets of the plant-derived compounds have yielded promising results, but the details of the anticancer mechanisms involved need to be clarified further. Meanwhile, the preclinical and clinical studies must be carried out to determine the potential of these plants in anti-cervical cancer. Many traditional medical formulations are characterized by apoptosis-inducing and antiviral activities, but only a few have been studied on their anticancer activities *in vitro* or *in vivo*. These investigations might provide more promising insights into pharmaceutical exploitation in the treatment of different human diseases in the near future. One of the most important ways to decrease the risk of cancer development and progression is modification of diet. Recent research suggests that bioactive food components may have the potential to reduce the risk and improve survival probability of patients with cancer. Semiological evidence also indicates that a high intake of fruits and vegetables leads to a significant reduction in cancer incidence rate, while the phytochemicals within fruits and vegetables have been proposed as responsible for these protective effects.

The reported anti-migration and/or anti-invasion effects of medicinal plants on cervical cancer mainly concentrate on

MMPs (TIMPs) family, while the other signaling pathways have not been involved, such as SDF-1/CXCR4, a c-Src/PKCi/FAK loop, u-PA (urokinase-type plasminogen activator) and MMPs, P2Y receptors and their downstream ERK1/2 (extracellular regulated kinases 1/2) and p38 protein kinases, p-JNK, p-ERK, p-p38, IκK and NF-κB signaling pathways, which are investigated in other human cancers. Overexpression of miR-10a has been substantiated to promote colony formation, migration, invasion and reduction of CHL1 (close homolog of L1) mRNA and protein levels in cervical cancer cells [46]. There is, however, information unavailable on the effects of medicinal plants on migration and invasion of human cervical cancer cells through these signaling pathways.

Novel information gathered from the current data is important to preservation of folk indigenous knowledge and discovery of novel and more effective compounds against cervical cancer. Therefore, the purpose of this review was to present and analyze the plant species against cervical cancer. The extract, CC, compound sort, name and family of plants, medicinal part of plants, activity and mechanism of action are given in **Tables 1 – 5**. Even though some effective anticancer drugs have been developed from botanical sources, there still remains an untapped resource in herbal medicines. Although some bioactive components of diets or medicinal plants have been identified for their cancer chemopreventive potential, many others remain unknown and/or untested. Therefore, numerous plants deserve further investigations *in vitro* and *in vivo* due to their significant antitumor activity.

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Declaration of interest

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