Biomedicine & Pharmacotherapy 162 (2023) 114590

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Basic research on curcumin in cervical cancer: Progress and perspectives

Xiaoyu Zhang [a], Lin Zhu [a], Xuezhen Wang [a], Hairong Zhang [b], Lianzhong Wang [c,*], Lei Xia [d,**]

[a] School of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China
[b] Department of Obstetrics and Gynecology, Shandong Provincial Third Hospital, Jinan, China
[c] Department of Respiratory and Critical Care Medicine of Second affiliated hospital, Shandong University of Traditional Chinese Medicine, Jinan, China
[d] Department of Pathology, Shandong University of Traditional Chinese Medicine, Jinan, China

ARTICLE INFO

Keywords:
Curcumin
Cervical cancer
Mechanism
Pathway
Plants

ABSTRACT

Curcumin is a polyphenolic substance extracted from plants such as Curcuma longa, Curcuma zedoaria, and radix curcumae, and it has attracted much attention because of the anti-inflammatory, antioxidant, anti-tumor, antibacterial and other multiple pharmacological effects. Cervical cancer is one of the most common malignant tumors in women. With the application of HPV (human papillomavirus) vaccine, the incidence of cervical cancer is expected to be reduced, but it remains difficult to promote the vaccine among low-income population. As a commonly used food additive, curcumin has recently been found to have a significant therapeutic effect in the treatment of cervical cancer. In recent years, numerous in vitro and in vivo studies have found that curcumin can have significant efficacy in anti-cervical cancer treatment by promoting apoptosis, inhibiting tumour cell proliferation, metastasis and invasion, inhibiting HPV and inducing autophagy in tumour cells. However, due to poor water solubility, rapid catabolism, and low bioavailability of curcumin, studies on curcumin derivatives and novel formulations are increasing. Curcumin has a wide range of mechanisms of action against cervical cancer and may become a novel antitumor drug in the future, opening up new ideas for the research of curcumin in the field of antitumor. There is a lack of systematic reviews on the mechanism of action of curcumin against cervical cancer. Therefore, this study is a review of the literature based on the mechanism of action of curcumin against cervical cancer, with a view to providing reference information for scientific and clinical practitioners.

1. Introduction

Cervical cancer is the fourth leading cause of death in women, with 310,000 deaths worldwide each year, seriously threatening the life and health of women [1–3]. The promotion and early screening of HPV vaccine has decreased the incidence of cervical cancer in developed countries, but in low- and middle-income countries, the incidence remains increasing with the low coverage rate of HPV vaccine.

Abbreviations: HPV, human papillomavirus; ROS, reactive oxygen; COX-2, cyclooxygenase - 2; ER, endoplasmic reticulum; HCFs, human corneal fibroblasts; THC., Tetrahydrocannabinol.; BDMC, Bisdemethoxycurcumin; ATM, ataxia telangiectasia-mutated gene; ATR, ataxia telangiectasia and Rad3-related; BRCA1, brest cancersuscetiility gene 1; DNA-PK, DNA-dependent protein kinase; MDC1, mediator of DNA damage check point protein 1; MGMT, Homo sapiens O-6-methylguanine-DNA methyltransferase; H2A.X, Recombinant Mononucleosomes; Ras, specific guanine nucleotide-releasing factor 1; ERK, extracellular signal-regulated kinase; iNOS, Inductible Nitric Oxide Synthase; c-myc, V-Myc Avian Myelocytomatosis Viral Oncogene Homolog; Hsp70, Heat shock protein 70; AIF, apoptosis inducing factor; IRE-1a, inosital-requiring enzyme-1; ATF6, activating transcription factor 6; ASK1, Apoptosis Signal Regulating Kinase 1; JNK, c-Jun N-terminal kinase; THC, Tetrahydrocannabinol; AKT, RAC-alpha serine/threonine-protein kinase; HDACs, histone deacetylases; CDKi, cyclin-dependent kinase inhibitors; CDK, cyclin dependent kinases; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; HIF-1α, Hypoxia-Inducible Factor 1-Alpha; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; GRB2, growth factor receptor-bound protein 2; Rho A, Ras homolog gene family,member A; uPA, uridylyl phosphate adenosine; NF-κB, nuclear factor kappa-B; AP-1, activator protein-1; FRA-1, FRA-1 polypeptide protein; c-fos, Cellular oncogene fos; PTPN13, protein tyrosine phosphatase non-receptor type 13; PCNA, Proliferating Cell Nuclear Antigen; TrxR, thioredoxin reductase; TGF-β, transforming growth factor-β; Pin1, Personal Identification Number 1; PDT, Photodynamic therapy; PS, photosensitizers; MRP1, multidrug resistance protein 1; Pgp1, P-glycoprotein 1; PLGA, poly lactic-co-glycolic acid; PBCA, polybutyl cyanoacrylate; NOD-SCID, non-obese diabetic severe combined immunodeficient; CDF, Curcumin difluoride; DDAB, dimethyldioctadecyl ammonium bromide; DMSO, dimethyl sulfoxide.

* Correspondence to: Second affiliated hospital, Shandong University of Traditional Chinese Medicine, 250031 Jinan, China.
** Correspondence to: Department of pathology, Shandong University of Traditional Chinese Medicine, Jinan 250355, China.
E-mail addresses: sdjnwlz@aliyun.com (L. Wang), pathology001@sina.com (L. Xia).

https://doi.org/10.1016/j.biopha.2023.114590
Received 31 December 2022; Received in revised form 14 March 2023; Accepted 22 March 2023
Available online 23 March 2023

Conventional treatments for tumours (surgery, chemotherapy, radiotherapy, etc.) are only effective in the early stages of cervical cancer and are less effective in the treatment of advanced cervical cancer[4]. Therefore, it is of great practical significance to find new mechanisms, new targets and new methods for the treatment of cervical cancer.

Curcumin is a acidic, polyphenolic, diketone compound that widely existing in rhizomes of a variety of plants, such as Curcuma longa, Curcuma zedoaria, radix curcumae, and Acorus calamus [5]. Curcumin is an orange-yellow crystalline powder with a slightly bitter taste, and its molecular formula is $C_{21}H_{20}O_6$ with a relative molecular mass of 368.37 [6]. Curcumin has a significant effect in different kinds of diseases and has pharmacological activities such as anti-inflammatory [7], antioxidant [8], hypolipidemic [9], antihypertensive [10], antibacterial [11], hepatoprotective [12], and anti-tumor [13]. In India and China, curcumin is commonly used as a colorant and food additive. Since Kuttan et al. [14] from India first proposed the anti-tumor effects of curcumin in 1985, a large number of research experiments on the anti-tumor activity of curcumin was conducted, confirming that curcumin had certain pharmacological effects on a variety of tumor cells including liver cancer, gastric cancer, lung cancer, breast cancer and prostate cancer [15–20]. Curcumin has been listed as the third generation of cancer prevention drugs in the United States. With the in-depth research on the basic pharmacological effects of curcumin on cervical cancer, it was found that curcumin can affect the development of cervical cancer through various mechanisms such as promoting apoptosis, anti-proliferation, anti-metastasis and invasion of tumour cells, and inducing autophagy of tumour cells (Table 1). However, curcumin has poor water solubility and is hardly absorbed into the blood through the gastrointestinal tract after oral administration, while curcumin also has adverse properties of rapid catabolism and low bioavailability. Therefore, the application prospect of new antitumor dosage forms of curcumin looks promising.

2. Mechanism of Curcumin against Cervical Cancer

2.1. Induction of tumor cell apoptosis

The promotion of apoptosis has become one of the most important strategies in anti-tumour therapy[21]. An important sign of cancer is the disruption of tumor cell apoptosis mechanisms [22], so whether tumor cells can be induced to apoptosis is one of the key factors when selecting anticancer drugs [23].

Shang et al. [24] found that curcumin induced cell death in HeLa cells of human cervical cancer through DNA damage and chromatin condensation. Further studies showed that curcumin increased the expression of DNA damage- and repair-related proteins (e.g., p-ATM, p-ATR, BRCA1, DNA-PK, MDC1 and MGMT), while promoted translocation of p-p53 and p-H2A.X^{Ser140} from cytosol to nucleus. The mechanism of DNA damage induced by curcumin may be related to ROS (reactive oxygen) generation. Singh et al. [25] reported that curcumin reduced COX-2 (cyclooxygenase – 2) expression while increased iNOS (Inductible Nitric Oxide Synthase) expression in HeLa cells, thereby leading to inhibition of telomerase activity and Ras (specific guanine nucleotide-releasing factor 1) & ERK (extracellular signal-regulated kinase) pathway, ultimately causing inhibition of cyclin D1, c-myc (V-Myc Avian Myelocytomatosis Viral Oncogene Homolog), Hsp70 (Heat shock protein 70), activation of AIF (apoptosis inducing factor), release of cytochrome c and induction of apoptosis through mitochondrial pathway. Unlike the above study, Kim et al. [26] suggested that curcumin mediated apoptosis in cervical cancer cells by promoting ROS generation, which in turn caused activation of ER (endoplasmic reticulum) stress proteins, such as PERK, IRE-1a (inositol-requiring enzyme-1), and ATF6 (activating transcription factor 6) and their downstream signaling proteins. Both articles indicated that curcumin-induced ROS generation in tumor cells varied according to cell type. Moreover, Kim et al. demonstrated that curcumin did not contribute to increasing ROS in normal cells.

Table 1
Possible mechanisms, real modules, targets, doses and reference of Curcumin in Cervical Cancer.

Possible mechanisms	Real modules (animal/cell)	Targets	Doses	Reference
Apoptosis	HeLa	p-ATM, p-ATR, BRCA1, DNA-PK, MDC1, MGMT, p-p53, p-H2A.X^{Ser140}	13 μM	24
	HeLa, SiHa, CaSki	COX2, iNOS, Ras, ERK, cyclin D1, c-myc, Hsp 70, AIF, cytochrome c	50 μM, 100 μM	25
	C33A, CaSki, HeLa, ME180	PERK, IRE-1a, ATF6	20 μM	26
	CaSki, SiHa	ASK1, P38, JNK	16 μM	27
	CaSki, BALB/c-nude female mice	COX-2, EGFR, p-ERK1&2, p-AKT	500 mg/kg, 300 mg/kg	29
	HeLa	NA	20 μM	30
	HeLa	ROS	5 μM	31
Proliferation	HeLa	Wnt, β-catenin, NF-κB, G2/M, G1	34.23 μM	35
	HeLa	G1/S, Bax, caspase-8	25 μg/mL	36
	SiHa	HDACs, P53, G1, P21, P27, CDKi ， CDK	50 μM	37
Migration	CaSki, BALB/c-nude mice	VEGF, EGFR	1000 mg/kg, 1500 mg/kg	40
	CaSki, BALB/c-nude female mice	HIF-1-α, VEGF, VEGFR-2	100 mg/kg, 300 mg/kg, 500 mg/kg	41
	HeLa	MMP-2, MMP-9, GRB2, Rho A, Ras, p-ERK1/2, uPA, MMP-2, MMP-9, N-cadherin, β-catenin, E-cadherin, NF-κB	7.5 μM	42
	HeLa	GRB2、RAS、Rho A、N-cadherin、β-catenin、uPA, pERK1/2, E-cadherin, NF-κB, p65, p50	5 μM	43
HPV	HeLa, SiHa, C33A	E6/E7, p53, Rb, PTPN13,	5 μM, 10 μM	48
	HeLa, SiHa, CaSki	E7, PCNA, Cyclin D1	50 μM, 100 μM	50
Autophagy	Siha	G2/M, p53, p21	40 μmol/L	55
	CaSki, SiHa	Akt	16 μM	27

Curcumin induced ROS generation in cervical cancer cells is also associated with NADPH- ubiquinone oxidoreductase (complex I). It is well-known that mitochondria are important sites of ROS generation, and complex I is an important link, Shao [27] et al. found that B5, an analogue of curcumin, could inhibit thioredoxin reductase activity in complex I, causing increased ROS generation, which in turn activated ASK1 (Apoptosis Signal Regulating Kinase 1) and regulated downstream p38/JNK protein.

THC (Tetrahydrocannabinol) is one of the major metabolites of curcumin, who is structurally similar to curcumin [28] but is more stable and bioavailable. Also, THC has stronger anti-ROS-generating and pro-apoptotic effects [29] and the mechanism is also related to inhibition of COX-2 expression. At the same time, THC has also been found to inhibit the activation of EGFR and downstream signals p-ERK1/2 and p-AKT, AKT (RAC-alpha serine/threonine-protein kinase) activation is known to be closely associated with metabolic regulation. Pani et al.

[30] indicated that curcumin decreased glucose uptake levels and lactate production, increased pyruvate levels, and reversed the Warburg effect in HeLa cells. Besides, the study also identified that the reduction of glucose consumption and lactate production prevented the growth of cancer cells and promoted apoptosis of cancer cells.

The pro-apoptotic effect of curcumin in tumor cells mostly achieves at higher concentrations, while under physiological conditions, the concentration of curcumin should not exceed 5 μM. Lewinska et al. [31] reported that curcumin had no significant effect on HCFs (human corneal fibroblasts) at lower concentrations (1 μM to 5 μM), but could significantly promote ROS generation and induce apoptosis in HeLa cells. However, Lewinska believed that curcumin did not have genotoxic effects at low concentrations, but achieved tumor suppression by promoting global DNA methylation levels, which was consistent with the study of Yang et al. [32]. (Fig. 1) ROS have a dual role on tumour cells, however, their physiological effects vary with concentration, duration and the tumour cell types on which they act. The specific concentration range at which ROS exerts different effects has not been clearly reported, and in the future it will be necessary to specify the concentration range at which ROS inhibits or promotes tumour cells, and to verify whether this concentration range has any significant effect on normal cell proliferation.

2.2. Inhibition of tumor cell proliferation

The cell cycle is the fundamental process of life activity and refers to the process that begins at the end of cell division and ends at the end of the next cell division. The cell cycle dysregulation leading to unrestricted cell proliferation is one of the important factors in the development of tumours[33,34].

Ghasemi et al. [35] found that curcumin promotes G2/M cell cycle arrest and promotes apoptosis in a subpopulation of G1-phase cells in cervical cancer cells by inhibiting the Wnt/β-catenin and NF-κB pathways. Ratheesh M et al. [36] showed that curcumin at 25 μg/mL was highly cytotoxic to HeLa cells and induced HeLa cell apoptosis by ROS-mediated mitochondrial damage, arresting the cell cycle in G1/S phase. Meanwhile, expression of Bax and caspase-8 in HeLa cells increased after 48 h of curcumin treatment. Roy et al. [37] concluded that curcumin promoted the expression of P53 by inhibiting HDACs, thereby blocking the cell cycle in G1 phase. At the same time, curcumin induced the expression of CDKi (cyclin-dependent kinase inhibitors) and inhibited the expression of CDK (cyclin dependent kinases) by up-regulating the expression of P21, P27 and Rb protein. (Fig. 2).

2.3. Inhibition of tumor cell metastasis and invasion

Cancer metastasis is the result from a combined action of tumor cells and cells in the tumor microenvironment [38]. Invasiveness of tumor cells is a key factor in the metastatic cascade [39], and inhibition of its metastasis and invasion plays a crucial role in cancer therapy. Previous study [40] noted that high-dose curcumin could inhibit the growth and angiogenesis of CaSki xenografts in nude mice, possibly by down-regulating the expression of VEGF (vascular endothelial growth factor) and EGFR (epidermal growth factor receptor). The team [41] further revealed that THC also significantly inhibited tumor angiogenesis by down-regulating HIF-1α (Hypoxia-Inducible Factor 1-Alpha) and VEGF/VEGFR-2 pathway, which identified the more pronounced anti-tumor effect of THC.

In the study by Lin et al. [42], methoxycurcumin prevented migration and invasion of human cervical cancer HeLa cells through (1) inhibiting MMP-2 (matrix metalloproteinase-2) and MMP-9 signaling pathways; (2) decreasing protein levels of GRB2 (growth factor receptor-bound protein 2), Rho A (Ras homolog gene family,member A), Ras, p-ERK1/2, uPA, MMP-2, MMP-9, N-cadherin and β -catenin; (3) increasing levels of E-cadherin and NF-κB.

BDMC (Bisdemethoxycurcumin) is structurally similar to curcumin and is one of the three main components of Curcuma longa, but is much less abundant than curcumin. Based on Liao's et al. [43] study who observed that BDMC significantly inhibited invasion and metastasis of HeLa cells, further studies showed that BDMC did not affect the expression of MMP-2 and MMP-9, but markedly decreased GRB2, RAS, Rho A, N-cadherin, β-catenin, and uPA (uridylyl phosphate adenosine)

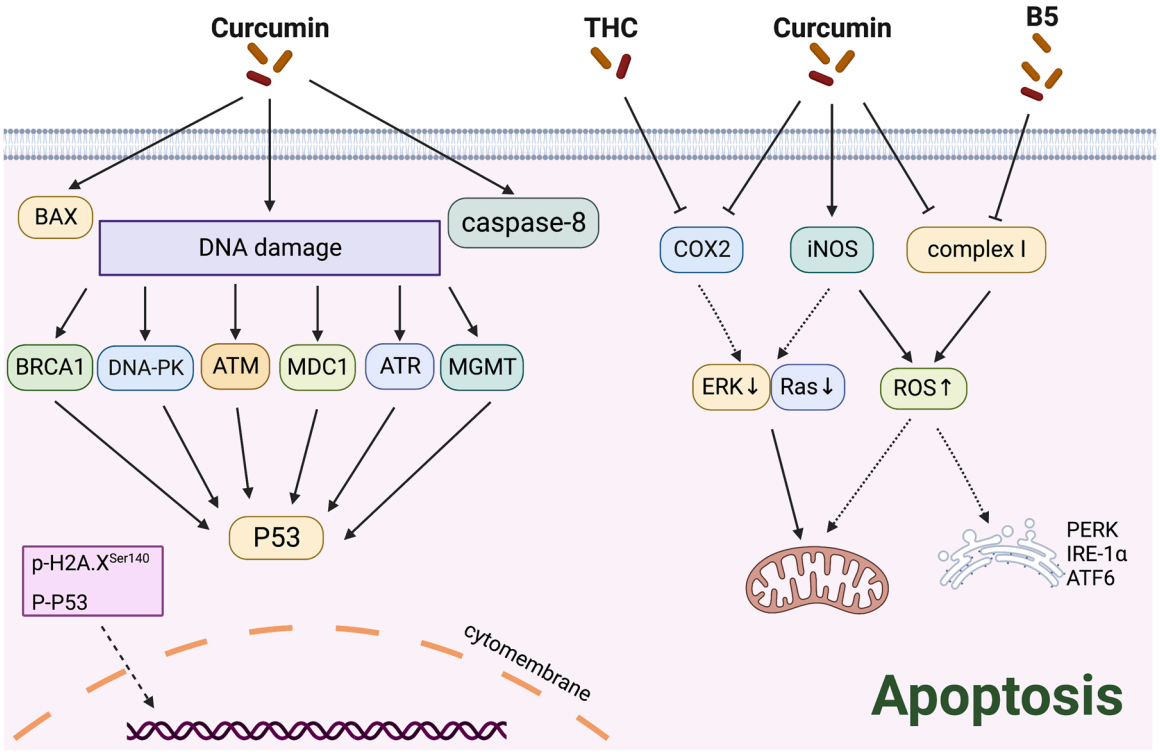

Fig. 1. Mechanism of curcumin inducing apoptosis in cervical cancer.

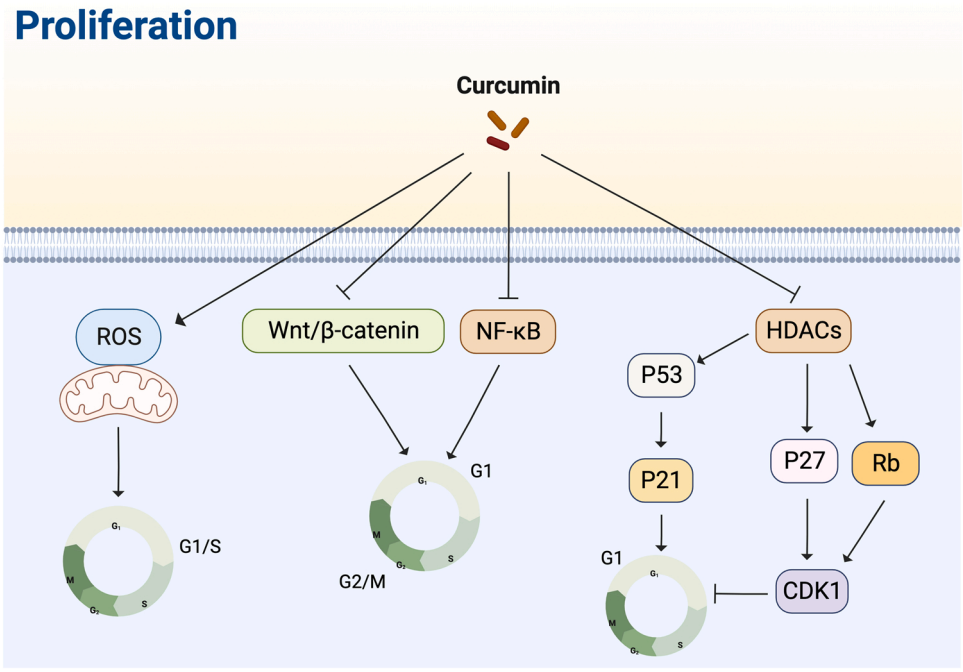

Fig. 2. Mechanism of curcumin suppressing proliferation in cervical cancer.

protein expression, while increasing pERK1/2, E-cadherin, and NF-κB (p65/p50) expression. Therefore, it was concluded that BDMC significantly inhibited migration and invasion of HeLa cells in vitro. (Fig. 3).

2.4. Inhibition of HPV

The occurrence of cervical cancer is closely related to high-risk HPV infection [44]. E6 and E7 genes in HPV genome are key oncogenes, which bind to p53 and pRb genes, respectively, affecting chromosome stability and inhibiting protein degradation, finally leading to apoptosis of tissue cells and promoting cancer cell transformation [45].

Divya et al. [46] found that curcumin was more cytotoxic to HPV16, 18-infected cervical cancer cells than non-virus-infected cells. Moreover, curcumin could inhibit the transcription and translation of E6 and E7 genes, which might be related to interference on AP-1 (activator protein-1) binding to DNA, and AP-1 was well-known to be associated

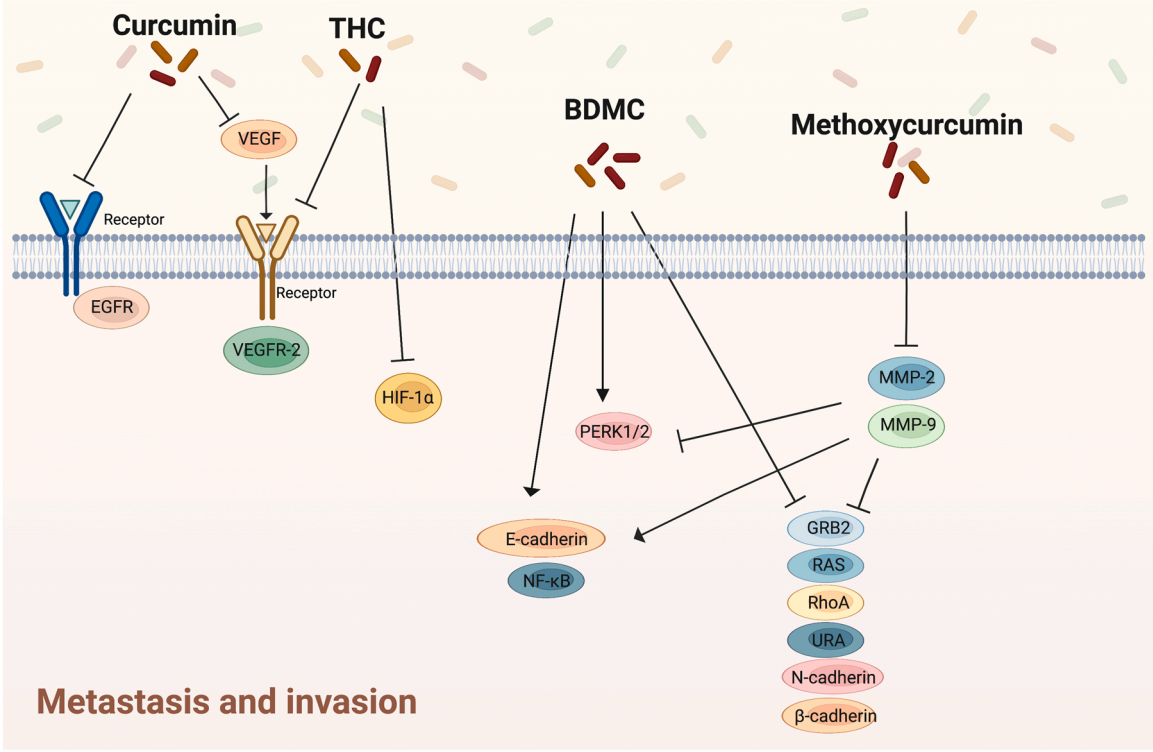

Fig. 3. Mechanism of curcumin suppressing metastasis and invasion in cervical cancer.

with the expression of multiple HPV viral genes. Prusty et al. [47] conducted in vivo and in vitro studies and concluded that over-expression of c-fos, down-regulation of FRA-1 (FRA-1 polypeptide protein) expression, and changes in the dimerization pattern of AP-1 complexes played a crucial role in the development and progression of cervical cancer. It was also demonstrated that curcumin could down-regulate c-fos (Cellular oncogene fos) and up-regulate FRA-1 expression in HeLa cells.

Maher et al. [48] also confirmed that curcumin inhibited HPV16 E6/E7 transcription in cervical cancer cell lines HeLa, SiHa, and C33A, and upregulated the expression of tumor suppressor proteins p53, Rb, and PTPN13 (protein tyrosine phosphatase non-receptor type 13). Moreover, curcumin was found to inhibit the cancer-promoting effect of benzopyrene who was a major carcinogen in tobacco, and its effect was also linked with the inhibition of E7 protein expression.

Estradiol has been identified as a risk factor for cervical cancer and has been shown to act synergistically with viral oncoproteins [49]. Singh et al. [50] pretreated cervical cancer cell strain with estradiol, and the results revealed that in HPV-positive cell lines, telomerase, viral oncoproteins E6 and E7, PCNA, p16, and cyclin D1 increased after estradiol treatment, but E7, PCNA (Proliferating Cell Nuclear Antigen) and cyclin D1 decreased after curcumin treatment without changes in E6, telomerase and p16. Therefore, it was concluded that curcumin was able to inhibit the proliferative response to estradiol and induce apoptosis. (Fig. 4).

2.5. Inducement of tumor cell autophagy

Tumor cell autophagy is an evolutionarily conserved process [51], with autophagosomes encasing cytoplasmic components of cells and transmitting them to lysosomes for degradation [52]. Autophagy has multiple pathological and physiological roles in addition to degradation of damaged organelles or biomacromolecules [53]. Besides, tumor cell autophagy remains a major part in many diseases including cancer [54].

Wang et al. [55] found that curcumin modulated intracellular ROS levels, induced autophagy and apoptosis, triggered G2/M cell cycle arrest, and mediated cellular senescence through the p53-p21 pathway. Shao et al. [27] reported that the curcumin analogue B5 not only promoted ROS generation and induced apoptosis by inhibiting TrxR (thioredoxin reductase), but also boosted cell death by inducing autophagy, which might involve inhibition of Akt signaling pathway and was not dependent on ROS. (Fig. 5).

2.6. Drug combination

For cancer patients, single drugs tend to cause drug resistance and have unsatisfactory efficacy, so anti-tumor drugs are often combined with antibodies [56], inhibitors [57] and sensitizers [58] to reduce the toxic and side effects of chemotherapeutic drugs and increase the anti-tumor effect of drugs. A large number of previous basic studies, both in vivo and in vitro, have demonstrated the efficacy of the combination of curcumin in the treatment of cervical cancer (Table 2).

Many currently used cytotoxic chemotherapeutic agents are initially purified from botanicals, and are still served as first-line treatments for many cancers. Several studies have shown that plant-derived compounds can effectively kill cervical cancer cells [59,60]. Pani et al. [61] found that the combination of curcumin with ellagitannins, quercetin and resveratrol significantly enhanced the cytotoxicity, anti-tumour metastasis and anti-tumour cell proliferation of HeLa cells. However, they did not conduct an in-depth study on the mechanism. Kumar et al. [62] investigated the synergistic anticancer properties of curcumin and ellagic. The results indicated that the combination of the two increased ROS production and was associated with increased DNA damage, which further led to apoptotic cell death. Moreover, the combination of curcumin and ellagic decreased the expression of HPV E6 mRNA, and as p53 was commonly degraded by HPV E6 oncoprotein in cervical cancer [63], the joint use restored p53 protein expression and promoted its downstream protein p21 expression. Mukherjee et al. [64] combined curcumin, resveratrol, and epicatechin gallate and found that the three drugs were most synergistic at a 4:1:12.5 ratio, and named this combination TriCurin. The results showed that both curcumin and TriCurin inhibited E6, induced p53 acetylation (activated p53), and activated caspase-3, but changes produced by TriCurin were several times greater than those by curcumin.

Thacker et al. [65] investigated the synergistic anti-cervical cancer effect of curcumin and emodin and implied that the combination of the

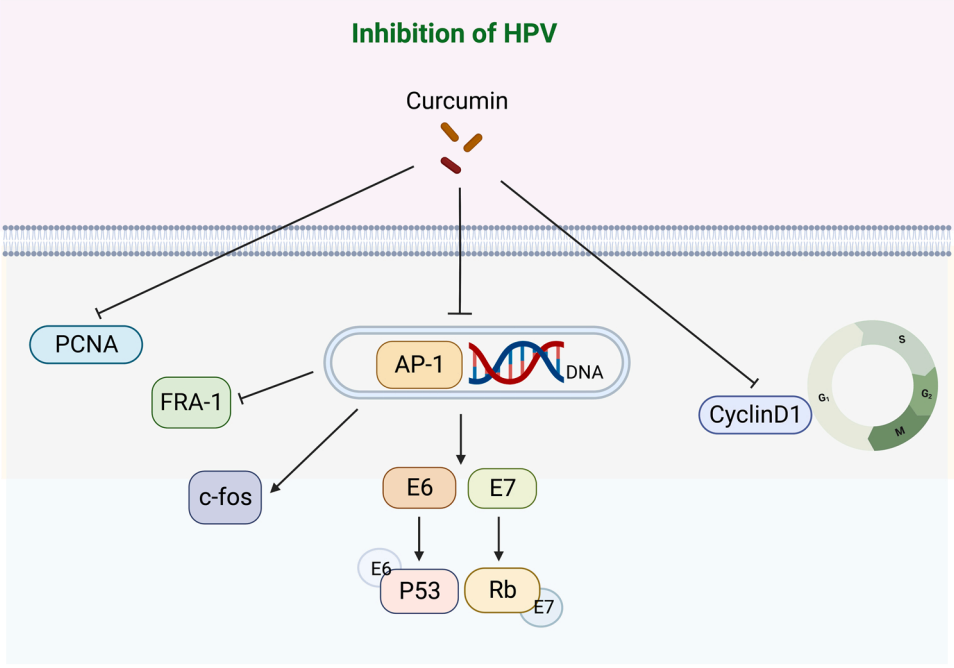

Fig. 4. Mechanism of curcumin suppressing HPV in cervical cancer.

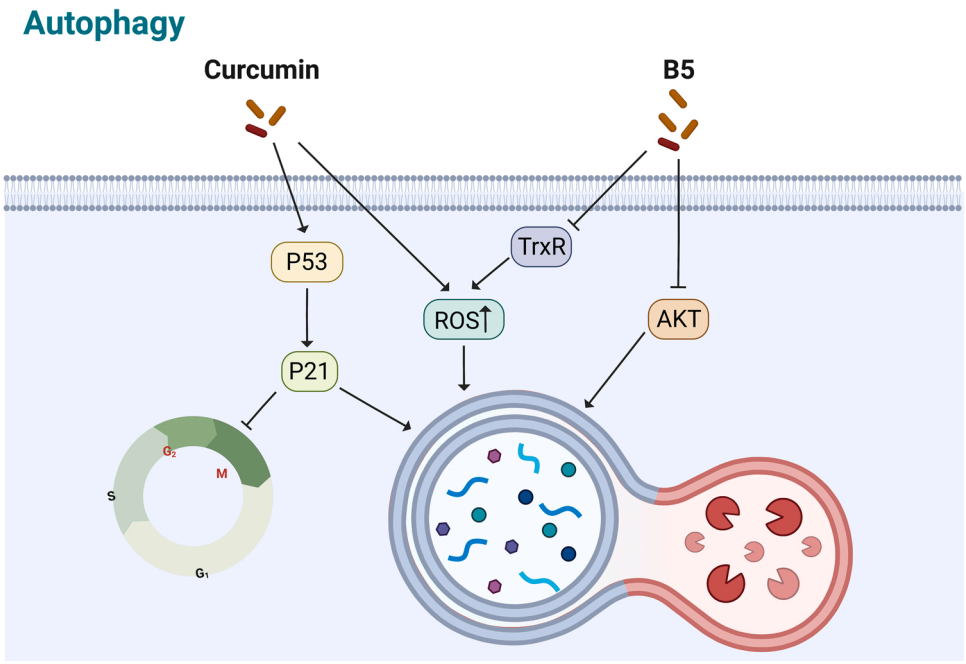

Fig. 5. Mechanism of curcumin inducing autophagy in cervical cancer.

Table 2
Drug combination, real modules, possible mechanisms, targets, doses and reference of Curcumin in Cervical Cancer.

Drug Combination	Real modules (animal/cell)	Possible mechanisms	Targets	Doses	Reference
Curcumin + Ellagic acid	HeLa	Migration	G2/M, EGFR	10 + 10 μ M	61
Curcumin + Quercetin	HeLa	Migration	G2/M, EGFR	10 + 10 μ M	61
Curcumin + Resveratrol	HeLa	Migration	G2/M, EGFR	10 + 10 μ M	61
Curcumin + Ellagic acid	HeLa	Apoptosis	ROS, p53, E6, p21	10.9 μ M	62
Curcumin + Resveratrol + Epicatechin gallate	Mice (C57BL6), TC-1, HeLa	HPV	E6, p53, caspase-3	4:1:12.5	64
Curcumin + Emodin	HeLa, SiHa	Migration	TGF-β, P-Smad3, Smad4, cyclinD1, p21, Pin1, Snail, Slug, Wnt, β-catenin, β-catenin	15/25 μM + 40 μM	65
Curcumin + Catechin Metabolites	Ca Ski	Proliferation, Apoptosis	VEGF, miR-210, miR-21, miR-126	NA	68
Curcumin + Paclitaxel	HeLa	Apoptosis	AKT, NF-κB, Bcl-2	5 μM + 5 μM	70
Curcumin + Paclitaxel	Ca Ski, HeLa	Apoptosis	E6, E7, p53, caspase3, NF - κB	10 μM + 5 μM	71
Curcumin + photodynamic therapy	Me180, Female BALB/c nude mice	Proliferation, Apoptosis	Notch1, NF-κB	NA	75
Curcumin + Ultrasound enhancement	HeLa, SiHa， C33A	NA	NA	10 μM curcumin with 8 s of 7.5 MHz ultrasound	77
Tetrahydrocurcumin + Celecoxib	CaSki, BALB/c-nude female mice	Tumor growth + tumor angiogenesis	VEGF, COX-2, EGFR	50 mg/kg + 50 mg/kg	79
Curcumin + Cisplatin	SiHa	NA	HDACs, E6, E7, G1/S, MRP1, Pgp1	50 μM + 0.1 μM	37
Curcumin + HPV16/18 L1-L2-E7	C3 tumor cells, C57BL/6 mice	NA	NA	40 μM + 50 μg	89
Nanocurcumin + HPV16/18 L1-L2-E7	C3 tumor cells, C57BL/6 mice	NA	NA	20 μM + 50 μg	89

two effectively down-regulated TGF-β (transforming growth factor-β) signaling pathway by decreasing the expression of TGF-β receptor II, P-Smad3 and Smad4, and balanced the tumorigenic effect of TGF-β by inhibiting TGF-β-induced migration and invasion. In response to curcumin and emodin treatment, the expression of downstream effectors cyclinD1, p21 and Pin1 (Personal Identification Number 1) in TGF-β signaling pathway was suppressed, while the expression of key interstitial markers (Snail and Slug) was also down-regulated. In addition, it was found that TGF-β activated the Wnt/β-catenin signaling pathway in HeLa cells, whereas curcumin and emodin downregulated this pathway by inhibiting β-catenin.

Catechin metabolites are produced by gut microbiota on the metabolic action of green tea in the gut [66], and play an important role in preventing diseases such as cancer [67]. The results of Khojaste et al. [68] documented that the combination of catechin metabolites and curcumin down-regulated the expression of oncogenes VEGF, miR-210 and miR-21, and up-regulated the expression of tumor suppressor gene miR-126.

Paclitaxel, the most widely used anticancer drug, is applied for the treatment of various types of malignant diseases[69]. Bava et al. [70] suggested that the synergistic anti-cervical cancer effect of curcumin and paclitaxel might be related to AKT/NF-κB signaling pathway. Paclitaxel and curcumin inhibit downstream NF-κB activation through activation of AKT. The synergistic effect of curcumin with paclitaxel might also be associated with decreased Bcl-2 expression, which was independent from the NF-κB pathway.

DANG et al. [71] showed that curcumin could amplify inhibition of paclitaxel on growth of HPV-positive human cervical cancer cell strains, and was associated with HPV E6/E7 protein inhibition and p53-dependent apoptosis. The transduction pathway involved in this synergism could be the NF-κB/p53/caspase-3 intrinsic apoptotic pathway.

PDT (Photodynamic therapy) involves the selective absorption of PS (photosensitizers), and PS can be activated when reaching cancer cells by light that matches the absorption spectrum of the PS, followed by a series of reactions that lead to tumor cell death [72,73]. Curcumin is also a novel PS and has been shown to have good efficacy in cervical cancer in coordinate with PDT [74]. He et al. [75] observed that curcumin combined with PDT inhibited proliferation and induced apoptosis of cervical cancer cells. The synergistic application of the two could down-regulate the expression of Notch1 and NF-κB, thus Notch signaling pathway might be one of the targets of curcumin combined with PDT therapy.

Ultrasound promotes drug absorption by increasing permeability [76]. R. Carr et al. [77] used curcumin combined with ultrasound to intervene cervical cancer cells, and the results showed that such combination could increase the necrosis of HeLa, SiHa and C33A cells by 9-, 12- and 16-fold, respectively, which was significantly greater compared with using curcumin alone. The mechanism might be related to the destruction of microtubule structure. However, it should be emphasized that different cervical cancer cells required different ultrasound frequencies and could cause different degrees of necrosis.

Celecoxib is a selective COX-2 inhibitor that has been reported to have anticancer effects [78]. Yoysungnoen et al. [79] reported that THC and celecoxib alone or in combination reduced tumor size by 70.40%, 65.11%, and 77.04%, respectively. Moreover, THC combined with celecoxib inhibited tumor growth and tumor angiogenesis by down-regulating the expression of VEGF, COX-2 and EGFR.

Cisplatin induces apoptosis by preventing DNA duplex unwinding and segregation, inhibiting cell division and inducing tumor cell apoptosis [80]. Meanwhile, cisplatin also induces ROS accumulation in mitochondria, thereby activating mitochondria-dependent apoptotic pathways [81]. However, the apparent nephrotoxicity, ototoxicity and drug resistance of cisplatin limit its clinical application [82]. Roy et al. [37] indicated that curcumin was also sensitizing to cisplatin-induced cervical cancer cell killing. By altering cell cycle regulatory proteins, inhibition of HDACs (histone deacetylases) and HPVs led to cell cycle arrest in G1/S phase. Inhibition of MRP1 (multidrug resistance protein 1) and Pgp1 (P-glycoprotein 1) by curcumin could sensitize cervical cancer cells and reduced the chemotherapeutic dose of cisplatin.

At present, there are three commercial prophylactic vaccines for HPV, but these vaccines have not shown therapeutic efficacy in HPV infected patients [83–86]. HPV L1, L2, and E7 proteins are the main target antigens for the development of therapeutic vaccines [87,88]. Kayyal et al. [89] found that curcumin and nanocurcumin could synergize with HSP70-L1-L2-E7 vaccine to inhibit tumor growth.

3. Dosage forms

Curcumin is composed of two ortho-methylated phenols as well as one β-diketone, and its chemical structure plays a critical role in exerting its biological activity [6]. However, disadvantages of curcumin greatly limit its clinical application such as low water solubility, poor stability, and low bioavailability [90]. Therefore, in addition to the study on curcumin derivatives, changes in dosage forms are also one of the research directions [91,92].

Curcumin nano-suspension is a colloidal dispersion formed by curcumin nanoparticles and a small amount of stabilizer, which can significantly improve the solubility of poorly soluble drugs and the dissolution rate, as well as enhance the bioavailability [93,94]. Nano drug-loading system is to combine drugs with carriers (e.g. metal ions, PLGA (poly lactic-co-glycolic acid) nanoparticles, solid lipid nanoparticles, PBCA (polybutyl cyanoacrylate) nanoparticles) in order to increase their therapeutic effect. Its in vitro activity, in vivo activity, drug entrapment efficiency and drug loading vary widely between materials.

Thulasidasan et al. [95] found that curcumin-entrapped in PLGA-PEG nanoparticles conjugated to folic acid (ppf-curcumin) displayed maximum cell death. Thereafter, this formulation was proved to improve curcumin bioavailability and half-life in Swiss albino mice. In addition, acute and chronic toxicity studies demonstrated the pharmacological safety of the formulation. The authors also assessed its potential for chemosensitivity to paclitaxel and validated this finding in a cervical cancer xenograft model in NOD-SCID (non-obese diabetic severe combined immunodeficient) mice.

CDF (Curcumin difluoride) is a novel and effective synthetic curcumin analogue that has been found to have significant effects in a variety of tumors [96,97]. Gawde et al. [98] encapsulated the folate-modified nanosomes with the purpose of improving the bioavailability and targeting of paclitaxel and CDF. The results showed that treated paclitaxel and CDF produced synergistic anticancer effects and such effects could be enhanced due to folate receptor-mediated targeted uptake and induction of apoptosis.

Recently, green synthesis of silver nanoparticles have been increasingly investigated because of its anticancer potential [99] in terms of making plant extract efficacy more sustained, promoting biocompatibility, functionalizing nanoparticles to further enhance their anticancer activity [100–103]. Murugesan et al. [104] biosynthesized nanosilver using the curcumin derivative ST06. The results revealed that HeLa cells had a significant growth inhibitory effect on human cervical cancer cells, and the mechanism was related to the intrinsic apoptotic pathway.

Matos et al. [74] used curcumin nanoemulsion as a photosensitizing agent and investigated its effect on viability of cervical cancer cells. The experimental results showed that nanoemulsion-curcumin could produce effective photodynamic response against cervical cancer cell lines. This approach induced an increase in caspase-3 and aspase-7 activity, suggesting that cell death occurs via apoptosis.

Liposome technology is the fourth generation of targeted drug delivery technology known as "biological missiles". The combination of liposome and curcumin can make curcumin smoother through the cell membrane, promote the gastrointestinal absorption, thereby increasing the plasma concentration and bioavailability of curcumin. Saengkrit et al. [105] found that modifying the surface charge of liposomes using DDAB (dimethyldioctadecyl ammonium bromide) improve the anticancer effect of curcumin.

Microspheres refer to the particle dispersion system formed by drug dispersion or adsorption in polymer matrix, which can not only increase the stability of drugs, but realize the sustained release and controlled release [106]. Bhatt et al. [107] adjusted the polymer matrix with solubilizers, DMSO (dimethyl sulfoxide), and Tween-20, and found that encapsulation of microspheres prolonged the sustained release of curcumin for up to 24 h. Moreover, curcumin encapsulated by chitosan-silica microspheres showed antiproliferative activity against cervical cancer HeLa cells. This has the potential to be a novel drug delivery system that improves the bioavailability of curcumin.

4. Conclusion and perspectives

Botanical extracts have now been widely recognized, especially its unique effects in tumors. As an effective antitumor compound with dose-dependent antitumor activity, curcumin is extracted from botanicals such as Curcuma longa, Curcuma zedoaria and radix curcumae. Curcumin has been reported to have good antitumor potential against malignancies such as breast cancer [108,109], lung cancer [110,111], liver cancer [112,113], and ovarian cancer [114–116].

Diet has been identified as an important and modifiable risk factor for cancer [117]. Therefore, dietary modification can be a potential strategy to prevent or reverse manifestations prior to the early stages,

including inclusion of functional food components with chemopreventive properties [118]. Curcumin has long been widely used in the food industry as a natural pigment and food additive. Perhaps, curcumin may have a subtly effect on malignancy in the daily diet.

Curcumin has been found to exert its effects against cervical cancer by inducing apoptosis, inhibiting tumor cell proliferation, inhibiting tumor cell metastasis and invasion, and inducing autophagy in tumor cells. However, its clinical application is greatly limited due to its low water solubility, poor stability, low bioavailability, and low absorption and utilization. At the same time, there is a lack of specific methods to effectively evaluate the content of curcumin analogues and derivatives in blood and tissues, whether the improvement of the biological activity of curcumin analogues and derivatives is caused by the increase of their bioavailability remains unclear [119]. In addition, the improvement of curcumin bioactivity, bioavailability and anti-tumor activity by analogues and derivatives is very limited, thus it is imperative to develop new formulations of curcumin. In recent years, novel nanotechnology-based formulations have shed light on the new use of curcumin. Researchers make curcumin into nanoparticles, nanoliposomes, green synthetic silver nanoparticles, microspheres, nanoemulsion and other dosage forms to promote its absorption in the human body.

Many questions remain to be explored regarding curcumin in the future. First, there are few clinical trials of curcumin against cancer, and its potential in the treatment of cervical cancer should be fully observed. Second, compared with curcumin, whether its derivatives and analogues will have an improved effect in cervical cancer. Third, novel formulations of curcumin still require to be innovated. Fourth, the optimal dose of curcumin for cervical cancer needs to be investigated. Fifth, as a potent anticancer drug, curcumin is also one of the future research directions in combination with other anticancer methods. Finally, when used as food additive and food colorant, whether curcumin can subtly influence cervical cancer in daily diet remains to be studied.

CRediT authorship contribution statement

Xiaoyu Zhang wrote the manuscript and drew the pictures. Lin Zhu collected and organize literature. Xuezhen Wang and Hairong Zhang proofread the manuscript. Lianzhong Wang and Lei Xia are fully responsible for the study designing, research fields, drafting, and finalizing the paper.

Conflict of interest statement

No conflict of interest exist in the submission of this manuscript, and manuscript is approved by all authors for publication.

References

[1] S.M. Kovachev, Cervical cancer and vaginal microbiota changes, Arch. Microbiol 202 (2) (2020) 323–327.
[2] M. Saei Ghare Naz, et al., Educational interventions for cervical cancer screening behavior of women: a systematic review, Asian Pac. J. Cancer Prev. 19 (4) (2018) 875–884.
[3] M. Arbyn, et al., Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis, Lancet Glob. Health 8 (2) (2020) e191–e203.
[4] D.H. Moore, Cervical cancer, Obstet. Gynecol. 107 (5) (2006) 1152–1161.
[5] R.R. Kotha, D.L. Luthria, Curcumin: biological, pharmaceutical, nutraceutical, and analytical aspects, Molecules 24 (2019) 16.
[6] K.M. Nelson, et al., The essential medicinal chemistry of curcumin, J. Med Chem. 60 (5) (2017) 1620–1637.
[7] D. Sun, et al., A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes, Mol. Ther. 18 (9) (2010) 1606–1614.
[8] V.P. Menon, A.R. Sudheer, Antioxidant and anti-inflammatory properties of curcumin, Adv. Exp. Med Biol. 595 (2007) 105–125.
[9] J.M. Zingg, S.T. Hasan, M. Meydani, Molecular mechanisms of hypolipidemic effects of curcumin, Biofactors 39 (1) (2013) 101–121.
[10] H.B. Li, et al., Curcumin ameliorates hypertension via gut-brain communication in spontaneously hypertensive rat, Toxicol. Appl. Pharm. 429 (2021), 115701.
[11] S.Z. Moghadamtousi, et al., A review on antibacterial, antiviral, and antifungal activity of curcumin, Biomed. Res Int 2014 (2014), 186864.
[12] S. Saadati, et al., Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial, BMC Gastroenterol. 19 (1) (2019) 133.
[13] A. Giordano, G. Tommonaro, *Curcumin Cancer* Nutr. 11 (2019) 10.
[14] R. Kuttan, et al., Potential anticancer activity of turmeric (Curcuma longa), Cancer Lett. 29 (2) (1985) 197–202.
[15] S.M. Plummer, et al., Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents, Cancer Epidemiol. Biomark. Prev. 10 (12) (2001) 1295–1299.
[16] A.S. Darvesh, B.B. Aggarwal, A. Bishayee, Curcumin and liver cancer: a review, Curr. Pharm. Biotechnol. 13 (1) (2012) 218–228.
[17] K. Sintara, et al., Curcumin attenuates gastric cancer induced by N-methyl-N-nitrosourea and saturated sodium chloride in rats, J. Biomed. Biotechnol. 2012 (2012), 915380.
[18] C.L. Yang, et al., Curcumin induces small cell lung cancer NCI-H446 cell apoptosis via the reactive oxygen species-mediated mitochondrial pathway and not the cell death receptor pathway, DNA Cell Biol. 31 (2) (2012) 139–150.
[19] S.R. Kim, et al., Curcumin down-regulates visfatin expression and inhibits breast cancer cell invasion, Endocrinology 153 (2) (2012) 554–563.
[20] V. Sundram, et al., Curcumin attenuates β-catenin signaling in prostate cancer cells through activation of protein kinase D1, PLoS One 7 (4) (2012), e35368.
[21] B.A. Carneiro, W.S. El-Deiry, Targeting apoptosis in cancer therapy, Nat. Rev. Clin. Oncol. 17 (7) (2020) 395–417.
[22] G. Pistritto, et al., Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies, Aging (Albany NY) 8 (4) (2016) 603–619.
[23] S.S. Bacus, et al., Taxol-induced apoptosis depends on MAP kinase pathways (ERK and p38) and is independent of p53, Oncogene 20 (2) (2001), 147-55.
[24] H.S. Shang, et al., Curcumin causes DNA damage and affects associated protein expression in HeLa human cervical cancer cells, Oncol. Rep. 36 (4) (2016) 2207–2215.
[25] M. Singh, N. Singh, Molecular mechanism of curcumin induced cytotoxicity in human cervical carcinoma cells, Mol. Cell Biochem 325 (1–2) (2009) 107–119.
[26] B. Kim, et al., Curcumin induces ER stress-mediated apoptosis through selective generation of reactive oxygen species in cervical cancer cells, Mol. Carcinog. 55 (5) (2016) 918–928.
[27] F.Y. Shao, et al., B5, a thioredoxin reductase inhibitor, induces apoptosis in human cervical cancer cells by suppressing the thioredoxin system, disrupting mitochondrion-dependent pathways and triggering autophagy, Oncotarget 6 (31) (2015) 30939–30956.
[28] C.S. Lai, C.T. Ho, M.H. Pan, The cancer chemopreventive and therapeutic potential of tetrahydrocurcumin, Biomolecules 10 (2020) 6.
[29] B. Yoysungnoen, et al., Effects of tetrahydrocurcumin on tumor growth and cellular signaling in cervical cancer xenografts in nude mice, Biomed. Res Int 2016 (2016), 1781208.
[30] S. Pani, et al., Phytocompounds curcumin, quercetin, indole-3-carbinol, and resveratrol modulate lactate-pyruvate level along with cytotoxic activity in HeLa cervical cancer cells, Biotechnol. Appl. Biochem 68 (6) (2021) 1396–1402.
[31] A. Lewinska, et al., Curcumin-mediated decrease in the expression of nucleolar organizer regions in cervical cancer (HeLa) cells, Mutat. Res Genet Toxicol. Environ. Mutagen 771 (2014) 43–52.
[32] J. Yang, et al., Studies of traditional Chinese medicine monomer on HeLa cell of cervical cancer, Pak. J. Pharm. Sci. 27 (4 Suppl) (2014) 1063–1068.
[33] M. Díaz-Coránguez, X. Liu, D.A. Antonetti, Tight junctions in cell proliferation, Int J. Mol. Sci. 20 (2019) 23.
[34] M. Cardano, C. Tribioli, E. Prosperi, Targeting proliferating cell nuclear antigen (PCNA) as an effective strategy to inhibit tumor cell proliferation, Curr. Cancer Drug Targets 20 (4) (2020) 240–252.
[35] F. Ghasemi, et al., Curcumin inhibits NF-kB and Wnt/β-catenin pathways in cervical cancer cells, Pathol. Res Pr. 215 (10) (2019), 152556.
[36] R. M, et al., Curcumin-galactomannoside complex inhibits the proliferation of human cervical cancer cells: possible role in cell cycle arrest and apoptosis, Asian Pac. J. Cancer Prev. 22 (6) (2021) 1713–1720.
[37] M. Roy, S. Mukherjee, Reversal of resistance towards cisplatin by curcumin in cervical cancer cells, Asian Pac. J. Cancer Prev. 15 (3) (2014) 1403–1410.
[38] Y. Suhail, et al., Systems biology of cancer metastasis, Cell Syst. 9 (2) (2019) 109–127.
[39] A.E. Dart, P.R. Gordon-Weeks, The role of drebrin in cancer cell invasion, Adv. Exp. Med Biol. 1006 (2017) 375–389.
[40] P. Yoysungnoen-Chintana, P. Bhattarakosol, S. Patumraj, Antitumor and antiangiogenic activities of curcumin in cervical cancer xenografts in nude mice, Biomed. Res Int 2014 (2014), 817972.
[41] B. Yoysungnoen, et al., Effects of tetrahydrocurcumin on hypoxia-inducible factor-1α and vascular endothelial growth factor expression in cervical cancer cell-induced angiogenesis in nude mice, Biomed. Res Int 2015 (2015), 391748.
[42] C.C. Lin, et al., Demethoxycurcumin suppresses migration and invasion of human cervical cancer HeLa cells via inhibition of NF-κB pathways, Anticancer Res 38 (5) (2018) 2761–2769.
[43] C.L. Liao, et al., Bisdemethoxycurcumin suppresses migration and invasion of human cervical cancer HeLa cells via inhibition of NF-κB, MMP-2 and -9 pathways, Anticancer Res 38 (7) (2018) 3989–3997.
[44] J. Zhu, et al., Arsenic-induced PML targeting onto nuclear bodies: implications for the treatment of acute promyelocytic leukemia, Proc. Natl. Acad. Sci. USA 94 (8) (1997) 3978–3983.

[45] M. Sadraeian, et al., Induction of antitumor immunity against cervical cancer by protein HPV-16 E7 in fusion with ricin B chain in tumor-bearing mice, Int J. Gynecol. Cancer 23 (5) (2013) 809–814.
[46] C.S. Divya, M.R. Pillai, Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis, Mol. Carcinog. 45 (5) (2006) 320–332.
[47] B.K. Prusty, B.C. Das, Constitutive activation of transcription factor AP-1 in cervical cancer and suppression of human papillomavirus (HPV) transcription and AP-1 activity in HeLa cells by curcumin, Int J. Cancer 113 (6) (2005) 951–960.
[48] D.M. Maher, et al., Curcumin suppresses human papillomavirus oncoproteins, restores p53, Rb, and PTPN13 proteins and inhibits benzo[a]pyrene-induced upregulation of HPV E7, Mol. Carcinog. 50 (1) (2011) 47–57.
[49] S. Jaakkola, et al., Postmenopausal estradiol-progestagen therapy and risk for uterine cervical cancer, Int J. Cancer 131 (4) (2012) E537–E543.
[50] M. Singh, N. Singh, Curcumin counteracts the proliferative effect of estradiol and induces apoptosis in cervical cancer cells, Mol. Cell Biochem 347 (1–2) (2011) 1–11.
[51] N.M. Kocaturk, et al., Autophagy as a molecular target for cancer treatment, Eur. J. Pharm. Sci. 134 (2019) 116–137.
[52] J.M.M. Levy, C.G. Towers, A. Thorburn, Targeting autophagy in cancer, Nat. Rev. Cancer 17 (9) (2017) 528–542.
[53] F. Nazio, et al., Autophagy and cancer stem cells: molecular mechanisms and therapeutic applications, Cell Death Differ. 26 (4) (2019) 690–702.
[54] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, Cell 147 (4) (2011) 728–741.
[55] T. Wang, et al., Curcumin induces G2/M arrest and triggers autophagy, ROS generation and cell senescence in cervical cancer cells, J. Cancer 11 (22) (2020) 6704–6715.
[56] S. Tavor, et al., High response rate for treatment with gemtuzumab ozogamicin and cytarabine in elderly patients with acute myeloid leukemia and favorable and intermediate-I cytogenetic risk, Clin. Lymphoma Myeloma Leuk. 12 (6) (2012) 438–443.
[57] F. Pein, et al., Dose finding study of oral PSC 833 combined with weekly intravenous etoposide in children with relapsed or refractory solid tumours, Eur. J. Cancer 43 (14) (2007) 2074–2081.
[58] L.E. van Vlerken, et al., Modulation of intracellular ceramide using polymeric nanoparticles to overcome multidrug resistance in cancer, Cancer Res 67 (10) (2007) 4843–4850.
[59] S. Shukla, et al., Elimination of high-risk human papillomavirus type HPV16 infection by 'Praneem' polyherbal tablet in women with early cervical intraepithelial lesions, J. Cancer Res Clin. Oncol. 135 (12) (2009) 1701–1709.
[60] P.S. Oh, K.T. Lim, HeLa cells treated with phytoglycoprotein (150 kDa) were killed by activation of caspase 3 via inhibitory activities of NF-kappaB and AP-1, J. Biomed. Sci. 14 (2) (2007) 223–232.
[61] S. Pani, et al., Shifting of cell cycle arrest from the S-phase to G2/M phase and downregulation of EGFR expression by phytochemical combinations in HeLa cervical cancer cells, J. Biochem Mol. Toxicol. 36 (1) (2022), e22947.
[62] D. Kumar, et al., Curcumin and Ellagic acid synergistically induce ROS generation, DNA damage, p53 accumulation and apoptosis in HeLa cervical carcinoma cells, Biomed. Pharm. 81 (2016) 31–37.
[63] D. Martinez-Zapien, et al., Structure of the E6/E6AP/p53 complex required for HPV-mediated degradation of p53, Nature 529 (7587) (2016), 541-5.
[64] S. Mukherjee, et al., Unique synergistic formulation of curcumin, epicatechin gallate and resveratrol, tricurin, suppresses HPV E6, eliminates HPV+ cancer cells, and inhibits tumor progression, Oncotarget 8 (37) (2017) 60904–60916.
[65] P.C. Thacker, D. Karunagaran, Curcumin and emodin down-regulate TGF-β signaling pathway in human cervical cancer cells, PLoS One 10 (3) (2015), e0120045.
[66] A. Hara-Terawaki, et al., Inhibitory activity of catechin metabolites produced by intestinal microbiota on proliferation of HeLa cells, Biol. Pharm. Bull. 40 (8) (2017) 1331–1335.
[67] T. Kuzuhara, M. Suganuma, H. Fujiki, Green tea catechin as a chemical chaperone in cancer prevention, Cancer Lett. 261 (1) (2008) 12–20.
[68] E. Khojaste, C. Ahmadizadeh, Catechin metabolites along with curcumin inhibit proliferation and induce apoptosis in cervical cancer cells by regulating VEGF expression in-vitro, Nutr. Cancer 74 (3) (2022) 1048–1057.
[69] T.M. Abu Samaan, et al., Paclitaxel's mechanistic and clinical effects on breast cancer, Biomolecules 9 (2019) 12.
[70] S.V. Bava, et al., Akt is upstream and MAPKs are downstream of NF-κB in paclitaxel-induced survival signaling events, which are down-regulated by curcumin contributing to their synergism, Int J. Biochem Cell Biol. 43 (3) (2011) 331–341.
[71] Y.P. Dang, et al., Curcumin improves the paclitaxel-induced apoptosis of HPV-positive human cervical cancer cells via the NF-κB-p53-caspase-3 pathway, Exp. Ther. Med 9 (4) (2015) 1470–1476.
[72] D.M. Sharp, S. Lai, C.M. Markey, Photodynamic therapy with verteporfin for choroidal neovascularization due to age-related macular degeneration and other causes: a New Zealand outcomes study, Clin. Exp. Ophthalmol. 35 (1) (2007) 24–31.
[73] A. Khdair, et al., Nanoparticle-mediated combination chemotherapy and photodynamic therapy overcomes tumor drug resistance in vitro, Eur. J. Pharm. Biopharm. 71 (2) (2009) 214–222.
[74] R.P.A. de Matos, et al., Effect of curcumin-nanoemulsion associated with photodynamic therapy in cervical carcinoma cell lines, Biomed. Res Int 2018 (2018), 4057959.
[75] G. He, et al., Effects of notch signaling pathway in cervical cancer by curcumin mediated photodynamic therapy and its possible mechanisms in vitro and in vivo, J. Cancer 10 (17) (2019) 4114–4122.
[76] F. Domenici, et al., Structural and permeability sensitivity of cells to low intensity ultrasound: Infrared and fluorescence evidence in vitro, Ultrasonics 54 (4) (2014) 1020–1028.
[77] K.R. Carr, et al., Combined ultrasound-curcumin treatment of human cervical cancer cells, Eur. J. Obstet. Gynecol. Reprod. Biol. 193 (2015) 96–101.
[78] D.V. Tudor, et al., COX-2 as a potential biomarker and therapeutic target in melanoma, Cancer Biol. Med 17 (1) (2020) 20–31.
[79] B. Yoysungnoen, et al., Combinational treatment effect of tetrahydrocurcumin and celecoxib on cervical cancer cell-induced tumor growth and tumor angiogenesis in nude mice, J. Med Assoc. Thai 99 (Suppl 4) (2016) S23–S31.
[80] S. Yu, et al., Galangin (GG) combined with cisplatin (DDP) to suppress human lung cancer by inhibition of STAT3-regulated NF-κB and Bcl-2/Bax signaling pathways, Biomed. Pharm. 97 (2018) 213–224.
[81] M. Kleih, et al., Direct impact of cisplatin on mitochondria induces ROS production that dictates cell fate of ovarian cancer cells, Cell Death Dis. 10 (11) (2019) 851.
[82] S. O'Grady, et al., The role of DNA repair pathways in cisplatin resistant lung cancer, Cancer Treat. Rev. 40 (10) (2014) 1161–1170.
[83] M. Bharadwaj, et al., HPV & HPV vaccination: issues in developing countries, Indian J. Med Res 130 (3) (2009) 327–333.
[84] E.A. Joura, et al., A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women, N. Engl. J. Med 372 (8) (2015) 711–723.
[85] D.M. Harper, L.R. DeMars, HPV vaccines - a review of the first decade, Gynecol. Oncol. 146 (1) (2017) 196–204.
[86] H.J. Kim, H.J. Kim, Current status and future prospects for human papillomavirus vaccines, Arch. Pharm. Res 40 (9) (2017) 1050–1063.
[87] K. Hoppe-Seyler, et al., The HPV E6/E7 oncogenes: key factors for viral carcinogenesis and therapeutic targets, Trends Microbiol 26 (2) (2018) 158–168.
[88] S.V. Graham, Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies, Future Microbiol 5 (10) (2010) 1493–1506.
[89] M. Kayyal, et al., Immunological responses and anti-tumor effects of HPV16/18 L1-L2-E7 multiepitope fusion construct along with curcumin and nanocurcumin in C57BL/6 mouse model, Life Sci. 285 (2021), 119945.
[90] X. Zhang, et al., Curcumin alleviates oxaliplatin-induced peripheral neuropathic pain through inhibiting oxidative stress-mediated activation of NF-κB and mitigating inflammation, Biol. Pharm. Bull. 43 (2) (2020) 348–355.
[91] B. Karolewicz, et al., Solid dispersions in pharmaceutical technology. Part I. Classification and methods to obtain solid dispersions, Polim. Med 42 (1) (2012) 17–27.
[92] S. Prasad, A.K. Tyagi, B.B. Aggarwal, Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice, Cancer Res Treat. 46 (1) (2014) 2–18.
[93] B.P. Sahu, et al., Curcumin-docetaxel co-loaded nanosuspension for enhanced anti-breast cancer activity, Expert Opin. Drug Deliv. 13 (8) (2016) 1065–1074.
[94] L. Casula, et al., Pulmonary delivery of curcumin and beclomethasone dipropionate in a multicomponent nanosuspension for the treatment of bronchial asthma, Pharmaceutics 13 (2021) 8.
[95] A.K.T. Thulasidasan, et al., Folic acid conjugation improves the bioavailability and chemosensitizing efficacy of curcumin-encapsulated PLGA-PEG nanoparticles towards paclitaxel chemotherapy, Oncotarget 8 (64) (2017) 107374–107389.
[96] S. Roy, et al., Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21, PLoS One 8 (7) (2013), e68543.
[97] S.K. Basak, et al., Liposome encapsulated curcumin-difluorinated (CDF) inhibits the growth of cisplatin resistant head and neck cancer stem cells, Oncotarget 6 (21) (2015) 18504–18517.
[98] K.A. Gawde, et al., Paclitaxel and di-fluorinated curcumin loaded in albumin nanoparticles for targeted synergistic combination therapy of ovarian and cervical cancers, Colloids Surf. B Biointerfaces 167 (2018) 8–19.
[99] N. Rani, et al., A review on green synthesis of silver nanoparticles and its role against cancer, Curr. Top. Med Chem. 22 (18) (2022) 1460–1471.
[100] K.C. Hembram, et al., Therapeutic prospective of plant-induced silver nanoparticles: application as antimicrobial and anticancer agent, Artif. Cells Nanomed. Biotechnol. 46 (sup3) (2018) S38–s51.
[101] M. Ovais, et al., Green synthesis of silver nanoparticles via plant extracts: beginning a new era in cancer theranostics, Nanomed. (Lond.) 11 (23) (2016) 3157–3177.
[102] M. Yadi, et al., Current developments in green synthesis of metallic nanoparticles using plant extracts: a review, Artif. Cells Nanomed. Biotechnol. 46 (sup3) (2018) S336–s343.
[103] M. Jeyaraj, et al., Biogenic silver nanoparticles for cancer treatment: an experimental report, Colloids Surf. B Biointerfaces 106 (2013) 86–92.
[104] K. Murugesan, et al., Effects of green synthesised silver nanoparticles (ST06-AgNPs) using curcumin derivative (ST06) on human cervical cancer cells (HeLa) in vitro and EAC tumor bearing mice models, Int J. Nanomed. 14 (2019) 5257–5270.
[105] N. Saengkrit, et al., Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy, Colloids Surf. B Biointerfaces 114 (2014) 349–356.

[106] Y. Cai, et al., Porous microsphere and its applications, Int J. Nanomed. 8 (2013) 1111–1120.
[107] H. Bhatt, et al., Influence of molecular interactions on structure, controlled release and cytotoxicity of curcumin encapsulated chitosan - Silica nanostructured microspheres, Colloids Surf. B Biointerfaces 208 (2021), 112067.
[108] L. Wang, et al., Curcumin derivative WZ35 inhibits tumor cell growth via ROS-YAP-JNK signaling pathway in breast cancer, J. Exp. Clin. Cancer Res 38 (1) (2019) 460.
[109] R. Li, et al., Transcriptome investigation and in vitro verification of curcumin-induced HO-1 as a feature of ferroptosis in breast cancer cells, Oxid. Med Cell Longev. 2020 (2020), 3469840.
[110] X. Tang, et al., Curcumin induces ferroptosis in non-small-cell lung cancer via activating autophagy, Thorac. Cancer 12 (8) (2021) 1219–1230.
[111] P. Chen, et al., Curcumin overcome primary gefitinib resistance in non-small-cell lung cancer cells through inducing autophagy-related cell death, J. Exp. Clin. Cancer Res 38 (1) (2019) 254.
[112] J. Zhu, et al., GPC3-targeted and curcumin-loaded phospholipid microbubbles for sono-photodynamic therapy in liver cancer cells, Colloids Surf. B Biointerfaces 197 (2021), 111358.
[113] Z. Deng, et al., Synergistic anti-liver cancer effects of curcumin and total ginsenosides, World J. Gastrointest. Oncol. 12 (10) (2020) 1091–1103.
[114] S. Sun, H. Fang, Curcumin inhibits ovarian cancer progression by regulating circ-PLEKHM3/miR-320a/SMG1 axis, J. Ovarian Res 14 (1) (2021) 158.
[115] S. Ghaderi, et al., Gemini curcumin suppresses proliferation of ovarian cancer OVCAR-3 cells via induction of apoptosis, Anticancer Agents Med Chem. 21 (6) (2021) 775–781.
[116] K.M. Terlikowska, et al., Potential application of curcumin and its analogues in the treatment strategy of patients with primary epithelial ovarian cancer, Int J. Mol. Sci. 15 (12) (2014) 21703–21722.
[117] M.C. Mentella, et al., Cancer and mediterranean diet: a review, Nutrients 11 (2019) 9.
[118] F. Plotti, et al., Diet and chemotherapy: the effects of fasting and ketogenic diet on cancer treatment, Chemotherapy 65 (3–4) (2020) 77–84.
[119] P. Anand, et al., Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature, Biochem Pharm. 76 (11) (2008) 1590–1611.