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REVIEW ARTICLE

Mechanisms and therapeutic applications of curcumin and its derivatives in head-and-neck squamous cell carcinoma

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Abstract

Primary head-and-neck squamous cell carcinoma (HNSCC) is a significant global health concern, strongly associated with smoking, alcohol consumption, human papillomavirus infection (particularly in oropharyngeal cancer), and carcinogen exposure. The term "head-and-neck cancer" broadly encompasses malignancies of the head-and-neck region, including nasopharyngeal and oral cancers. Due to its complex anatomy and occult nature, most patients are diagnosed at an advanced local stage (Stage III/IV). Treatment frequently results in recurrence and metastasis, leading to poor 5-year survival rates. Curcumin, an extract from traditional Chinese medicine, exhibits anti-inflammatory, antioxidant, and multitargeted anticancer activities. Compared to conventional formulations, curcumin derivatives demonstrate enhanced stability, solubility, and pharmacokinetics, offering therapeutic potential in HNSCC. This review highlights recent advancements in the antitumor mechanisms of curcumin and its derivatives in primary HNSCC. The objective is to provide innovative insights that could inform the development of more comprehensive and effective treatment strategies for HNSCC. A comprehensive search of the PubMed database was conducted using advanced filters and Boolean logic with relevant Medical Subject Headings terms and keywords, covering publications from 1987 to April 17, 2025. After screening titles and abstracts, 272 publications were selected, including 158 published in the last decade and 85 within the past 5 years. Curcumin and its derivatives demonstrate antitumor properties by disrupting the cell cycle, inducing apoptosis, modulating key signaling pathways, inhibiting invasion and metastasis, regulating epigenetic activities, and inducing oxidative stress and autophagy. They also show synergy with radiochemotherapy, immunotherapy, and photodynamic therapy. Their multifaceted antitumor properties and favorable safety profiles underscore their potential as effective adjuvant therapies in the treatment of HNSCC.

Keywords: Curcumin; Head-and-neck squamous cell carcinoma; Antitumor mechanism; Derivatives; Drug delivery

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1. Introduction

Head-and-neck cancer, comprising cancers of the oral cavity, nasal cavity, pharynx, and larynx, accounts for the sixth-highest incidence of malignant tumors worldwide. According to recent global data, there are approximately 800,000 new cases of head-and-neck cancer and more than 400,000 associated mortalities annually. A substantial proportion of head-and-neck cancers are classified as head-and-neck squamous cell carcinoma (HNSCC), constituting over 90% of cases. The 5-year survival rate for patients presenting with advanced-stage HNSCC is <50%.[1,2] Despite recent advancements in the treatment of HNSCC, the high cost of treatment and the presence of drug resistance in some patients have limited improvements in overall survival.[3]

Curcumin, a natural polyphenolic acidic compound extracted from the rhizomes of *Curcuma longa* in the family Zingiberaceae, has low toxicity and broad-spectrum antitumor activity. It has demonstrated potential in the treatment of HNSCC.[4-6] However, curcumin exhibits limited solubility, poor stability, and low bioavailability, which limits its clinical application. Two improvement strategies have been identified. The first strategy involves the optimization of the chemical structure of curcumin, i.e., the synthesis of curcumin derivatives via chemical modifications (e.g., the introduction of hydroxyl, methoxy, and other functional groups), which can improve its water solubility and targeting properties. The second strategy focuses on enhancing delivery methods, such as using nanocrystals, liposomes, and solid dispersions as carriers. These approaches can enhance the bioavailability of curcumin and thus its efficacy in HNSCC therapy.[6,7]

This review provides a synopsis of the pertinent mechanisms of curcumin and its derivatives in the context of HNSCC, along with their potential for clinical application over the past decade. The search strategy and study selection framework are illustrated in Figure 1. Specifically, a systematic search of the PubMed database was conducted using advanced filters and Boolean logic with relevant Medical Subject Headings terms and keywords, covering publications from 1987 to April 17, 2025. The search strategy is as follows: ((("Squamous carcinoma of the head and neck" [tw]OR "Head and Neck Squamous Cell Carcinoma"[tw] OR HNSCC[tw] OR "Squamous Cell Carcinoma of Head and Neck"[Mesh]) OR ("nasopharyngeal carcinoma"[tw] OR "cancers of the nose and throat"[tw] OR NPC[tw] OR "Nasopharyngeal Carcinoma"[Mesh]) OR ("laryngeal cancer"[tw] OR laryngocarcinoma[tw] OR "laryngeal carcinoma"[tw] OR "cancer of the larynx"[tw] OR "throat cancer"[tw] OR "Laryngeal Neoplasms"[Mesh]) OR ("tongue cancer"[tw] OR "carcinoma of the tongue"[tw] OR "Tongue Neoplasms"[Mesh]) OR ("oral cancer"[tw] OR "mouth cancer"[tw] OR "oral cavity cancer"[tw] OR "oral cavity carcinomas"[tw] OR "Mouth Neoplasms"[Mesh]) OR ("gum cancer"[tw] OR "gingival cancer"[tw] OR "carcinoma of gingiva"[tw] OR "carcinoma of the gingiva"[tw]) OR ("epiglottic cancer"[tw] OR "carcinoma of epiglottis"[tw])) AND (curcumin[tw] OR "Curcumin derivatives*" [tw] OR "Curcumin derivative"[tw] OR "Curcumin"[Mesh])) NOT (review[Publication Type]). After screening titles and abstracts, 272 publications were selected, including 158 published within the last decade and 85 within the past 5 years. The objective is to establish a systematic framework for the study of curcumin-based treatments for HNSCC, thereby facilitating the identification of novel concepts for subsequent research (Table 1).

2. Inhibition of cell cycle progression

The cell cycle comprises the interphase (G1, S, and G2) and division (M) phases, and its operation is closely related to the proliferation of cell populations. A multitude of studies have demonstrated that curcumin and its derivatives possess the capacity to impede the proliferation of HNSCC cells and elicit anticancer effects.[8-13] These effects are primarily mediated through regulating the cell cycle-related protein expressions and affecting cellular energy metabolism and signaling pathways. Consequently, HNSCC cells are arrested in the G1/S or G2/M phase.

S-phase kinase-related protein 2 (SKP2) is a proto-oncogenic protein, and its expression has been demonstrated to influence the onset and progression of HNSCC. SKP2 facilitates cell cycle progression through the ubiquitin-mediated degradation of the G1 checkpoint cyclin-dependent kinase (CDK) inhibitors p21 (encoded by *CDKN1A*) and p27 (encoded by *CDKN1B*). In the study by Khan *et al.*,[14] HNSCC cell lines (human papillomavirus-positive [HPV^+] and HPV^-) were treated with curcumin, resulting in the downregulation of SKP2 expression and a concomitant upregulation of the activities of p21 and p27. In addition, the study also found that phosphorylation of the retinoblastoma protein was inhibited, thereby blocking the G1/S phase transition. Similarly, Feng *et al.*[15] discovered that curcumin impeded SKP2 expression by increasing the expression of microRNA-7. Conversely, Shao *et al.*[16] reported that curcumin impeded the proliferation of nasopharyngeal carcinoma (NPC) cells by modulating survivin, cyclin D1, p53, and p21.

Further studies have demonstrated that curcumin induces G2/M phase arrest by inhibiting cyclin B1/CDK1 complex activity and reducing cell division cycle 25 phosphatase expression, thereby suppressing cell

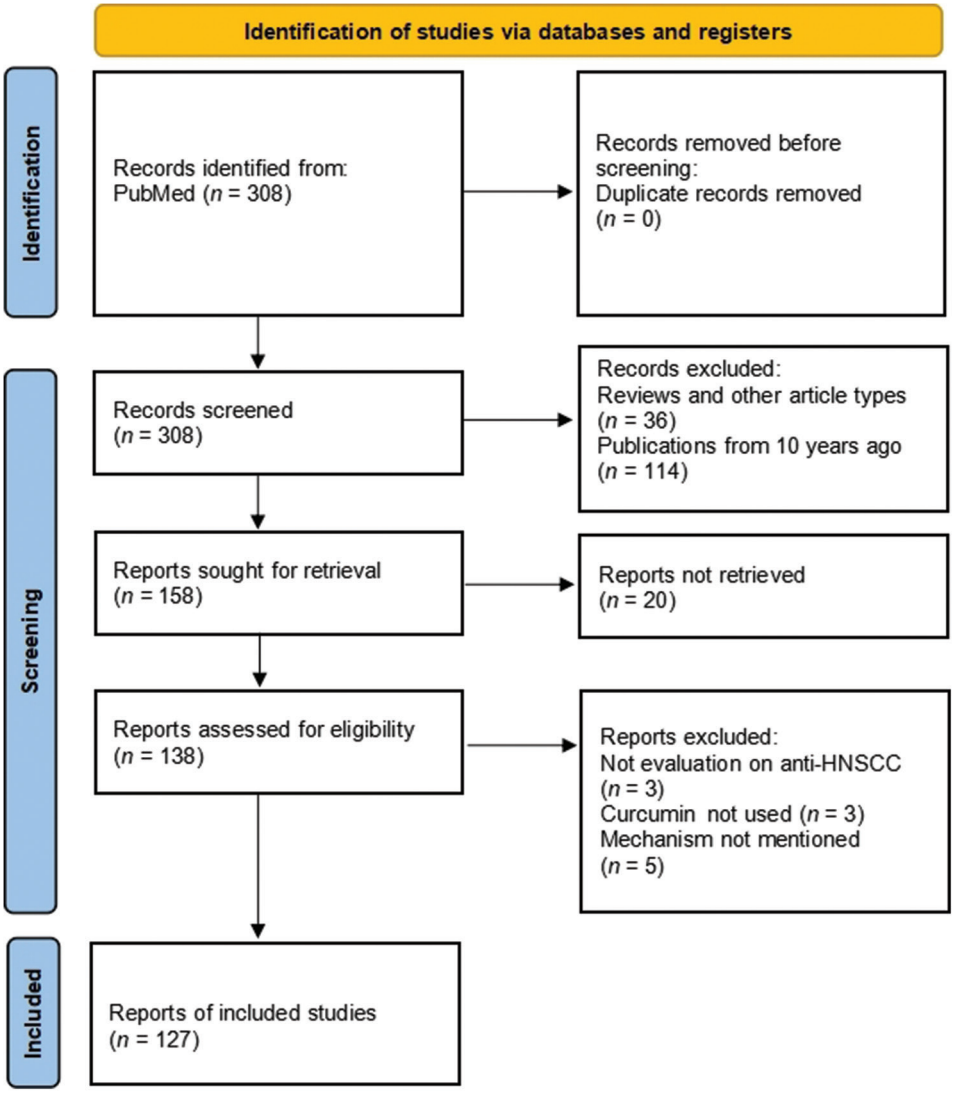

Figure 1. Framework for the identification of studies via databases and registers
Abbreviation: HNSCC: Head-and-neck squamous cell carcinoma.

proliferation.[7] For example, Liu *et al.*[17] treated different HNSCC cell types with the curcumin derivative WZ37 and found G2/M cycle arrest across all cell lines. Similarly, Su *et al.*[18] investigated the curcumin derivative FLLL32 in oral cancer cells and observed an augmentation in the proportion of cells in the G2/M phase. Hanna and Saad[19] demonstrated that nanocurcumin selectively inhibited Hep-2 cell growth in a dose- and time-dependent manner, with the most potent half-maximal inhibitory concentration (IC_{50}) value (17 ± 0.31 μg/mL) achieved after 48 h. The results indicated G2/M phase arrest and an increase in apoptotic cells in the sub-G1 phase. In contrast, curcumin exhibited no cytotoxic effects on normal cells. In a separate study, Liu *et al.*[20] observed that the curcumin derivative T63 induced G2/M phase arrest and reduced the viability of CNE2 and CNE2R cells after 48 h. Similarly, Chien *et al.*[21] found that the curcumin derivative GO-Y078 exerted a cytostatic effect on OSCC cells, attributable to G2/M phase blockage. Besides, Liu *et al.*[17] also observed a dose-dependent cytotoxic effect of curcumin lipid nanoemulsion on oral squamous carcinoma cells, with a gradual decrease in the proportion of cells in the proliferative phase (S + G2/M) over time. Finally, Ma *et al.*[22] discovered that the curcumin derivative AC17 induced cellular arrest primarily by activating forkhead box protein O3 signaling pathways.

3. Induction of tumor cell apoptosis

Apoptosis is a form of programmed cell death, defined as an active process of cell death. It is important to note

Table 1. Mechanisms associated with the anti-head-and-neck squamous cell carcinoma effects of curcumin and its derivatives over the past 5 years

Experimental drugs	Tumor cells	Concentration of the drug	Regulatory mechanisms	References
Curcumin	SCC25 cells, FaDu cells, SCC090 cells	10, 20, 40 μM	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells	14
Curcumin	HN5 cells	24 h/48 h IC_{50} of 12.5 μM	Downregulation of BCL-2; Upregulation of the BAX/BCL-2 ratio; Upregulation of caspase-9 expression; Downregulation of STAT3 expression	26
Curcumin	SCC-9 cells	5, 10, 20, 40, 80 μg/mL	Inhibition of proliferation; Promotion of apoptosis; Upregulation of BAX/BCL-2 protein and mRNA expression in cells	36
Curcumin	AMC-HN4 cells	24 h IC_{50} of 0.5 μM	Induction of apoptosis, with non-toxicity to human normal thylakoid cells and human normal umbilical vein cells; Downregulation of c-FLIP and MCL-1; Upregulation of proteasome subunit α5 expression; Generation of ROS	39
Curcumin	PE/CA-PJ15 cells	0.5, 1.0, 3.37, 6.75 μM	Inhibition of proliferation; Promotion of apoptosis; Targets the pSTAT3 and NRF-2 signaling pathways; Upregulation of the chemosensitivity of cisplatin; Amelioration of cisplatin-induced ototoxic adverse effects	45
Curcumin	Hep2 cells, Hep2-max cells	48 h IC_{50} of 29.27 μM (Hep2), 22.78 μM (Hep2-max)	Enhancement of radiotherapy-induced DNA damage and apoptosis; Inhibition of proliferation; Inhibition of IKKγ expression; Inhibition of radiation-induced NF-κB activation; Upregulation of the expression of NF-κB downstream genes *BCL2L1, BCL2*, and *CCND1*	46
Curcumin	HSC-4 cells, Ca9-22 cells	10, 15, 20 μM	Inhibition of c-Met expression and ERK pathway; Inhibition of EMT and cell migration	70
Curcumin	SCC-25 cells	0, 2.5, 5, 10, 15, 30 μM	Decrease the expression of MMP-2 and MMP-9 to inhibit cancer cell invasiveness; Regulation of the expression of EMT markers, such as Snail, Twist, and E-cadherin; Induction of p53 expression	71
Curcumin	H357 cells	0, 10, 20, 30 μM	Coinhibition of nectin-4-mediated angiogenesis with PARP inhibitors; Association with PI3K-AKT-mediated nitroxide response	72
Curcumin	HSC-3 cells	48 h IC_{50} of 85 μM	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; Association with HIF-1α-mediated angiogenesis	73
Curcumin	Tu686 cells, AMCHN-8 cells	48 h IC_{50} of 20 μM	Inhibition of cell cycle progression; Promotion of apoptosis; Downregulation of FLNA expression by inhibiting E2F1, thereby suppressing the malignant phenotype and angiogenesis of cells	74
Curcumin	H-357 cells, SCC-9 cells	24 h IC_{50} of 10 μM (H-357), 11 μM (SCC-9)	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; Comodulation of the BER cascade with PARP inhibitors (BMN and olaparib) to enhance PARP capture activity	84
Curcumin	Tu212 cells	20 μM	Inhibition of radiation-mediated overexpression of GLUT1; Enhancement of cellular autophagy; Induction of apoptosis in tumor cells; Increment of radiosensitivity; Mediation of the AMPK–mTOR–MAPK–Beclin1 signaling pathway	92

(Cont'd...)

Table 1. ***(Continued)***

Experimental drugs	Tumor cells	Concentration of the drug	Regulatory mechanisms	References
Curcumin	Tu212 cells	2 mg	Inhibition of cell proliferation; Induction of apoptosis in tumor cells; Enhancement of cellular autophagy; Enhancement of radiosensitivity	100
Curcumin	CNE-2 cells	20 μM	Enhancement of radiosensitization by regulating the hsa-circRNA-102115–hsa-microRNA-335-3p–MAPK1 interaction network enhancing radiosensitivity	102
Curcumin	SAS cells	5, 10, 25, 50 μM	Downregulation of *FUT8* mRNA level; Upregulation of *FUT3* mRNA levels	118
Curcumin	Hep-2 cells	10, 25 μM	Enhancement of cisplatin-induced increase in mitochondrial ROS and cell death levels by activation of TRPM2; Reduction of cisplatin-induced drug resistance	120
Curcumin	Hep-2 cells	40 mg/kg	Low dose of cisplastin-induced CSC-like phenotype by inhibiting RXRα	121
Curcumin	UDSCC1 cells, UDSCC4 cells	5, 10, 20 μg/mL	Downregulation of the expression of the EMT transcription factors Snail and Twist; Downregulation of CCL22 chemokine; Inhibition of the attraction effect of polyinosinic: polycytidylic acid on regulatory T cells; Inhibition of NF-κB nuclear translocation	130
Curcumin	4-nitroquinoline-1- oxide-induced oral cancer model	50 mg/kg	Upregulation of T-cell proliferation, expression of tumor-infiltrating lymphocytes and effector cytokines; Decreased expression of PD-1, TIM-3, inhibitory immune checkpoint receptors and their ligands (PD-L1, PD-L2, and galactoglucan-9) in tumor microenvironments	131
Curcumin	H-357 cells, SCC-25 cells	30 h IC_{50} of 26.0±0.5 μM (H-357), 31.0±0.4 μM (SCC-25)	Coinduction of apoptosis in tumor cells with olaparib; Induction of DNA damage by inhibiting expression of BER components	138
Curcumin	H-357 cells	24 h IC_{50} of 10 μM	Inhibition of cell cycle progression; Synergistic olaparib indirectly suppresses chromatin remodeling through PARP-1 capture	139
Curcumin	OECM1 cells, SAS cells	5, 10, 15 μM	Inhibition of ATP-binding cassette G2 expression, leading to increased accumulation of protoporphyrin IX, thereby enhancing the efficiency of photodynamic therapy; Inhibition of p-EGFR (Tyr1068), p-AKT (Ser473) and NRF-2 expression	149
FLLL32	HSC-3 cells, SCC-9 cells, SG cells	1, 2, 4, 8, 16 μM	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; Upregulation of caspase-3; Activation of HO-1 through the MAPK-p38 pathway	18
T63	CNE2 cells, CNE2R cells	0.1, 0.3, 0.5 μM	Induction of apoptosis in tumor cells; Enhancement of radiosensitivity; Downregulation of the BAX/BCL-2 ratio; Activation of caspase-8, caspase-9, caspase-3 and PARP; Mediation of PTEN/PI3K/AKT signaling pathway	20
GO-Y078	SCC-9 cells, HSC-3 cells	0.5, 1, 2, 4 μM	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; The process of up-regulation of SMAC/DIABLO and HO-1 has been shown to induce caspase-mediated apoptosis; Upregulation of AP-1 DNA-binding activity	21

(Cont'd...)

Table 1. ***(Continued)***

Experimental drugs	Tumor cells	Concentration of the drug	Regulatory mechanisms	References
			transcriptionally induces upregulation of the *HMOX1* gene; Mediating the p38/JNK1/2 pathway	
MTH-3	CAL27 cells	24 h IC_{50} of 9 μM	Induction of apoptosis in tumor cells; Upregulation of autophagy-related proteins; Upregulation of caspase-3 and caspase-9 activity; Downregulation of mitochondrial membrane potential; Potential targets are the transcription factor EB	27
PAC	Ca9-22 cells	1, 2.5, 5, 10 μM	PAC is cytotoxic to tumor cells but not to normal human gingival cells; Suppression of oncogene (cyclin D1) expression; Inhibition of cyclin-dependent kinase inhibitor 1 expression; Increases *TP53* gene expression; Inhibition of EMT	28
HO-3867	SCC-9 cells, HSC-3 cells	2.5, 5, 10, 20 μM	Inhibition of cell cycle progression; Activation of caspase 3, caspase 8, caspase 9, and PARP formation; Induction of apoptosis in tumor cells; Mediating the JNK1/2 pathway to induce apoptosis	29
WZ37	HEP-2 cells, CNE-1 cells, CNE-2 cells, CNE-2Z cells, 5-8F cells	0.625, 1.25, 2.5, 5, 10, 20, 40 μM	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; Induction of ROS-dependent mitochondrial damage and endoplasmic reticulum stress; Reduction of AKT/mTOR phosphorylation; Upregulation of BAD and PTEN expression	40
B63	CNE1 cells, CNE2 cells, CNE2R cells	24 h IC_{50} of 51 μM (CNE1), 55 μM (CNE2), 38 μM (CNE2R); 48 h IC_{50} of 3.3 μM (CNE1), 4.0 μM (CNE2), 3.0 μM (CNE2R)	Inhibition of proliferation; Promotion of apoptosis; Induction of endoplasmic reticulum stress	42
BDMC-A	Hep-2 cells	48 h IC_{50} of 20 μM	Inhibition of NF-κB, p65, c-Jun, c-Fos, STAT3, STAT5, PPAR-γ, and β-catenin; Downregulation of MMP-9, VEGF, TGFβ, IL-6, and IL-8 expression; Upregulation of TIMP-2 level	47
L48H37	SCC-9 cells, HSC-3 cells	2.5, 5, 10, 20 μM	Inhibition of proliferation; Promotion of apoptosis; Upregulation of caspase-3 and downregulation of cellular inhibitor of apoptosis 1 and X-linked inhibitor of apoptosis protein; Involvement in JNK/p38-mediated caspase activation to induce apoptosis	48
PAC	Ca9-22 cells	1, 2.5, 5, 10 μM	Enhancement of cisplatin efficacy; Inhibition of cell proliferation; Induction of apoptosis in tumor cells; Enhancement of cellular autophagy, ROS, and mitochondrial oxidase production; Inhibition of mitochondrial membrane potential; Inhibition of EMT genes (E-cadherin)	89
EF-24	HONE-1 cells, NPC-39 cells, NPC-BM cells	0.25, 0.5, 1 μM	Interference with nuclear translocation of NF-κB and the JNK pathway; Inhibition of *MMP9* gene transcription; Inhibition of cancer cell invasion	139
L48H37	NPC-BM cells, NPC-39 cells	0.5, 1, 2 μM	Inhibition of cancer cell invasion and migration without inducing cytotoxicity; Downregulation of the expression level and enzymatic activity of MMP-9; Inhibition of the TPA-mediated JNK pathway	140

(Cont'd...)

Table 1. ***(Continued)***

Experimental drugs	Tumor cells	Concentration of the drug	Regulatory mechanisms	References
CUR-Nes (loaded with lipid nanoemulsions)	HSC-3 cells	5, 10, 15, 20 μM	Inhibition of cell cycle progression; Upregulation of microRNA-199a expression; Downregulation of PI3K/AKT/mTOR protein expression	17
Curcumin NPs (nanocurcumin with an average diameter of 28 nm)	Hep-2 cells	48 h IC_{50} of 17±0.31 μg/mL	Inhibition of cell cycle progression; Induction of apoptosis in tumor cells; Upregulation of p53, BAX and caspase-3; Downregulation of BCL-xL	19
Nanocurcumin (200 nm size)	KB 3-1 cells	24 h IC_{50} of 14.14 μM	Synergistic cytotoxicity with cetuximab	24
Tetrahydrocurcumin phytosomes	SCC4 cells	48 h IC_{50} of 60.06 μg/mL	Inhibition of cell proliferation; Induction of apoptosis in tumor cells; Upregulation of BAX and caspase-8	25
Demethoxycurcumin	FaDu cells	24 h IC_{50} of 37.78±2 μM	Induction of apoptosis in tumor cells; Upregulation of FasL, caspase-8, BAX, BAD, caspase-9, caspase-3, and PARP; Downregulation of BCL-xL and BCL-2; Inhibition of NF-κB phosphorylation; Blockage of the transport of NF-κB from the cytoplasm to the nucleus	30
Indole analog of curcumin (molecular weight: 354.4 g/mol)	Hep-2 cells	48 h IC_{50} of 24 μg/mL	Activation of cell cycle regulation and induction of apoptosis through epigenetic modulation; Affect the methylation status of ATM gene promoter sequences	85
Curcumin/chitosan deoxycholic acid NPs	CNE-2 cells	20 μM	Enhancement of microRNA-593 expression; Suppression of transcription and translation of the *MDR1* gene; Reduction of radiotherapy resistance; Inhibition of proliferation; Promotion of apoptosis	98
Bio-enhanced turmeric formulation capsules	Oral cancer patients	1, 1.5 g/day	Reduction of severe oral mucositis, dysphagia, oral pain, and dermatitis caused by radiotherapy	103
Cis/CUR–NPs (using niosome NPs to coencapsulate curcumin and cisplatin with an average size of 220.9 nm)	OECM-1 cells	0.7, 1.4, 2.8, 5.6, 11.2 μM	Enhancement of cisplatin efficacy; Inhibition of cell proliferation; Induction of apoptosis in tumor cells; Reduction of side effects	117
Mesoporous silica NPs preloaded with chlorin e6 and curcumin (size: 120 nm)	CAL27 cells	20 mg/mL	Cytotoxic effects; Interference with the ROS defense system by inhibiting TrxR activity and decreasing TrxR-2 expression, thus enhancing the killing power of PDT on cancer cells	146
Novel conjugated carbon dots combined with folic acid and curcumin	H413 cells	-	Enhancement of PDT efficacy by increasing the intrinsic ROS generation and nuclear targeting ability of carbon dots	147

Abbreviations: AKT: Protein kinase B; AMPK: AMP-activated protein kinase; AP-1: Activator protein 1; ATM: Ataxia telangiectasia mutated; BAD: BCL2-associated death promoter; BAX: B-cell lymphoma 2-associated X; BER: Base excision repair; BCL-2: B-cell lymphoma 2; BCL-xL: BCL-extra large; CCL22: C-C motif chemokine 22; c-FLIP: cellular FLICE-inhibitory protein; c-Met: Hepatocyte growth factor receptor; CSC: Cancer stem cell; EGFR: Epidermal growth factor receptor; EMT: Epithelial–mesenchymal transition; ERK: Extracellular signal-regulated kinase; FasL: Fas ligand; FLNA: Filamin A; GLUT1: Glucose transporter 1; HIF-1α: Hypoxia-inducible factor 1-alpha; HO-1: Heme oxygenase-1; IKKγ: I-kappa-B kinase-gamma; IL-6: Interleukin 6; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MCL-1: Myeloid cell leukemia 1; MMP-2: Matrix metalloproteinase-2; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa B; NP: Nanoparticle; NRF-2: Nuclear factor erythroid 2-related factor 2; PARP: Poly (ADP-ribose) polymerase; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PDT: Photodynamic therapy; PI3K: Phosphatidylinositol 3-kinase; PTEN: Phosphatase and tensin homolog; ROS: Reactive oxygen species; RXRα: Retinoid X receptor-alpha; SMAC: Second mitochondria-derived activator of caspase (also known as DIABLO); STAT3: Signal transducer and activator of transcription 3; TGF-β: Tumor growth factor-beta; TIM-3: T cell immunoglobulin and mucin domain 3; TIMP-2: Tissue inhibitor of metalloproteinases 2; TPA: Tissue-type plasminogen activator; TRPM2: Transient receptor potential cation channel subfamily M member 2; TrxR: Thioredoxin reductase; VEGF: Vascular endothelial growth factor.

that cancer cells are characterized by an anti-apoptotic property; however, under certain conditions, they may undergo natural apoptosis or be induced by therapeutic interventions. It has been demonstrated that curcumin and its derivatives can initiate apoptotic signaling pathways in HNSCC cells. For example, Hussein and Khaphi[23] found that curcumin induced apoptosis in tongue squamous cell carcinoma fibroblasts at a rate of 58.8%, with no significant effect on normal human gingival fibroblasts. Moreover, curcumin has been shown to initiate apoptosis in HNSCC cells by increasing the activity of apoptotic proteins, such as caspase-3, caspase-8, and caspase-9. This increase in protein activity leads to the execution phase of apoptosis, resulting in the death of HNSCC cells and subsequent inhibition of tumor growth.[18-20,24-34]

The present study investigates the hypothesis that curcumin induces the initiation of the apoptotic program through the mitochondrial pathway. The findings demonstrate that curcumin upregulates the expression of pro-apoptotic proteins (e.g., B-cell lymphoma 2 [BCL-2]-associated X [BAX] and BCL-2 homologous antagonist/killer) and downregulates the expression of anti-apoptotic proteins (e.g., BCL-2 and BCL-extra large [BCL-xL]). The increase in permeability of the outer mitochondrial membrane, the formation of pore channels, and the release of cytochrome C and other apoptotic factors into the cytoplasm are promoted by this process. As demonstrated, cytochrome C binds to apoptotic protease-activating factor-1, recruiting caspase-9 to form vesicles, which initiate the caspase cascade and induce apoptosis in tumor cells.[35-37] Similarly, Tsai *et al.*[27] reported that the curcumin derivative MTH-3 increased the activities of caspase-3 and caspase-9 in human oral squamous carcinoma CAL27 cells. Moreover, they demonstrated that MTH-3 treatment resulted in a decrease in mitochondrial membrane potential, confirming activation of the intrinsic apoptotic pathway. Meanwhile, Abdolahinia *et al.*[26] and Lee *et al.*[30] found that the ratio of BAX/BCL-2 and the activation of caspase-9 in the HNSCC cell line HN5 were elevated with increasing curcumin doses, indicating a dose-dependent effect.

Furthermore, curcumin has been demonstrated to induce apoptosis through the death receptor pathway. Specifically, curcumin upregulates the Fas ligand (FasL)[30] and tumor necrosis factor-related apoptosis-inducing ligand receptors (e.g., death receptor 4 [DR4] and DR5),[38] thereby enhancing exogenous apoptotic signaling. For example, Lee *et al.*[30] conducted a study on demethoxycurcumin (DMC) and its effects on FaDu cells. The study revealed that DMC binds to Fas via upregulated FasL, leading to Fas trimerization and recruitment of articulatory proteins. This interaction results in the formation of a death-inducing signaling complex via death domain interaction, activating caspase-8 and caspase signaling. This cascade also induces bid cleavage, serving as a crosstalk point between extrinsic and intrinsic pathways, and ultimately results in apoptosis in FaDu cells.

It has also been found that curcumin promotes apoptosis by decreasing the expression of the apoptosis inhibitory protein, cellular FLICE-inhibitory protein (c-FLIP), and the anti-apoptotic molecule, myeloid cell leukemia 1 (MCL-1).[39] For example, Seo *et al.*[39] showed that thioridazine alone in AMC-HN4 cells did not induce apoptosis. However, its combination with curcumin significantly increased apoptosis in cancer cells, when sparing human mesenchymal stromal cells and normal umbilical vein cells (EA.hy926). This combination therapy enhanced proteasome activity via increased expression of proteasome subunit α5 (PSMA5), which in turn led to the downregulation of c-FLIP and MCL-1 expression levels.

Activation of the protein kinase RNA-like endoplasmic reticulum (ER) kinase/activating transcription factor 4/CCAAT-enhancer-binding protein homologous protein (CHOP) pathway has been demonstrated to induce the apoptotic program, through promoting the unfolded protein response and triggering ER stress.[40,41] Pan *et al.*[42] observed that the curcumin derivative B63 inhibited the proliferation of NPC cells and induced apoptosis in a dose- and time-dependent manner *in vivo*. Notably, a *CHOP* gene knockdown attenuated B63-induced apoptosis, suggesting that the apoptotic pathway is ER stress-dependent. In contrast, the same dose of curcumin did not activate ER stress, confirming that B63 exerts a superior antitumor effect compared to curcumin in NPC cells.

4. Modulation of key signaling pathways

The nuclear factor kappa B (NF-κB) pathway is inextricably linked to cancer, and persistent activation of NF-κB provides tumor cells with signals for growth, proliferation, resistance to apoptosis, and invasiveness. Curcumin has been demonstrated to inhibit I-kappa-B kinase (IKK) phosphorylation, prevent NF-κB nuclear translocation,[35,43] and reduce nuclear accumulation of the p65 subunit.[44,45] These, in turn, decrease the expression of downstream pro-inflammatory factors (e.g., tumor necrosis factor-alpha [TNF-α] and interleukin 6 [IL-6]) and anti-apoptotic genes (e.g., *BCL2* and *BIRC5*). In addition, Deng *et al.*[46] found that the expression of IKKγ was further increased in human laryngeal carcinoma Hep-2 cells, resulting in elevated expression of NF-κB downstream genes, including *BCL2L1*, *BCL2*, and *CCND1*. Curcumin has been shown to inhibit NF-κB and enhance irradiation-

induced DNA damage and apoptosis in Hep-2 cells by inhibiting the expression of IKKγ. In a recent study, Mohankumar *et al.*[47] investigated the comparative efficacy of curcumin and its derivative BDMC-A in modulating the expression of NF-κB and p65 transcription factors, as well as the levels of inflammatory factors, including IL-6 and IL-8, in Hep-2 cells. The findings revealed that BDMC-A exhibited greater inhibitory activity compared to curcumin, highlighting its potential as a therapeutic agent in the treatment of laryngeal cancer.

The mitogen-activated protein kinase (MAPK) pathway comprises three principal branches, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, which are implicated in a variety of processes related to tumor cell proliferation, metastasis, epigenetic regulation, and tumor angiogenesis. Several studies have identified curcumin derivatives (e.g., FLLL32,[18] GO-Y078,[21] PAC,[28] HO-3867,[29] and L48H37[48]) as potential regulators of apoptosis in HNSCC, with these effects being mediated through the ERK1/2, JNK, and p38 pathways.[49,50] In their study, Chen *et al.*[29] found that phosphorylation levels of ERK1/2, JNK1/2, and p38 increased following the treatment of oral squamous carcinoma cells with the curcumin derivative HO-3867. Concurrently, the expression of cleaved caspase 3, caspase 8, caspase 9, and poly(ADP-ribose) polymerase 1 (PARP-1) also increased, indicating that HO-3867 induces apoptosis via the MAPK pathway. Conversely, Chien *et al.*[21] observed low levels of mitochondrial pro-apoptotic proteins, diablo homolog (DIABLO, also known as a second mitochondria-derived activator of caspases [SMAC]) and heme oxygenase-1, in primary tumor tissues from head-and-neck cancer patients. The curcumin derivative GO-Y078 induced caspase-mediated apoptosis in oral squamous carcinoma cells through the activation of the p38/JNK1/2 pathway, which facilitates the binding of SMAC/DIABLO to activator protein 1. Furthermore, the study revealed an increase in *HMOX1* gene expression.

The signal transducer and activator of transcription 3 (STAT3) protein is a pivotal member of the STAT family and plays a central role in the development, progression, metastasis, and drug resistance of HNSCC. STAT3 is usually highly activated in HNSCC and is closely associated with HNSCC tumor stage, lymph node metastasis, and poor prognosis of patients.[51] The Janus kinase family member STAT3 exerts anti-apoptotic effects through activating the downstream gene *BCL2*.[52] In contrast, curcumin has been demonstrated to inhibit STAT3 expression and phosphorylation.[53,54] Abdolahinia *et al.*[26] found that curcumin decreased *BCL2* and *STAT3* expression when increasing the BAX/BCL-2 ratio in HN-5 cells. These results suggest that the inhibition of STAT3 activity by curcumin enhances apoptosis in HN-5 cells. In the study by Mohankumar *et al.*,[47] it was demonstrated that the curcumin analog BDMC-A inhibited STAT3 phosphorylation and dimerization in Hep-2 cells. This led to the suppression of STAT3 transcriptional activity and the downregulation of genes associated with invasiveness, angiogenesis, and metastasis, such as *VEGF* and *MMP9*. These findings suggest that BDMC-A inhibits the malignant progression of laryngeal cancer cells through STAT3 inhibition.

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is one of the most significant oncogenic pathways, associated with cell proliferation, energy metabolism, and protein synthesis in tumors. Liu *et al.*[17] found that curcumin nanoemulsions inhibited the proliferation of HSC-3 cells by inhibiting the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway and upregulating the expression of microRNA-199a, which targets PI3K, thereby counteracting the effects of microRNA-199a inhibition on the HSC-3 cell cycle. In addition, Zhang *et al.*[40] found that treating Hep-2 cells with the curcumin derivative WZ37 for 24 h decreased AKT/mTOR phosphorylation when increasing the expression of BCL2-associated death promoter and phosphatase and tensin homolog. This, in turn, induced G2/M phase arrest, mitochondrial damage, ER stress, and further induction of apoptosis. Similarly, Mou *et al.*[55] found that curcumin inhibited the expression of PI3K protein and the phosphorylation of AKT protein in human laryngeal cancer cells through upregulating microRNA-15a expression.

5. Inhibition of tumor invasion and metastasis

Tumor cell invasion and metastatic ability have been demonstrated to be associated with a range of biological processes, including epithelial–mesenchymal transition (EMT), extracellular matrix degradation, and tumor angiogenesis.[56-60] A multitude of studies have demonstrated the ability of curcumin to suppress the invasion and metastasis of HNSCC.[61-67] For example, Essawy *et al.*[68] reported that nanocurcumin exhibited the ability to reduce the migration of cancer cells by 25%. Similarly, Gonçalves *et al.*[69] ascertained that curcumin led to a reduction in the expression of genes associated with EMT. Ohnishi *et al.*[70] found that hepatocyte growth factor (HGF) signaling induced EMT in HSC-4 and Ca9-22 oral squamous carcinoma cell lines through the activation of the HGF receptor (c-Met) and downstream prosurvival ERK pathway. The study demonstrated that curcumin effectively inhibited the upregulation of HGF-induced waveform protein levels by downregulating the phosphorylation of c-Met. This inhibition of HGF-induced waveform

protein levels suppressed EMT and cell motility in HSC-4 and Ca9-22 cells. In a study by Lee *et al*.,[71] SCC-25 cells were treated with curcumin, resulting in reduced matrix metalloproteinase 2 (MMP-2) and MMP-9 expression. This finding led to the inhibition of the invasive behavior of oral cancer cells. Furthermore, the study revealed that curcumin regulated EMT markers (e.g., Snail, Twist, and E-cadherin) and induced the expression of p53, which is essential for the inhibition of EMT. As Shao *et al*.[16] demonstrated, curcumin inhibited NPC cell metastasis by regulating the gene expression of *MMP2*, *MMP9*, and *FAK*. Moreover, Chatterjee *et al*.[72] found that curcumin inhibited angiogenesis in endothelial cells induced via the secretion of nectin-4 from H357 oral cancer cells. This was achieved through the inhibition of the PI3K-AKT-mediated endothelial nitric oxide synthase pathway. Furthermore, Jayaraman *et al*.[73] reported that curcumin promoted angiogenesis in oral cancer cells via hypoxia-inducible factor 1-alpha. Similarly, Xie *et al*.[74] observed that curcumin inhibited the malignant phenotype and angiogenesis of laryngeal squamous carcinoma cells by preventing the downregulation of filamin A expression via the transcription factor E2F1. Similarly, Sathe *et al*.[75] reported that curcumin-induced alterations in the phosphorylation of multiple kinases (including activated CDC42 kinase 1, Fyn-related kinase, Tyrosine protein kinase receptor UFO, and MAPK12) and phosphatases (e.g., protein tyrosine phosphatase non-receptor type 6, protein tyrosine phosphatase receptor type kappa, and ectonucleotide pyrophosphatase/phosphodiesterase family member 1) modulated processes such as cell proliferation and migration. Gao *et al*.[76] found that curcumin inhibited epithelial growth factor and C–C motif chemokine ligand 2 production in macrophages and cancer cells, respectively, and blocked the feedback loop, thereby inhibiting the migration and invasion of HNSCC cells.

6. Epigenetic regulation

The development of cancer is closely related to the expression and mutation of proto-oncogenes and oncogenes in cells.[77-81] Furthermore, DNA modification is a widespread phenomenon in living organisms. HNSCC has been associated with the epigenetic silencing of a variety of genes, such as *DAPK*, ataxia telangiectasia mutated (*ATM*), *BRCA1*, *CDKN2A*, *VHL*, and *RASSF1A*.[82,83] The most prevalent epigenetic change observed in these genes is DNA methylation. In a study by Chatterjee *et al*.,[84] it was found that curcumin exhibited the highest DNA-damaging ability in comparison to resveratrol and 5-fluorouracil. Furthermore, Chandramohan *et al*.[85] demonstrated that indole curcumin reversed DNA methyltransferase 1 activity by inhibiting the methylation silencing status of oncogenes in Hep-2 cells. Concurrently, the messenger RNA (mRNA) expression analysis of *TP53*, *ATM*, and *DAPK* genes indicated that indole curcumin exerted a substantial influence on the methylation status of the *ATM* gene's promoter sequence.

Furthermore, Mishra *et al*.[35] reported that curcumin exhibited selective inhibition effects on the transcription of the *E6* oncogene during oncogenesis in oral cancer cells. Similarly, Yang *et al*. found[86] that curcumin inhibited the expression of epidermal growth factor receptor (EGFR), STAT3, and growth factor receptor-binding protein 2 by regulating the circular RNA (circRNA)-microRNA-mRNA network. It has also been demonstrated that curcumin exhibits binding affinity for small non-covalent DNA hairpin complexes, facilitating cellular delivery.[87] This complex demonstrates heightened toxicity when bound to 5-fluoro-2'-deoxyuridine nucleotides, suggesting its potential for application in advanced-stage cancer therapy.

7. Involvement in oxidative stress, autophagy, and metabolic regulation

The accumulation of reactive oxygen species (ROS) in tumor cells disrupts the redox balance, inducing DNA damage and apoptosis. As Lee *et al*.[67] demonstrated, curcumin induced ROS accumulation and elevated nuclear factor erythroid 2-related factor 2 (NRF-2) level, which plays a pivotal role in regulating oxidative stress within cells. Similarly, Zhang *et al*.[40] found that WZ37 induced apoptosis in Hep-2 cells through ROS-mediated mitochondrial damage and ER stress. Pre-treatment with the ROS scavenger N-acetylcysteine resulted in a decrease in the anticancer activity of WZ37 in Hep-2 cells. Conversely, curcumin-loaded mesoporous silica nanoparticles induced apoptosis and autophagy in HN5 cells through a ROS-mediated mechanism.[88] Concurrently, Semlali *et al*.[89] reported that the utilization of the curcumin derivative PAC augmented ROS generation in oral cancer cells. In contrast, Seo *et al*.[39] determined that concomitantly treating AMC-HN4 cells with curcumin and thioridazine engendered intracellular ROS accumulation, catalyzed by NADPH oxidase 4. This, in turn, activated the NRF-2/antioxidant response element signaling pathway, elevated the expression of PSMA5, and consequently induced proteasome activity. The downregulation of c-FLIP and MCL-1 post-transcriptional expression has been demonstrated to participate in the apoptosis of AMC-HN4 cells. Furthermore, curcumin has been observed to trigger cytoprotective forms of autophagy in cellular contexts.[90,91] Dai *et al*.[92] found that curcumin, in combination with glucose transporter 1 small interfering RNA, promoted Tu212 autophagy in laryngeal cancer cells through the AMP-activated protein kinase–mTOR–serine/

threonine protein kinase–beclin1 signaling pathway. Ravera *et al.*[93] found that curcumin inhibited OHSU-974 cell growth by inhibiting ATP synthase. This inhibition led to a decrease in the oxygen consumption rate and ATP/AMP ratio. These effects were associated with a decrease in lipid peroxidation accumulation levels. In addition, there was a slight increase in the activities of glutathione reductase and catalase.

8. Enhancement of radiotherapy efficacy

In the treatment of HNSCC, approximately 70% of patients require radiotherapy at various stages of the disease. For early lesions of laryngeal and nasopharyngeal cancers, the 5-year survival rate with radical radiotherapy can reach 80 – 90% when also preserving organ functions, such as phonation and deglutition. Radiotherapy serves not only as a radical treatment for patients with locally advanced or inoperable disease but also as an important adjuvant to reduce the risk of recurrence after surgery. Nevertheless, radiotherapy for HNSCC continues to encounter limitations and challenges, including radiation resistance in cancer cells, the necessity of targeting the core area of radiotherapy, i.e., tumor stem cells, and the potential for radiation-induced damage to normal tissues. The combination of curcumin and radiotherapy has been shown to enhance the anticancer effect and address the challenges in HNSCC.[94-96]

Wang *et al.*[97] reported that curcumin enhanced the radiosensitivity of C6661-IR cells to X-rays by modulating the expression of microRNA-205-5p and tumor protein p53-inducible nuclear protein 1. Besides, Deng *et al.*[46] found that curcumin enhanced irradiation-induced DNA damage and apoptosis by inhibiting the expression of IKKγ and NF-κB downstream genes, including *BCL2L1*, *BCL2*, and *CCND1*, resulting in a radiosensitizing effect. In the study by Zeng *et al.*,[98] the combination of radiotherapy and curcumin or curcumin-loaded nanoparticles resulted in a higher rate of apoptosis in poorly differentiated human NPC cell line (CNE2) compared to cells treated with radiotherapy alone. The study found that curcumin effectively inhibited the growth of CNE2 cells by reducing radioresistance in NPC, mainly through enhancing the expression of microRNA-593. This, in turn, inhibited the transcription and translation of multidrug resistance gene 1.[98,99]

Dai *et al.*[100] established a BALB/c mouse xenograft model for *in vivo* experiments using Tu212 laryngeal carcinoma cells. The findings revealed that the combination of curcumin and 10 Gy of radiotherapy inhibited tumor growth by inducing apoptosis and enhancing autophagy in laryngeal cancer cells. It was demonstrated that administering curcumin alongside a reduced radiotherapy dose (5 Gy) resulted in a more pronounced effect than that observed with high-dose radiotherapy (10 Gy) alone. This finding serves to substantiate the notion that curcumin enhances the radiosensitivity of Tu212 laryngeal cancer cells. Similarly, Tolentino *et al.*[101] also found that the combination of curcumin and radiotherapy was more effective than single-dose radiotherapy at 4, 8, and 12 Gy.

In the study by Zhu *et al.*,[102] the authors compared the differences in circRNA levels in NPC cell lines following radiotherapy and treatment with curcumin. The findings demonstrated that curcumin enhanced the radiosensitivity of NPC cells by regulating tumor stem cells through the hsa-circRNA-102115–hsa-microRNA-335-3p–MAPK1 interaction network. This study investigated the function of this interaction network in the regulation of tumor stem cells to enhance the radiosensitivity of NPC cells. Furthermore, Soni *et al.*[103] conducted a 6-week randomized, double-blinded, placebo-controlled clinical trial and found that the administration of a curcumin preparation capsule (BTF group) alongside radiotherapy significantly mitigated the occurrence of Grade 3 oral mucositis, Grade 3 dysphagia, Grade 3 oral pain, and Grade 3 dermatitis induced by radiotherapy for oral cancer, in comparison to the placebo group. Moreover, these adverse effects were reduced when a dose of 1.5 g/day was administered in comparison with a dose of 1 g/day.

9. Enhancement of chemotherapy efficacy

It is estimated that 60 – 70% of patients diagnosed with locally advanced or metastatic HNSCC require chemotherapy, frequently in combination with radiation therapy (concurrent chemoradiotherapy), as a standard treatment option. Chemotherapy has been demonstrated to reduce the size of tumors, thus facilitating surgical resection or serving as a curative treatment for patients ineligible for surgery. For recurrent or metastatic patients, the combination of chemotherapy and immunotherapy (for example, programmed cell death protein 1 [PD-1] inhibitors) has become a first-line option, with a significant increase in survival rates reported.[104-106] For example, a combination of neoadjuvant chemotherapy and immunotherapy achieved a complete tumor pathology remission rate of 37%, significantly enhancing surgical success and preserving organ function.[107] Nevertheless, chemotherapy continues to be afflicted by various issues, including chemoresistance, damage to normal tissue cells, and inadequate targeting. The combination of curcumin with chemotherapy has the potential to enhance the anticancer effects and address these challenges in HNSCC.

A multitude of studies have demonstrated the potential of curcumin to function as an adjuvant in chemotherapy,

thereby enhancing the efficacy of chemotherapeutic agents.[108-116] For example, Saberian *et al.*[117] encapsulated both cisplatin and curcumin in nanoparticles using a combination of the reverse microemulsion method and the thin film dispersion method, resulting in nanoparticles with an average particle size of 220.9 nm. Their *in vitro* experiments demonstrated that the nanoparticles were capable of releasing cisplatin and curcumin concurrently and that the optimal cisplatin/curcumin ratio for achieving a synergistic effect on OECM-1 cells was 1:6. In the study by Mehta *et al.*,[118] curcumin demonstrated efficacy equivalent to cisplatin in the treatment of SAS tongue cancer cells, leading to downregulation of *FUT8* mRNA level and the upregulation of *FUT3* mRNA level. The study, thus, concluded that curcumin may target abnormal glycosylation changes in cancer cells and synergize with cisplatin in the treatment of tongue cancer. Similarly, Semlali *et al.*[89] established that the combination of PAC (a curcumin analog) and cisplatin in the treatment of Ca9-22 oral cancer cells reduced the required dose of cisplatin, thus mitigating its adverse effects. The IC_{50} of different concentrations of cisplatin was reduced by 10-fold when PAC was used at 5 μM. In comparison with cisplatin alone, the combination with curcumin inhibited mitochondrial membrane potential, induced caspase activation, enhanced autophagy, increased ROS and MitoSOX production, and inhibited the EMT gene, *CDH1*, in Ca9-22 oral cancer cells. These actions exerted anticancer effects via apoptosis, autophagy, oxidative stress, and cancer cell migration.

On the other hand, Liu *et al.*[119] reported that the combination of curcumin and paclitaxel significantly inhibited cell growth and induced apoptosis by decreasing the expression of BCL-2 and the BCL-2/BAX ratio, when increasing the expression of BAX and active caspase-3, in comparison with either agent alone. Moreover, Kütük *et al.*[120] established that the administration of cisplatin resulted in an augmentation of apoptosis in Hep-2 cells, characterized by a decline in intracellular glutathione peroxidase and glutathione concentrations, elevated ROS production, and augmented calcium efflux. The coadministration of curcumin with cisplatin enhanced the anticancer effects of cisplatin. This study further demonstrated that curcumin synergized with cisplatin mainly by increasing lipid peroxidation, promoting intracellular and mitochondrial oxidative stress, and activating transient receptor potential cation channel subfamily M member 2 channels. In addition, curcumin reduced cisplatin-induced drug resistance in Hep-2 cells.

However, cisplatin also exerts cytotoxic effects on normal renal MPK cells, resulting in renal cell death, a process that was attenuated by the combined use of curcumin. Fetoni *et al.*[45] found that curcumin increased cisplatin chemosensitivity and attenuated its ototoxic adverse effects by targeting the pSTAT3 and NRF-2 signaling pathways. Similarly, Jiang *et al.*[121] established that curcumin plays a pivotal role in suppressing cancer cell metastasis, tumor recurrence, and chemoresistance through inhibiting retinoid X receptor-α, consequently preventing the upregulation of tumor stem cells induced by low-dose cisplatin.

10. Enhancement of immunotherapy efficacy

The mechanism of action of immunotherapy is to restore the antitumor activity of T cells by blocking the binding of PD-1 and programmed death-ligand 1 (PD-L1) or by producing antibodies that target and eliminate tumor cells, thus effectively inhibiting tumor growth and metastasis. However, cancer cells possess the capacity for immune evasion, allowing them to avoid recognition and eradication by the immune system through modifying surface antigens and activating immune checkpoints.[122] It has been demonstrated that curcumin and its derivatives possess immunomodulatory properties, enabling them to activate the body's immune system and enhance the antitumor immune response through multiple pathways.[63]

Curcumin has been demonstrated to reverse the suppressive state of the tumor immune microenvironment and enhance T-cell recruitment.[123-126] Sun *et al.*[127] found that curcumin reduced tumor load by downregulating myeloid-derived suppressor cells and M2 macrophages, when upregulating cluster of differentiation 8-positive ($CD8^+$) T cells, natural killer cells, and M1 macrophages. Concurrently, the secretion of the chemokine, CXC motif chemokine 1, was diminished, while the secretion of interferon-gamma and TNF-α was augmented in the tumor samples. Similarly, Focaccetti *et al.*[128] found that curcumin promoted increased $CD4^+$/$CD8^+$ T lymphocyte infiltration. Kötting *et al.*[129] reported that the combination of curcumin and a synthetically produced double-strand RNA, polyinosinic:polycytidylic acid (PIC), exerted immunomodulatory effects in HNSCC, promoting immune cell activation by decreasing the level of C-C motif chemokine 22 and thus effectively inhibiting the regulatory T (Treg) cell induced by PIC. Similarly, Liu *et al.*[130] found that curcumin increased T cell proliferation, tumor-infiltrating lymphocytes (TILs), and effector cytokines in a 4-nitroquinoline-1-oxide-induced oral cancer mouse model. The presence of TILs and effector cytokines decreased the expression of ligands for inhibitory immune checkpoint receptors (e.g., PD-L1, PD-L2, and galectin-9). This effect restored the cytolytic activity of $CD8^+$ T cells against cancer cells.

Furthermore, curcumin has been demonstrated to inhibit the expression of $CD4^+CD25^+FoxP3^+$ Treg cells, as well as PD-1 and T cell immunoglobulin and mucin domain 3 (TIM-3). Curcumin can reactivate defective T cells through a number of mechanisms, including the inhibition of multiple immune checkpoint axes (e.g., PD-1 and TIM-3) and multilevel immune checkpoint axis inhibition (e.g., immune checkpoint receptor and its ligands). Consequently, the combination of curcumin with conventional targeted therapy or immune checkpoint blockade therapy results in a synergistic effect. In line with the findings of Dash *et al.*,[131] a reduction in PD-1 and PD-L1 levels was observed following the administration of curcumin.

11. Enhancement of targeted therapy efficacy

The mechanism of action of targeted therapy is to control tumor growth by acting on the corresponding molecules and blocking key signaling pathways, thereby inhibiting tumor proliferation and survival and ultimately inducing tumor cell apoptosis. However, the efficacy of targeted drugs in the treatment of recurrent/metastatic HNSCC is limited, and the response to targeted therapy largely depends on the molecular characteristics of the patient's tumor. The low response rate and frequent drug resistance observed in some cases emphasize the necessity for the development of a personalized, targeted treatment strategy for patients.[132] The potential of curcumin to synergize with targeted agents to enhance efficacy is attributable to its broad-spectrum anticancer properties.[133-136]

Mukherjee *et al.*[24] found that treatment with 200 nm-sized nanocurcumin in combination with cetuximab (an EGFR inhibitor with an IC_{50} of 14.14 μM at 24 h) resulted in a significant increase in cell death in a large number of KB 3-1 oral squamous carcinoma cells compared to cetuximab alone. Similarly, Chatterjee *et al.*[84] reported that the combination of curcumin with two PARP inhibitors (BMN and olaparib) reduced the base excision repair (BER) cascade and enhanced PARP trapping to a greater extent than either drug alone, thereby increasing apoptosis in oral cancer cells. Molla *et al.*[137] found that curcumin synergized with the PARP inhibitor (olaparib) to exert anticancer effects. The combined administration of curcumin and olaparib in oral cancer cells resulted in DNA damage, which subsequently triggered apoptosis and reduced tumor size. This effect was achieved by modulating the expression levels of short-patch and long-patch components of the BER pathway.

As demonstrated by Molla *et al.*,[138] the combination of curcumin and olaparib treatment resulted in the upregulation of PARP-1 and adenomatous polyposis coli genes, as well as the downregulation of other BER proteins within the chromatin fraction. However, these effects were not observed in the nuclear fraction, leading to the cell cycle arrest of H-357 cells in the S phase. This combination has also been demonstrated to inhibit poly(ADP-ribosyl) ation, alter the interaction of PARP-1 with representative BER proteins, and cause S-phase arrest. In a related study, Xie *et al.*[74] found that the combination of curcumin derivative WZ37 with the AKT inhibitor MK-2206 promoted apoptosis in cancer cells. Similarly, Su *et al.*[139] reported that the combination of the curcumin derivative EF-24 and a JNK inhibitor exhibited a synergistic effect in the inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced invasion, migration ability, and MMP-9 activity in NPC cells. A similar mechanism of action was identified with the curcumin analog L48H37.[140]

12. Enhancement of the efficacy of photodynamic therapy (PDT) and sonodynamic therapy

PDT is a therapeutic modality that utilizes the generation of ROS through the synergistic action of photosensitizers, a specific wavelength of light source, and oxygen. The therapeutic action of PDT is confined to the area enriched with photosensitizers, sparing the surrounding normal tissues. This is advantageous as it helps preserve the function of vital organs, such as the larynx and oral cavity. PDT is particularly efficacious in the treatment of early or superficial HNSCC, including oral mucosal lesions.[141,142] However, the therapeutic efficacy is often limited by the inefficient utilization of ROS in tumors, which results from the cellular redox balance.

A multitude of studies have demonstrated that curcumin enhances the efficacy of PDT.[143-145] For example, Wu *et al.*[146] found that curcumin nanoparticles effectively interfered with the ROS defense system, inhibited thioredoxin reductase (TrxR) activity, and reduced the expression of TrxR-2, thus enhancing the cytotoxic effects of PDT on CAL-27 cancer cells. Furthermore, curcumin nanoparticles have been demonstrated to possess tumor-homing capabilities, enabling selective accumulation within tumor tissues and significant inhibition of tumor growth. Moreover, Nasrin *et al.*[147] synthesized novel conjugated carbon dots, which function as two-photon-activated photosensitizers that release ROS for use in PDT. The combined use of curcumin nanoprobes has been demonstrated to increase ROS generation, induce DNA damage in oral cancer cells, and improve PDT efficiency. Yang *et al.*[148] found that curcumin increased the accumulation of protoporphyrin IX in oral cancer cells by inhibiting the expression of ATP-binding cassette G2, thus improving the efficiency of PDT treatment.

Sonodynamic therapy is a non-invasive cancer treatment modality that combines low-intensity ultrasound and a sonosensitizer. The destruction of tumor cells is achieved through the synergistic action of ultrasound and chemical acoustic sensitizers. As demonstrated in the study by Sowa-Kasprzak *et al*.,[149] curcumin enhanced the acoustic kinetic effect in SCC-25 (a tongue cancer) and FaDu (a hypopharyngeal cancer) cells.

13. Summary and outlook

A summary analysis of all the above research results shows that these studies confirm that curcumin and its derivatives exhibit multitargeted synergistic antitumor potential against HNSCC and mitigate damage to normal tissues caused by antitumor treatments (such as radiotherapy and chemotherapy). At the same time, many studies have shown that various derivatives of curcumin are more effective than natural curcumin in treating HNSCC.[150-162] Among them, carriers such as liposomes and polymer nanoparticles have made significant breakthroughs in targeted delivery and potency enhancement, significantly improving the bioavailability of curcumin. Structurally modified curcumin analogs can enhance the ability to modulate the tumor microenvironment.

Several factors may account for discrepancies among studies investigating the same mechanisms of action, as well as for the limitations observed in existing research:

(i) Cell-type specificity: Different studies use different cancer cell lines (e.g., HPV status, anatomical location, and genetic background)
(ii) Drug variability: Natural curcumin, its various derivatives, or nanoformulations may exhibit different specificity or potency
(iii) Concentration and time dependency: Some studies explicitly highlight dose and time dependency, while others may have used varying treatment conditions
(iv) Isolated pathway studies: Most studies focus on a single or a few target points/pathways, lacking a comprehensive, systematic study of curcumin regulation in a specific cellular context that integrates these scattered findings
(v) Unclear upstream signaling events: Research on how curcumin triggers downstream effector molecules is relatively scarce
(vi) Underexplored derivative mechanisms: Exploration of the mechanisms of action of derivatives is typically less thorough than that of natural curcumin
(vii) Insufficient normal cell controls: Not all studies adequately assess the effects of curcumin or its derivatives on normal cells, and specificity requires broader validation.

Future research can be advanced through the following key areas:

(i) Mechanistic integration: Systematically study how curcumin/specific highly effective derivatives coordinate and regulate multiple key pathways to produce antitumor effects in specific HNSCC models. Employ omics technologies (e.g., transcriptome, proteome, and phosphoproteome) to map global changes
(ii) Elucidation of upstream regulatory mechanisms: Conduct in-depth studies on the initial molecular events triggered by curcumin/derivatives, such as the modulation of kinases/phosphatase activity and the activation/inhibition of transcription factors, which in turn ultimately regulate downstream cell cycle-related proteins
(iii) Mechanistic studies of derivatives: Curcumin derivatives exhibiting strong tumor-inhibitory effects should undergo more in-depth mechanistic studies to clarify their advantages over natural curcumin and define their target specificity
(iv) *In vivo* validation and efficacy assessment: Evaluate the antitumor effects observed *in vitro* using head-and-neck cancer animal models (such as xenograft and genetically engineered models) and assess antitumor efficacy, biodistribution, and effects on normal tissues
(v) Overcoming bioavailability limitations: Continue to develop novel delivery systems (e.g., optimized nanomedicines, liposomes, and polymer carriers) to enhance oral bioavailability and tumor targeting, thereby overcoming key obstacles to clinical application
(vi) Translational research and biomarker discovery: Identify curcumin-induced molecular changes (such as specific microRNA and protein expression/phosphorylation levels) that could serve as prognostic indicators or predictors of therapeutic response
(vii) Subtype-specific sensitivity comparisons: Systematically compare the antitumor efficacy and mechanistic differences of curcumin and its derivatives across different HNSCC subtypes (e.g., HPV^+ vs. HPV^- and different anatomical origins) and varying degrees of tumor differentiation
(viii) Clinical validation: Conduct large-scale clinical studies to validate its safety as an adjuvant therapy or preventive agent, and its synergistic potential in combination with radiotherapy and chemotherapy.

The treatment of HNSCC still faces numerous challenges. Based on this review, the therapeutic potential of curcumin and its derivatives in the treatment of HNSCC has been well-established through extensive basic research. With

the increasing integration of interdisciplinary technologies and the clinical demand for further improvement in the efficacy of HNSCC treatment, curcumin-based compounds hold promise for clinical translation, potentially becoming an important component of comprehensive treatment strategies for HNSCC.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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