J Appl Biotechnol Rep. 2025 March;12(1):1517-1527

Journal of
Applied Biotechnology Reports

doi 10.30491/jabr.2024.455865.1728

Systematic Review

Effectiveness of Curcumin as a Low-cost Adjuvant Alternative to Vaccines in the Treatment of Human Papillomavirus-induced Cervical Cancer: A Systematic Review of *In vitro* and *In vivo* Studies

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Received May 5, 2024; **Accepted** August 27, 2024; **Online Published** March 20, 2025

Abstract

Introduction: Cervical cancer remains a significant public health concern, with high mortality rates among women despite available preventive, screening, and therapeutic approaches. Human papillomavirus (HPV) infections, particularly types 16 and 18, are primary factors in cervical cancer development. Curcumin, a bioactive polyphenolic compound from turmeric, has been extensively studied for its therapeutic effects against HPV-induced cervical cancer. This systematic review aims to evaluate the efficacy and mechanisms of curcumin as an affordable dietary supplement alternative to vaccines in treating HPV-associated cervical cancer.

Materials and Methods: This systematic review was conducted following the PRISMA guidelines. We searched PubMed, ISI Web of Science, and Scopus using keywords such as "HPV," "curcumin," and "cervical cancer" without time and language restrictions. Two researchers independently performed data extraction and quality assessment based on predefined criteria.

Results: Out of 105 initially identified articles, 22 met the inclusion criteria. The findings suggest that curcumin selectively inhibits the expression of viral oncogenes E6 and E7, mediators and growth-inducing factors, migration, and induces cell cycle arrest and apoptosis in cervical cancer cells.

Conclusions: Curcumin shows promise in influencing apoptosis, migration, and invasion of cervical cancer cells through various regulatory mechanisms. These preclinical findings suggest a potential basis for future research on curcumin as a therapeutic agent for HPV-associated cervical cancer.

Keywords: HPV, Curcumin, Cervical Cancer

Citation: Alavian F, Ghiasvand S. Effectiveness of Curcumin as a Low-cost Adjuvant Alternative to Vaccines in the Treatment of Human Papillomavirus-induced Cervical Cancer: A Systematic Review of *In vitro* and *In vivo* Studies. J Appl Biotechnol Rep. 2025;12(1):1517-1527. doi:10.30491/jabr.2024.455865.1728

Introduction

Cervical cancer is the third most common type of cancer and the fourth leading cause of mortality among women. Annually, 310,000 individuals worldwide lose their lives due to this disease, thus seriously threatening women's lives and health.[1,2] The occurrence of cervical cancer is strongly associated with persistent infections with human papillomavirus (HPV), especially HPV types 16 and 18. Of the 200 types of HPV, over 50% and 13% of cervical cancers are associated with HPV 16 and HPV 18, respectively. Studies have shown that the integration of this virus's DNA into host cells leads to significant alterations in many downstream signaling pathways, resulting uncontrolled cell proliferation and viral infection progression.[3,4] Over prolonged infection periods, these alterations result in malignant progression and cancer in various parts of the reproductive organs. Although early-stage cervical carcinoma is treatable, it becomes resistant to available treatment options in later stages. Furthermore, recurrent cervical cancer exhibits a poor prognosis.[5]

By examining various cellular signaling pathways and their alterations in cervical cancer, it becomes evident that different mechanisms are involved in cancer progression and invasion. These mechanisms overcome checkpoints in the cell cycle, evade chemotherapy strategies, and develop drug resistance in cancer cells. These are just some of the mechanisms elucidated to date explaining why therapeutic interventions, although harmful to cancer cells, have largely failed in achieving therapeutic success; hence, auxiliary factors capable of providing specific toxicity to cancer cells or synergistic effects with nonspecific and harmful chemical agents are highly needed.[6]

In addition to incomplete efficacy, conventional chemotherapy methods are expensive, highly nonspecific,

and invasive, leading physicians to discontinue treatment due to off-target cell toxicity and severe pathological side effects. This situation creates conditions for cancer cells to develop resistance. The development of resistant and metastatic cancers heralds arduous treatment options that ultimately lead to severe complications and death.[7] The use of the HPV (Human Papillomavirus) vaccine is expected to reduce cervical cancer incidence. Early screening with HPV vaccination has reduced cervical cancer incidence in developed countries, but in low- and middle-income countries with low HPV vaccination coverage, cervical cancer rates continue to rise.[8] Traditional tumor treatments (surgery, chemotherapy, radiotherapy, etc.) are only effective in the early stages of cervical cancer and are not effective in treating advanced cervical cancer.[9] Therefore, finding new mechanisms, new targets, and new methods for cervical cancer treatment is of great practical importance. Replacing the current treatment method with a safe, natural product-based approach would be a suitable option.

Curcumin is a type of polyphenolic compound that has garnered significant attention due to its anti-inflammatory, antioxidant, anti-tumor, antibacterial, and other pharmacological effects.[10] It has recently been found that curcumin, as a common dietary supplement, has a considerable therapeutic effect in treating cervical cancer.[8] Multiple *in vitro* and *in vivo* studies have shown that curcumin can significantly inhibit proliferation and migration, induce apoptosis, and induce autophagy in tumor cells, thereby demonstrating notable efficacy in treating cervical cancer.[11,12] Interestingly, curcumin has been introduced as the third generation of cancer-preventive drugs in the United States.[8] What has been established is that curcumin has a wide range of mechanisms against cervical cancer and may become a new anti-tumor drug in the future, generating new ideas for further cancer research. Considering the lack of systematic studies on the effects of curcumin against cervical cancer, this review study was designed to provide comprehensive information on the mechanism-based effects of curcumin against cervical cancer. In this review study, we attempted to provide brief and comprehensive information on the intervention of curcumin in the prevention and treatment of HPV-induced cervical cancer.

Materials and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews guidelines and includes articles published between 2005 and 2023, with no language restrictions.[13] Figure 1 provides an overview of the stages involved in the study design.

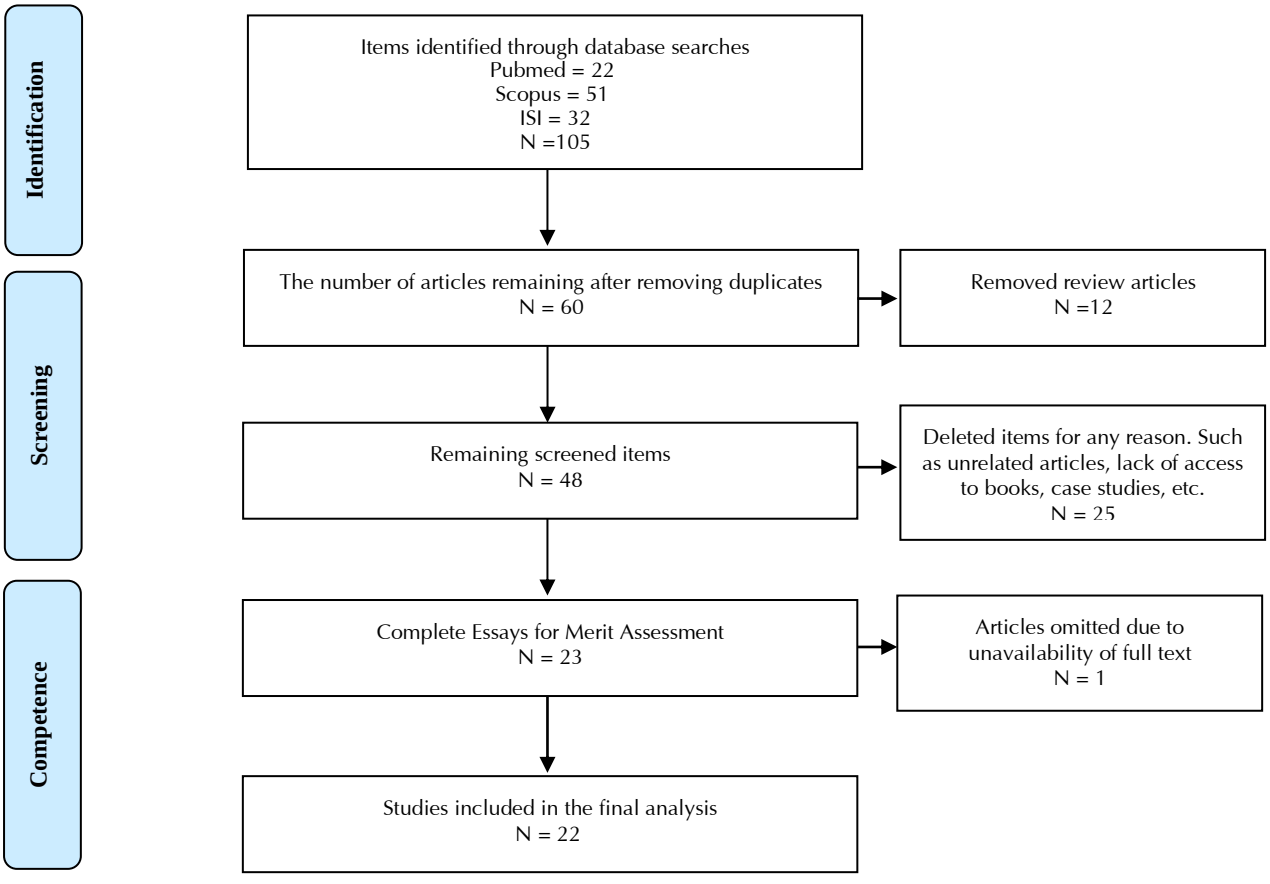

Figure1. Flowchart of the Steps of the Article Selection Method.

PICO Components

Population (P): Individuals with HPV-induced cervical cancer.
Intervention (I): Treatment with curcumin.
Comparison (C): Studies without curcumin treatment or with different interventions.
Outcome (O): Effectiveness of curcumin in treating HPV-induced cervical cancer.

Search Strategy

A comprehensive literature search was conducted to identify studies investigating the use of curcumin in the treatment of HPV-induced cervical cancer, both in laboratory settings and *in vivo*. The PubMed, Web of Science (ISI), and SCOPUS databases were systematically searched for relevant articles published until August 2023, without any language limitations.

PubMed Search Strategy

(Curcumin [Mesh] OR Curcumin [tiab]) AND (“Human Papillomavirus Viruses” [Mesh] OR “Human Papillomavirus Viruses” [tiab] OR “Papillomavirus Virus, Human” [tiab] OR “Human Papillomavirus” [tiab] OR “HPV, Human Papillomavirus Viruses” [tiab] OR “Human Papillomavirus, HPV” [tiab]) AND ("Uterine Cervical Neoplasms" [Mesh] OR "Uterine Cervical Neoplasms" [tiab] OR "Cervical Neoplasm, Uterine" [tiab] OR "Cervical Cancer" [tiab] OR "Cancer, Cervical" [tiab] OR "Uterine Cervical Cancer" [tiab] OR " Cervical Cancer, Uterine" [tiab] OR "Cancer, Uterine Cervical" [tiab] OR "Cancer of Cervix" [tiab] OR "Cervix Cancer" [tiab] OR "Cancer, Cervix" [tiab] OR "Neoplasms, Cervix" [tiab] OR "Cervix Neoplasm" [tiab] OR "Cancer of the Uterine Cervix" [tiab] OR "Cancer of the Cervix" [tiab]).

Scopus Search Strategy

(TITLE-ABS-KEY (Curcumin)) AND (TITLE-ABS-KEY (“Human Papillomavirus Viruses”) OR TITLE-ABS-KEY (“Papillomavirus Virus, Human”) OR TITLE-ABS-KEY (“Human Papillomavirus”) OR TITLE-ABS-KEY (“HPV, Human Papillomavirus Viruses”) OR TITLE-ABS-KEY (“Human Papillomavirus, HPV”)) AND (TITLE-ABS-KEY ("Uterine Cervical Neoplasms") OR TITLE-ABS-KEY (“Cervical Neoplasm, Uterine") OR TITLE-ABS-KEY ("Cervical Cancer") OR TITLE-ABS-KEY ("Cancer, Cervical") OR TITLE-ABS-KEY ("Uterine Cervical Cancer") OR TITLE-ABS-KEY (“Cervical Cancer, Uterine”) OR TITLE-ABS-KEY (“Cancer, Uterine Cervical”) OR TITLE-ABS-KEY (“Cancer of Cervix”) OR TITLE-ABS-KEY (“Cervix Cancer”) OR TITLE-ABS-KEY (“Cancer, Cervix”) OR TITLE-ABS-KEY (“Neoplasms, Cervix”) OR TITLE-ABS-KEY (“Cervix Neoplasm”) OR TITLE-ABS-KEY (“Cancer of the Uterine Cervix”) OR TITLE-ABS-KEY (“Cancer of the Cervix”).

ISI Search Strategy

(TS=(Curcumin)) AND (TS=(“Human Papillomavirus Viruses”) OR TS=(“Papillomavirus Virus, Human”) OR TS=(“Human Papillomavirus”) OR TS=(“HPV, Human Papillomavirus Viruses”) OR TS=(“Human Papillomavirus, HPV”) AND (TS=("Uterine Cervical Neoplasms") OR TS=(“Cervical Neoplasm, Uterine") OR TS=("Cervical Cancer") OR TS=("Cancer, Cervical") OR TS=("Uterine Cervical Cancer") OR TS=(“Cervical Cancer, Uterine”) OR TS=(“Cancer, Uterine Cervical”) OR TS=(“Cancer of Cervix”) OR TS=(“Cervix Cancer”) OR TS=(“Neoplasms, Cervix”) OR TS=(“Cervix Neoplasm”) OR TS=(“Cancer of the Uterine Cervix”) OR TS=(“Cancer of the Cervix”).

Data Extraction

Following the extraction of articles, their titles and abstracts were independently reviewed by the authors (F.A & S.GH) to identify relevant articles. Subsequently, the full texts of potentially relevant articles were evaluated to determine their suitability for inclusion in the present paper. Any discrepancies were resolved by the authors before final decisions were made.

Inclusion Criteria

The studies considered in this paper had to address at least curcumin, HPV, and cervical cancer under either laboratory or *in vivo* conditions.

Exclusion Criteria

Studies focusing on combined therapies involving curcumin with other substances were excluded from this study. Additionally, studies concerning other types of cancer and factors unrelated to HPV were omitted from the analysis. Review articles were only utilized to identify relevant articles missed in the initial search strategy. One article was excluded due to the unavailability of its full text.

Quality Assessment

The quality of each article was independently assessed by the authors (F.A @ S.GH) using modified NIH and QualSyst quality assessment tools (Table 3).[14]

PRISMA Checklist

To further enhance clarity, we have included a PRISMA checklist in supplementary files to better visualize our screening and selection process.

Statistical Analysis

Given the significant differences in how the key variables were assessed and the primary outcomes were defined across the included studies, we determined that a meta-analysis would not be a suitable approach for synthesizing the results.

Results

The initial investigation covered 105 articles, of which, after initial review, 22 articles met the inclusion criteria and were included in the final analysis (Figure 1).

The summary of features extracted from these articles is presented in Table 1 (virus type and identification method, investigation of curcumin toxicity, curcumin mechanism of action, and therapeutic outcomes) and Table 2 (*In vivo* and *in vitro* analysis). According to the results presented in the tables, the majority of studies conducted on the subject of

Table 1. Key Details of Studies Included in the Current Review

No.	Study location	HPV type	HPV identification method	Curcumin toxicity assessment method and outcome	Outcomes Assessed	Ref
1	India	HPV16 and HPV18	PCR, Northern blotting, EMSA, and Western blotting	MTT assay (selective toxicity against cancer cells).	Selective suppression of HPV18 transcription, reduced AP-1 transcription factor binding, decreased c-fos expression, reduced p53 expression, and increased fra-1 expression.	15
2	India	HPV16 and HPV18	Antibodies, RT-PCR, and Western blotting against viral oncogenes E6 and E7.	. Curcumin cytotoxic effect on cervical cancer cells identified through MTT assay.	Cellular proliferation inhibition, apoptosis induction in cancer cells, selective inhibition of viral oncogene E6 and E7 expression. Reduced NFκB activation from TNFα. Decreased COX-2 expression, AP-1 inhibition, and its binding reduction.	16
3	USA	HPV16	Antibodies against HPV 16 E7 and RT-PCR for HPV16 E6 and HPV16 E7	Curcumin effect on cell survival determined by flow cytometry.	Tumor inhibition and suppression of cancer cell growth, apoptosis induction and cell death, cellular migration inhibition, HPV16 E6/E7 transcriptional inhibition, and restoration of tumor-suppressive proteins p53 and PTPN13 expression; and suppression of HPV E7 oncoprotein increase due to BaP.	17
4	India	HPV16 and HPV18	Western blotting and flow cytometry	ND	Telomerase (hTERT) inhibition, reduction of p53 downregulating factors, cancer cell proliferation reduction, cytochrome c release induction, apoptosis induction via Bax, AIF regulation, and caspase 3 and 9 activity increase, negative regulation of anti-apoptotic factors Bcl-2, Bcl-XL; and negative regulation of Hsp 70, COX-2, Inos, and cyclin D1.	18
5	India	HPV16 and HPV18	PCR-ELISA kit PCR-ELISA kit, Western blotting, and immunohistochemistry	Flow cytometry and MTT assay	Inhibition of estradiol proliferative effects, apoptosis induction, telomerase activity reduction, PCNA levels reduction, cyclin D1 reduction, positive regulation of E6 and E7 oncoproteins via estradiol in HPV-infected cervical cancer cell lines.	19
6	USA	HPV 16, HPV 18, and HPV68	Western blotting and immunofluorescence	WST-1 assay Selective elimination of HPV cancer cells	Elimination of cervical cancer cells in culture, E6 antigen suppression, significant EGFR expression reduction, and simultaneous p53 induction	20
7	India	ND	Western blotting	Resazurin reduction assay Toxicity induction against cancer cells	TGF-β signaling downregulation, cellular migration inhibition, growth suppression, balancing tumorigenic effects of TGF-β with migration inhibition due to TGF-β.	21
8	India	HPV 16	Antibodies against E6 and E7	Flow cytometry and MTT assay Cancer cell sensitization.	HPV inhibition, increased p53 expression, and cell cycle arrest at the G1-S phase	22
9	Malaysia	HPV16 and HPV18	RT-PCR for viral oncogenes E6 and E7	MTT assay Selective toxicity against replication and apoptosis induction in cervical cancer cells.	Apoptosis and reduced E6 and E7 oncoprotein expression in HPV16 and HPV18-infected cervical cancer cells.	23
10	USA	ND	Western blotting and qRT-PCR	Flow cytometry	Cellular growth inhibition, apoptosis induction, and cell cycle arrest, reduction of BaP (a cigarette component) oncogenic effects by IL-6 expression reduction	24
11	USA	HPV18	ND	Curcumin is toxic to HPV-18-infected HeLa cells.	Increased dose-dependent necrosis and apoptosis of HeLa cells with increased curcumin concentration.	25
12	India	HPV16	Fluorescent-labeled specific antibodies and qPCR.	ND	AP-1 activity reduction, decreased c-Fos and c-jun expression, Fra-1 induction, loss of cell proliferation ability, apoptosis induction, and weak tumorigenicity of cells.	26
13	Malaysia	HPV16 and HPV18	qRT-PCR	ND	Cytotoxic activity, anti-proliferative, apoptosis induction, increased cell adhesion, upregulation of anti-cancer genes, and downregulation of cancer-causing genes	27
14	Chile	HPV16	qRT-PCR	MTS assay	Cellular migration reduction in cervical cancer cells.	28

15	Germany	HPV16 and HPV18	ND	MTT assay Toxicity elimination by encapsulating liposomal curcumin.	Significant reduction in cellular migration abilities, and apoptosis induction; also, increased tumor cell death.	29
16	Mexico	ND	Western blotting	MTT assay Selective toxicity against cancer cells.	Increased half-life and p53 level, increased NQO1 and P21 levels (p53 receptor); and increased p53-NQO1 interaction.	30
17	Iran	HPV16 and HPV18	Elisa and antibody use.	MTT assay Selective toxicity against tumor cells, higher than curcumin in nanoform.	Tumor growth reduction.	31
18	USA	HPV18	Western blotting	-	p53 stabilization, proliferation halt, and apoptosis induction.	32
19	Iran	HPV16 and HPV18	RT-PCR and Western blotting	Flow cytometry and MTT assay	Significant reduction in cancer cell survival dependency. Inhibition of proliferation and apoptosis induction in HPV-infected cervical cancer cells with VEGF reduction.	33
20	India	Only mentioned E6 and E7 oncogenes	ND	Flow cytometry and MTT assay Selective cytotoxic activity against cervical cancer cells.	Cellular migration reduction, cell cycle arrest shift from the S phase to the G2/M phase, and EGFR expression reduction	34
21	Iran	HPV16 and HPV18	RT-PCR and Western blotting	Flow cytometry and MTT assay	Reduction in live cancer cell percentage, apoptosis induction, E6, and E7 expression inhibition, and increased P53 and Rb expression	35
22	China	HPV16 and HPV188	Western blotting	MTT assay	Apoptosis induction, dose- and time-dependent growth inhibition, cellular migration inhibition Expression inhibition of Bcl-2 ،N-cadherin and Vimentin ،expression induction of C-Bax, caspase-3, E-cadherin and P53 and selective inhibition of viral Oncoproteins E6 and E7	36

Electrophoretic mobility shift assay (EMSA), epidermal growth factor receptor (EGFR), Benzo[a]pyrene (BaP), Reverse transcription-quantitative real-time polymerase chain reaction (Qrt-PCR), Quantitative real-time PCR (qPCR), NAD (P) H: Quinone oxidoreductase 1 (NQO1), Real-Time PCR (RT- PCR), Human dermal fibroblast cells (ATCC), proliferating cell nuclear antigen (PCNA), human telomerase reverse transcriptase (hTERT), apoptosis-inducing factor (AIF), not determined (ND).

this research were carried out in India (8 cases). Additionally, 12 studies on both HPV16 and 18 viruses were conducted in one research, where HPV68 was also investigated in addition to 16 and 18. Four articles focused on HPV16, two on HPV18, and four did not directly specify the type of virus. The most common virus identification methods included PCR (various methods), Western blotting, and antibodies against viral oncoproteins E6 and E7. MTT assay was the predominant method for investigating curcumin toxicity. In cell culture, most studies were conducted on cervical carcinoma cell lines HeLa (16 cases), SiHa (10 cases), and CaSki (7 cases), and fewer studies were performed on other cell lines. Additionally, multiple cell culture environments were utilized in many cases. The longest response time after treatment was reported to be 14 days, while the shortest was 45 minutes. In animal and living environment models, three murine models, one rabbit model, and one human model were introduced. The age of specimens was reported in two cases, the method of use in three cases (vaginal, intratumoral, and intraperitoneal injection), and the number of specimens in two cases. The doses administered ranged from 5 nanomoles to 200 micromoles, with the most significant observed effects seen with doses ranging from 4 to 100 micromoles. Finally, based on some of the mechanisms of curcumin action in suppressing cervical cancer (resulting in apoptosis and programmed cell death, cell migration, autophagy induction, cell cycle arrest, etc.) reported in selected articles, the following can be noted: selective suppression of HPV18 transcriptional regulation, activation and binding of transcription factor AP-1, inhibition of EGFR expression, telomerase inhibition, downregulation of c-fos and c-jun expression, reduction of VEGF expression, reduction of PCNA levels, negative regulation of TGF-β signaling, inhibition of proliferation (by reducing cyclin D1 expression and cell cycle arrest in the G1-S phase), and induction of apoptosis in cancer cells, necrosis induction, cytochrome c release induction, inhibition of cell migration and increase in cell adhesion, selective inhibition of viral oncoproteins E6 and E7 expression. Reduction of TNFα-induced NFκB activation, reduction of BaP (a compound in cigarettes) oncogenic effects through decreased IL-6 expression, negative regulation of Hsp 70, negative regulation of Inos, reduction of COX-2 expression, reduction of Bcl-2, Bcl-XL, N-cadherin, and Vimentin expression, inhibition of estradiol proliferative effects, telomerase activity reduction, increase in tumor suppressor protein p53 expression and its lifespan, increase in Rb, fra-1, AIF (apoptosis-inducing factor) expression, Bax increase, increase in caspase 3 and 9 activity, and effective cytotoxic activity targeting cervical cancer cells.

Quality Assessment: The quality of each article was independently evaluated by the authors using modified NIH and QualSyst quality assessment tools (maximum score: 30) (Table 3).[14] Quality assessment findings related to the articles included in the study are presented in Table 3. Scores of 25 to 27 were considered excellent, scores of 20 to 24 were good,

Table 2. Conditions *In vitro* and *In vivo* Studies

	In vivo		*In vitro*				
No.	**Cell line and number**	**Incubation with Curcumin Dose and Optimal Action Time**	**Sample Age**	**Method Used**	**Number of Samples**	**Human or animal**	**Ref**
1	HPV16 and HPV18-positive Human Endometrial Carcinoma Cells (HeLa), N=130 tissue sample	Incubation with doses of 50, 100, and 200 micromoles. AP-1 binding activity decreases within 2 hours and completely disappears within 4 to 5 hours.	-	-	-	-	15
2	Human Cervical Cancer Cell Lines HeLa, SiHa, and C33A	Incubation with doses of 5, 10, 20, 40, and 60 micromoles. Curcumin showed a decrease in AP-1 binding activity to DNA within 45 minutes, and complete inhibition of binding activity within 1 hour.	-	-	-	-	16
3	HeLa and C33A Cell Lines	Incubation with doses of 10, 20, 40, and 80 micromoles. Optimal action time: 6 hours after treatment.	-	-	-	-	17
4	HeLa, SiHa, and CaSki Cell Lines	Incubation with doses of 50 and 100 micromoles. Optimal action time: 24 hours after treatment.	-	-	-	-	18
5	HeLa, SiHa, CaSki, and C33A Cell Lines	Incubation with doses of 25 and 50 micromoles. Optimal action time: 24 hours after treatment.	3 months,	Intravaginal injection	-	Mouse Model	19
6	ATCC, HeLa, ME-180, SiHa, and SW756 Cell Lines	Incubation with doses of 20, 40, 60, 80, and 100 micromoles. Optimal action time: 96 hours after treatment.	3 months,	Vaginal cream with concentrations of 2, 5, 10, and 20%	-	Mouse Model	20
7	SiHa and HeLa Cell Lines	Incubation with a dose of 15 micromoles for SiHa cells and 25 micromoles for HeLa cells. Optimal action time: 24 and 48 hours after treatment.	-	-	-	-	21
8	SiHa Cell Line	Incubation with doses of 0, 0.5, 1, 10, and 50 micromoles. Optimal action time: 24 hours after treatment.	-	-	-	-	22
9	HeLa and CaSki Cell Lines	Incubation with doses of 1.6, 3.1, 6.3, 12.5, 25, 50, and 100 micromoles. Optimal action time: 24, 48, and 72 hours after treatment.	-	-	-	-	23
10	Caski and SiHa Human Cervical Cancer Cell Lines	Incubation with doses of 2.5, 5, 10, 15, and 20 micromoles. Optimal action time: 24 and 48 hours after treatment	6 weeks,	Intratumoral injection of curcumin	-	Mouse Model	24
11	HeLa Cell Line	Incubation with doses of 50 and 100 micromoles. Optimal action time: 24 hours after treatment.	-	-	-	-	25
12	SiHa and C33a Cell Lines	Incubation with doses of 5, 15, and 25 micromoles. Optimal action time: 10 days after treatment.	8-10 weeks	Was announced in a table that could not be accessed	Was announced in a table that could not be accessed	Mouse Model	26
13	HeLa and CaSki Cell Lines	Incubation with doses of 4, 6, and 9 micromoles. Optimal action time: 24 hours after treatment.	-	-	-	-	27
14	SiHa Cell Line	Incubation with doses of 10, 20, and 30 micromoles. Optimal action time: 24 hours after treatment.	-	-	-	-	28
15	HeLa, HNSCC, and UD-SCC-2 Cell Lines	Incubation with doses of 0, 20, 40, 60, 80, and 100	-	-	-	Rabbit Model	29

		micromoles per liter. Optimal action time: 14 days after treatment.					
16	HeLa, SiHa, CaSki, and MDA-MB-231 Cell Lines	Incubation with doses of 10 and 20 micromoles. Optimal action time: 24 hours after treatment	-	-	-	-	30
17	C3 (Tumor) and HEK-293T (Non-Tumor) Cell Lines	Incubation with doses of 5, 10, 15, 20, 25, 30, 35, and 40 micromoles. Optimal action time: 3 and 16 hours after treatment	5-7 weeks,	Intraperitoneal administration	96 mice	Mouse Model	31
18	HeLa Cell Line	Incubation with doses ranging from 5 nanomoles to 20 micromoles. Optimal action time: 24 and 48 hours after treatment.	-	-	-	-	32
19	CaSki Cell Line	Incubation with doses of 67, 1.34, 2.5, 5, 10, 20, 40, and 80 micromoles. Optimal action time: 24, 48, and 72 hours after treatment.	-	-	-	-	33
20	HeLa Cell Line	96 hours after treatment.	-	-	-	-	34
21	HeLa Cell Line	Incubation with various doses of Nano curcumin - fibroblasts and Nano curcumin - HeLa cells. Optimal action time: 48 hours after treatment	-	-	-	-	35
22	HeLa & CaSki Cell Lines	Incubation with doses of 20, 40, and 60 micromoles, Optimal action time: 24 hours after treatment.	-	-	-	-	36

Low-grade intraepithelial lesion (LSIL), High grade squamous intraepithelial lesion (HSIL).

Table 3. Qualitative Assessment of Articles

ref	Quality	Score	Q15	Q14	Q13	Q12	Q11	Q10	Q9	Q8	Q7	Q6	Q5	Q4	Q3	Q2	Q1	
15	Excellent	27	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	P	Y	Y	1
16	Good	20	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	P	N	P	Y	2
17	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	3
18	acceptable	19	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	4
19	Excellent	27	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	P	Y	Y	5
20	Excellent	26	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	6
21	acceptable	19	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	P	Y	7
22	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	8
23	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	9
24	Good	24	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	10
25	Acceptable	15	Y	N	Y	Y	N	Y	P	N	Y	N	N	P	N	P	Y	11
26	Excellent	26	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	12
27	Acceptable	18	Y	N	Y	N	Y	Y	P	Y	Y	N	N	Y	N	P	Y	13
28	Good	21	Y	N	Y	Y	Y	Y	P	Y	Y	N	P	Y	N	P	Y	14
29	Good	24	Y	Y	Y	Y	N	Y	P	Y	Y	Y	P	Y	N	Y	Y	15
30	Acceptable	19	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	P	Y	16
31	Excellent	25	Y	Y	Y	Y	Y	Y	P	N	Y	Y	N	Y	Y	Y	Y	17
32	Acceptable	19	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	P	Y	18
33	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	19
34	Acceptable	17	Y	N	Y	Y	N	P	Y	Y	Y	N	N	P	N	P	Y	20
35	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	21
36	Good	21	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	22

Q: Question; Y: Yes (Score=2); P: PARTIAL (Score = 1); N: No (Score = 0)

Q1: Is the research question or objective clearly stated?

Q2: Is the study design clear and appropriate?

Q3: Is the study population clearly and fully described (e.g., age, sample size, etc.)?

Q4: Are the statistical methods or evaluation tools well described?

Q5: Are the entry and exit criteria for participation in the study specified?

Q6: Was the study conducted under In vivo conditions?

Q7: Was the study conducted under In vitro conditions?

Q8: Has the necessary time frame for reaching a specified result been determined?

Q9: Has the mechanism of action of curcumin been specified?

Q10: Has the exact type of virus been identified?

Q11: Has the virus identification method been specified?

Q12: Has the method of cellular toxicity assessment been specified?

Q13: Are the criteria for concluding valid and reliable?

Q14: Has the type of sample (human or animal) been specified?

Q15: Is the conclusion of the article supported by the results?

and scores of 15 to 19 were acceptable. In this review, all articles scored 15 or higher, indicating the favorable status of the selected articles.

Discussion

The findings of our study demonstrate that curcumin can effectively regulate apoptosis, migration, and invasion of cervical cancer cells through specific molecular mechanisms. The investigation revealed that curcumin impacts cervical cancer cells by selectively suppressing HPV18 transcriptional regulation, activating and binding transcription factor AP-1, inhibiting EGFR expression, and reducing telomerase activity. It also downregulates c-fos and c-jun expression, reduces VEGF and PCNA levels, negatively regulates TGF-β signaling, and inhibits proliferation by reducing cyclin D1 expression and inducing cell cycle arrest in the G1-S phase. Additionally, curcumin induces apoptosis in cancer cells, selectively inhibits viral oncoproteins E6 and E7 expression, reduces TNFα-induced NFκB activation, and mitigates BaP oncogenic effects through decreased IL-6 expression. It also negatively regulates Hsp 70 and Inos, decreases COX-2 expression, and reduces the expression of Bcl-2, Bcl-XL, N-cadherin, and Vimentin. Furthermore, curcumin inhibits the proliferative effects of estradiol, increases tumor suppressor protein p53 expression and its lifespan, upregulates Rb, fra-1, and AIF expression, enhances Bax expression, increases caspase 3 and 9 activity, and exhibits effective cytotoxic activity targeting cervical cancer cells.

Targeting molecular markers, especially in the process of invasion and metastasis treatment, prevents the occurrence and development of cervical cancer. The balance between tumor cell proliferation and apoptosis, as well as the induction or inhibition of certain signaling molecules and transcription factors, plays a vital role in regulating tumor cell growth.[37] Plant extracts are currently widely recognized, particularly for their unique effects on tumors. Curcumin, as a chemotherapeutic and preventive agent, has a high anticancer potential. This compound affects a wide range of cellular pathways and can have multiple functions (Figure 2). It has been reported that curcumin has good antitumor potential against malignancies such as breast cancer,[38,39] lung cancer,[40] liver cancer,[41] and ovarian cancer.[42,43] Curcumin possesses antioxidant, antibacterial, antifungal, antiviral, and anti-inflammatory effects. It reduces drug resistance, increases the sensitivity of chemotherapy-resistant cells, and enhances the antitumor effects of drugs at various cellular levels.[44,45] The multiple effects of curcumin stem from its ability to interact with various molecules, regulate multiple molecular pathways, and target their objectives. This chemical compound exerts its effects on cervical cancer by inducing apoptosis, inhibiting tumor cell proliferation, suppressing metastasis, inducing tumor cell autophagy, and affecting signaling pathways (Figure 2). The results of this study demonstrate that curcumin, as an anticancer drug, has a selective modulatory effect on the proliferation, apoptosis, and cellular signaling pathways of cervical cancer cells caused by HPV. However, the findings of Diwya et al. (2006) indicate that epigenetic regulators such as histone deacetylases and viral oncoproteins (E6/E7) are overexpressed in cervical cancer cells. These researchers demonstrated that curcumin is more cytotoxic to HPV 16 and HPV 18-infected cervical cancer cells than to non-infected cells. Indeed, one of the convincing properties of curcumin that makes it suitable for therapeutic use is its low toxicity, such that even consumption of up to 10 grams per day does not cause any adverse effects.[46] Nevertheless, high doses of curcumin prevent the proliferation of cancer cells without harming healthy cells.[44] Curcumin can inhibit the transcription and translation of E6 and E7 genes, which may interfere with the binding of AP-1 to DNA. Increased DNA binding activity and expression of AP-1 components change with the severity of cervical lesions. It has been shown that the transcription factor AP-1 plays a major role in regulating the transcription of specific types of high-risk human papilloma-viruses such as HPV16 and HPV18, which are associated with the etiology of cervical cancer. Additionally, changes in the heterodimerization pattern of AP-1 towards c-Fos preferentially with JunB and conventional dimerization with c-Jun in both *in vivo* and *in vitro* studies worsen the malignant effects of AP-1 in tumor progression.[15,16] It appears that the heterodimer between c-Fos and c-Jun plays a central role in regulating the expression of viral oncogenes. Furthermore, in individuals with cervical cancer, there is a specific pattern of gradual increase in c-Fos and simultaneous decrease in fra-1 expression (tumor suppressor), which is consistent with the progression of this cancer.[47]

Other researchers have confirmed that curcumin increases the expression of tumor suppressor proteins p53, Rb, and PTPN13 (non-receptor tyrosine phosphatase 13). Moreover, it has been shown that curcumin inhibits the carcinogenic effects of benzo[a]pyrene, the primary carcinogen in tobacco, which is also associated with the inhibition of E7 protein expression.[17] Furthermore, since factors involved in proliferation, pro-inflammatory responses, and angiogenesis associated with aggressive tumor growth are regulated by the nuclear factor NFκB, factors that can inhibit NFκB activation have potential anticancer effects. Curcumin inhibits NFκB activation by preventing phosphorylation and degradation of IkBa.[16] Daiyan et al. (2011) demonstrated for the first time that exposure to Benzo [a] pyrene (BaP), a tobacco carcinogen, increases the expression of HPV E7 oncoprotein, indicating a molecular link between smoking and cervical cancer. Cigarette smoke and/or BaP activate both NFkB and AP-1 pathways in various cell types, either independently or through cross-talk between the two pathways. Crucially, curcumin reduces BaP-induced HPV

E7 oncoprotein expression by decreasing the activity of NFkB and AP-1.[17]

In addition to the aforementioned, estradiol has been identified as a risk factor for cervical cancer, acting synergistically with viral oncoproteins. Estradiol induces HPV proliferation in HeLa, SiHa, and CaSki cell lines. E6, an HPV-encoded oncoprotein, mediates the degradation of the tumor suppressor factor p53 via ubiquitination. One hypothesis establishing the role of estradiol as a risk factor in cervical cancer suggests it increases E6 and E7 expression, thus potentially acting as a carcinogen.[19] To demonstrate the synergistic role of estradiol, Singh et al. (2011) pretreated cervical cancer cell lines with estradiol. Their results showed increased expression of telomerase, viral oncoproteins E6, E7, PCNA, p16, and cyclin D1, resulting in inhibition of apoptosis and uncontrolled cell proliferation. However, after treatment with curcumin, it was able to suppress the proliferative response to estradiol, induce apoptosis, and inhibit cyclin D1. Cyclin D1 plays a crucial role in transitioning cells from the G1 phase to the S phase of the cell cycle, and its overexpression has been considered a significant marker for monitoring cervical cancer progression.[19]

Finally, in addition to the aforementioned destructive effects of curcumin on tumor cells, previous studies have shown that this compound has significant protective effects on normal body cells. Indeed, curcumin reduces cellular toxicity in normal cells. Tumor cells show preferential uptake of curcumin compared to normal cells; such that in one study, the uptake and fluorescence intensity of curcumin in tumor cells were significantly higher compared to normal cells. This effect may be due to differences in the membrane structure of normal and cancer cells, as well as the larger size and composition of proteins in cancer cells.[48]

Ultimately, the protective mechanisms of curcumin against cervical cancer are much broader than those mentioned in this article. However, what is undeniable is that curcumin can be used as an effective agent in inhibiting and controlling cancers, improving clinical symptoms, and preventing tumor proliferation and metastasis. This fundamental study provides a basis for future research on the prevention and treatment of cervical cancer.

Strengths and Limitations

Strengths

Curcumin is an affordable and readily available dietary supplement that can potentially be used for daily consumption.

Limitations

- The primary studies included in this review may be subject to various sources of bias, such as selection bias, performance bias, and diagnosis bias, which affect the validity and reliability of the findings.
- The review methods used, including literature search, study selection, and data extraction, may have introduced potential biases that could affect the results obtained.
- Curcumin has known limitations, such as poor water solubility, rapid metabolism, and low bioavailability, which limit its therapeutic potential.
- The number of *in vivo* studies included in the review was limited (only 7) and more studies under these conditions are needed to further evaluate the efficacy of curcumin in cervical cancer models.

Conclusion

Our research suggests that curcumin may play a role in regulating apoptosis, migration, and invasion of cervical cancer cells, potentially through the modulation of carcinogenic and anti-cancer genes. However, these findings are based on preclinical evidence, and further research is necessary to confirm these mechanisms in clinical settings.

Several questions regarding curcumin remain unanswered. Firstly, there is a need for more clinical trials to evaluate the efficacy of curcumin in cancer treatment, particularly for cervical cancer. Secondly, it is important to investigate whether curcumin derivatives and analogs offer improved therapeutic effects compared to curcumin itself. Thirdly, new combinations of curcumin should be developed to enhance its effectiveness. Fourth, the optimal dosing of curcumin for cervical cancer treatment needs to be determined. Fifth, exploring the potential of curcumin in combination with other anti-cancer therapies is a promising area for future research. Lastly, given the low bioavailability of curcumin, improved delivery methods, such as the use of nanoparticles, should be explored.

Therefore, while curcumin shows promise as a food additive and dietary supplement, further studies are required to determine its potential impact on cervical cancer within daily dietary regimes.

Authors' Contributions

Authors contributed equally to this work.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Acknowledgment

The authors would like to thank the valuable cooperation of the Research Vice-Chancellery of Farhangian University and the Research Vice-Chancellery of Malayer University. We would also like to extend our thanks to the artificial intelligence services that assisted with the translation of this manuscript. It is important to note that while artificial intelligence was utilized for translation purposes, the research content and findings presented in this article are

the sole result of the researchers' original work and investigation.

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