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Nanocurcumin Mediated Modulation of Apoptotic Pathways in Cervical Cancer: A Systematic Review

Wandha O. Savira[1], Subandi Subandi[2], Happy K. Permatasari[3], Bayu Lestari[4], and Oktalia N. Aisyah[1*]
[1]Master Program in Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[2]Department of Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[3]Department of Biochemistry and Biomolecular, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[4] Department of Pharmacology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Abstract
Cervical cancer is the fourth most common malignancy in women, driven largely by HPV oncoproteins E6 and E7, which degrade the tumor suppressors p53 and retinoblastoma protein and blunt apoptosis. Curcumin is pro-apoptotic but clinically limited by poor solubility, instability, and low bioavailability, motivating nanoformulation. This systematic review evaluated the apoptotic mechanisms, physicochemical characteristics, and preclinical efficacy of nanocurcumin in cervical cancer. Following PRISMA 2020, four databases (PubMed, Scopus, ScienceDirect, SpringerLink) were searched; 16 preclinical studies (2015–2025) met eligibility from 1,604 records. Nanocurcumin induced apoptosis through four convergent mechanisms: the intrinsic mitochondrial pathway (Bax/Bcl-2 modulation, caspase activation), ROS-mediated oxidative stress, suppression of HPV E6/E7 with restoration of p53 and Rb, and inhibition of PI3K/AKT/mTOR and NF-κB signaling. Formulations ranged from ~52 to 390 nm with encapsulation efficiencies often above 85%; folate receptor–mediated targeting gave the most reproducible uptake gains. Combination strategies consistently outperformed monotherapy in vivo, including extended survival. However, the near-absence of systemic pharmacokinetic and long-term toxicity data, non-representative models, and scalability challenges indicate that substantial development is needed before clinical evaluation.

Keywords: Apoptosis, Cervical cancer, Drug delivery systems, Nanocurcumin

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*Corresponding author:
oktalianurul@student.ub.ac.id

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Modulasi Jalur Apoptosis oleh Nanokurkumin pada Kanker Serviks: Tinjauan Sistematis

Abstrak
Kanker serviks merupakan keganasan keempat tersering pada wanita, yang sebagian besar dipicu oleh onkoprotein HPV E6 dan E7. Kedua onkoprotein ini mendegradasi protein penekan tumor p53 dan retinoblastoma serta menumpulkan apoptosis. Kurkumin bersifat pro-apoptotik, tetapi pemanfaatan klinisnya terbatas oleh kelarutan yang buruk, ketidakstabilan, dan bioavailabilitas yang rendah, sehingga mendorong pengembangan nanoformulasi. Tinjauan sistematis ini mengevaluasi mekanisme apoptosis, karakteristik fisikokimia, dan efikasi praklinis nanokurkumin pada kanker serviks. Mengikuti panduan PRISMA 2020, penelusuran dilakukan pada empat basis data (*PubMed, Scopus, ScienceDirect, SpringerLink*); dari 1.604 rekaman, 16 studi praklinis (2015–2025) memenuhi kriteria kelayakan. Nanokurkumin menginduksi apoptosis melalui empat mekanisme yang konvergen: jalur intrinsik mitokondria (modulasi Bax/Bcl-2 dan aktivasi kaspase), stres oksidatif yang diperantarai ROS, supresi HPV E6/E7 dengan pemulihan p53 dan Rb, serta inhibisi pensinyalan PI3K/AKT/mTOR dan NF-κB. Ukuran formulasi berkisar dari sekitar 52 hingga 390 nm dengan efisiensi enkapsulasi yang kerap melampaui 85%; penargetan melalui reseptor folat memberikan peningkatan *uptake* yang paling *reproducible*. Strategi kombinasi secara konsisten mengungguli monoterapi secara *in vivo*, termasuk perpanjangan kelangsungan hidup. Namun, nyaris tidak adanya data farmakokinetik sistemik dan toksisitas jangka panjang, model yang belum representatif, serta tantangan skalabilitas menunjukkan bahwa pengembangan lebih lanjut yang substansial masih diperlukan sebelum evaluasi klinis.

Kata Kunci: Apoptosis, Kanker serviks, Nanokurkumin, Sistem penghantaran obat

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide, with an estimated 660,000 new cases and 350,000 deaths in 2022, 94% of which occurred in low- and middle-income countries.[1] Several countries across Asia and Oceania bear a disproportionately high burden, with age-standardized incidence rates exceeding 20 per 100,000 and mortality surpassing 10 per 100,000.[2] Since 1999, concurrent chemoradiotherapy, which combines platinum based chemotherapy with external-beam radiotherapy and brachytherapy, has been the international standard of care.[3] Yet even with surgery for early stage disease and chemoradiotherapy for advanced disease, treatment outcomes remain suboptimal.[4] A central reason is that tumors readily develop resistance to the single agent regimens commonly used.[5] Such resistance frequently emerges when agents like paclitaxel, cisplatin, or gemcitabine are given without combination partners.[6,7] In the case of cisplatin, resistance arises through the dysregulation of multiple molecular pathways, including enhanced DNA repair, drug efflux via P-glycoprotein, disruption of Bcl-2 family apoptotic signaling, and changes in the tumor microenvironment driven by hypoxia and elevated growth factors, which together sustain cancer cell survival and worsen patient prognosis.[8]

Cervical cancer is closely linked to persistent infection with high risk human papillomavirus (HPV), whose oncoproteins E6 and E7 are the principal drivers of malignant transformation. E6 forms a complex with E6-associated protein (E6AP) to target p53 for degradation through the ubiquitin–proteasome pathway, while E7 binds and inactivates the retinoblastoma protein (pRb), disrupting the pRb E2F complex and triggering uncontrolled cell cycle progression9. The simultaneous loss of p53 and pRb function disables both cell cycle control and apoptosis induction, conferring resistance to programmed cell death. This state sustains tumor cell survival while limiting the effectiveness of conventional therapy10. Therapeutic strategies capable of restoring apoptotic competence, particularly those acting on the E6/E7–p53/Rb axis, therefore carry a mechanistic relevance specific to cervical cancer.

Medicinal plants offer promising potential in cancer therapy, not only through tumor suppression but also by enhancing immune function and reducing the side effects of conventional treatments such as chemotherapy and radiotherapy.[11] Plant secondary metabolites containing bioactive compounds such as polyphenols, tannins, flavonoids, and glycosides have demonstrated anticancer activity, making them potential candidates for safer cervical cancer therapy.[12] Curcumin, in particular, exerts anticancer activity by modulating multiple molecular pathways governing proliferation, the cell cycle, apoptosis, metastasis, angiogenesis, and inflammation. It can also target cancer stem cells and sensitize tumor cells to chemotherapy and radiotherapy.[13] Its clinical use, however, is severely constrained by very low aqueous solubility, poor absorption, rapid metabolism, and high systemic clearance, all of which make effective concentrations in plasma and target tissues difficult to achieve.[14] These limitations have motivated the development of nanomedicine-based delivery systems, which can deliver drugs selectively to tumor sites and thereby improve therapeutic efficacy, minimize toxicity, and enhance clinical outcomes.[15]

Although a number of studies have evaluated nanocurcumin formulations in cervical cancer models, a systematic synthesis of this evidence remains limited and fragmented. Existing systematic reviews have not specifically examined the intersection of curcumin nanoformulation, apoptotic pathways, and cervical cancer in an integrated way. One prior review synthesized the anticancer activity of curcumin, gingerol, and shogaol in cervical cancer across various signaling pathways, but explicitly excluded nanocarrier based formulations and did not center apoptotic pathways as its focus16. Another reviewed nanocurcumin comprehensively but spanned multiple cancer types, so cervical cancer was treated as only one component and not examined in depth.[17]

As a result, three things remain poorly synthesized: the relationship between the physicochemical characteristics of nanocurcumin and its apoptotic efficacy, the convergence of diverse formulations on shared molecular pathways, and the action specific to the HPV E6/E7–p53/Rb axis in cervical cancer. This systematic review therefore aims to evaluate the molecular mechanisms of apoptosis, physicochemical characteristics, and preclinical efficacy of nanocurcumin formulations in cervical cancer, in order to clarify the determinants of apoptotic activity and identify the translational gaps that must be bridged before clinical application.

2. Materials and Methods

2.1. Study Design

This systematic literature review's design to evaluate the apoptotic mechanisms, physicochemical characteristics, and preclinical efficacy of nanocurcumin in cervical cancer. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews.[35]

2.2. Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) original research articles published in peer-reviewed journals, (2) published in English from 2015 onwards 2025, the year 2015 was selected as the lower bound to ensure the review captured a recent, decade spanning body of evidence reflecting current nanoformulation design, characterization, and testing practices, (3) investigated the effects of nanocurcumin or curcumin-based nanoformulations on cervical cancer cell lines or animal models, and (4) reported outcomes related to apoptosis or apoptotic molecular pathways. Studies were excluded if they were review articles, systematic reviews, meta-analyses, book chapters, conference proceedings, editorial, or meeting abstracts. For the purpose of this review, the term "nanocurcumin or curcumin–based nanoformulations" in criterion was defined broadly by design to capture the full range of nanoscale delivery strategies reported for curcumin in cervical cancer. Studies conducted exclusively on non–cervical cancer models without relevant apoptotic data were also excluded.

2.3. Search Strategy

A comprehensive literature search was conducted across four electronic databases: PubMed, Scopus, ScienceDirect, and SpringerLink. The search was performed using the following Boolean query: ("cervical cancer" OR "cervical carcinoma" OR "cervical neoplasm" OR "Uterine Cervical Neoplasms" OR HPV OR Hela OR Siha OR Caski) AND (curcumin OR nanocurcumin OR "nano curcumin" OR "curcumin nano" OR "curcumin nanoparticle") AND (apoptosis OR apoptotic OR "programmed cell death" OR caspase). No additional filters beyond language and publication year were applied during the initial search

2.4. Study Selection

Search result from all databases were imported into Parsif.ai, which performed automated deduplication; any additional duplicates identified during manual screening were subsequently flagged and marked as duplicate. The selection process was carried out in two sequential phases. In the first phase, titles and abstracts were screened against the eligibility criteria. In the second phase, full texts of potentially eligible records were retrieved and assessed in detail. Records that could not be retrieved were noted and excluded. Title/abstract screening and full-text assessment were performed independently by two reviewers (ONA and WOS). Disagreements at either stage were resolved through discussion, with a third reviewer consulted if consensus could not be reached. The entire selection process is summarized in a PRISMA 2020 flow diagram (Figure 1).

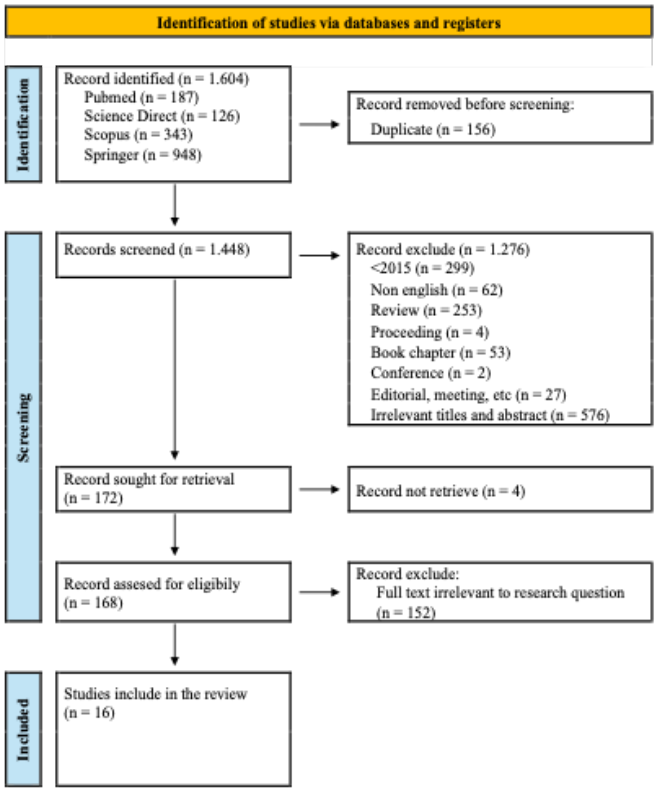

Figure 1. Flowchart of the article screening procedure in PRISMA Diagram. Only 16 articles were included in this review

2.5. Data Extraction

Relevant data were extracted from each included study using a standardized extraction form. The following information was collected: author(s) and year of publication, study design, cell line or animal model used, type of nanofromulation, physicochemical characteristics, molecular targets and apoptotic pathways reported, and key findings related to apoptosis outcomes (Table. 1)

2.6. Quality Assesment

The methodological quality of each included article was evaluated using the JBI Critical Appraisal Checklist18, consisting of 9 items tailored for quasi-experimental studies. Assessment was conducted independently by two evaluators (ONA, WOS), with each item rated as “yes”, “no”, “unclear”, or “not applicable (N/A). Disagreements between evaluators were resolved through discussion until consensus was reached.

Table 1. Characteristics of Included Studies

Ref	Study design	Model	Nanoformulation	Apoptosis Assay	Physicochemical Characteristics	Key Molecular Finding
Khan et al. (2016)20	In vitro	HeLa, SiHa, CaSki, C33a	Curcumin-loaded chitosan nanoparticles (CLCsNPs) ± methyl jasmonate	TUNEL	Size ~197±16.8 nm; zeta +71±6.4 mV; EE ~85%; DL 5.6%	↑Bax, ↓Bcl-2; TUNEL-assessed apoptosis; nuclear morphology changes.
Jaiswal & Mishra (2018)24	In vitro	HeLa, MCF-7	Curcumin serratiopeptidase nanoparticles (Cur-SPD NPs)	Single cell gel electrophoresis (Comet)	Size ~175±15 nm (SEM ~181±21); zeta −37±3 mV; release ~95% (8 hour)	Apoptosis (DAPI); ROS↑; DNA damage (Comet assay)
Wang et al. (2024)30	In vitro + in vivo	HeLa; xenograft mouse model + photothermal therapy (PTT)	CaCO3-encircled hollow CuS nanovehicles (CUR/HCA)	TUNEL	Diameter ~250 nm (DLS); zeta 25.78→5.31 mV post-loading; CUR loading 8.53 wt%	Mitochondrial Ca^{2+} overload → caspase activation; mitochondrial damage ATP↓ → apoptosis
Karimi et al. (2025)25	In vitro + in vivo	TC-1 (HPV16 E6/E7); mouse model	Curcumin nanoemulsion (Cur-NE)	Flow cytometry	Size 52.5 nm; PDI 0.03; zeta −13.1 mV; drug content 96.3%	↓E6/E7; apoptosis↑ (superior to free curcumin)
Wang et al. (2019)31	In vitro + in vivo	HeLa; xenograft mice	Folic acid modified PEGylated liposomal curcumin ((DSPE)-PEG2000-FA-LPs/CUR)	Flow cytometry	Size 112.3 nm; PDI 0.19; zeta −15.3 mV; EE 87.6%; DL 7.9%; uptake 66.4%	Apoptosis/kematian sel meningkat (dibanding non-FA dan Cur bebas); targeting folate receptor
Xiong et al. (2024)34	In vitro + in vivo	HeLa; xenograft mice	Curcumin analog CA7 liposome (CA7-LP)	Flow cytometry	Size 92.43 nm; PDI 0.27; EE 97.79%; DL 3.23%; zeta −6.69 mV	↑Total Apoptosis (flow cytometry); G2/M cell cycle arrest; superior to free CU and cisplatin injection
de Matos et al. (2018)22	In vitro	CasKi, SiHa; HaCaT (normal)	Curcumin nanoemulsion + photodynamic therapy (CNE + PDT)	Caspase 3/7 activity	PDI <0.2 (monodisperse); cyroplasmic internalization up to 36–48 h	↑ Caspase-3/7 activity (executioner): apoptosis via caspase pathway (intrinsic/ extrinsic)
Luong et al. (2017)27	In vitro	HeLa, SKOV3	FA-conjugated polymeric micelles (FA-SMA-CDF; curcumin difluorinated analog)	Annexin V/7-AAD	↑Size post-FA conjugation; negative zeta potential; altered drug loading post-FA	↑PTEN; ↓NF-κB; ↑apoptosis (Annexin V/7-AAD)
Thulasidasan et al. (2017)28	In vitro	HeLa vs HaCaT; paclitaxel combination	FA-PLGA-PEG nanoparticles (PPF-curcumin)	Caspase 9/3 activity	Size 100–200 nm (TEM); sustained release; uptake via FOLR1	↓survival signals (p38, NF-κB, AP-1, IAPs, p-Akt, p-Erk) → apoptosis; ↑ cleavage caspase-9/3

Salehi et al. (2022)36	Formulasi + in vitro	HeLa	Thermosensitive vaginal hydrogel containing curcumin-loaded thiolated chitosan NPs (PF127-CRC-TCNPs)	Cell viability only	High EE/LE (concentration-dependent); positive charge facilitates mucoadhesion	No specific apoptotic markers reported; outcomes focused on cell viability
Vahedian Sadeghi et al. (2022)26	In vitro (+ referenced in vivo)	HeLa; BALB/c tumor-bearing mice (referenced)	Nano-curcumin OA400 dendrosome	Flow cytometry	Diameter ~200 nm; PDI 0.4; zeta ~7; loading efficiency 87%	↓E6/E7 → ↑p53 & Rb; ↑apoptosis (flow)
Nath et al. (2023)21	In vitro	SiHa (HPV16+) + HEK-293 (normal)	Iron oxide silver curcumin nanocomposite (Cur-NC)	Western blot	Drug loading 98.51%; ↑internalisasi (1.64); pH-dependent release	↑Bax/↓Bcl2; cytochrome-c → ↑Apaf1 → ↑caspase-9/3/7 cleavage; PARP1/DFF45 mediated DNA fragmentation; ↓PI3K/AKT/mTOR
Ma et al. (2015)32	In vitro + in vivo (post-surgical recurrence prevention)	HeLa (in vitro); KM mice (U14) tumor recurrence model (in vivo)	Nanofibers co-loaded with cisplatin + curcumin (cis-cur/fiber)	Flow cytometry	Fiber diameter 588–703 nm; EE curcumin 87%; EE cisplatin 60%	Markedly ↑ Late apoptosis with combination (62,7%); synergistic local delivery effect
Elbialy et al. (2020)33	In vitro	HeLa; HepG2	PEG-coated mesoporous silica nanoparticles (PEG-MSNPs-Cur)	Morphology	Size ~184.6±13.69 nm; zeta 20.8±4.28 mV; drug loading ~92.4%	Apoptosis morphology; cell cycle arrest; pH-responsive/sustained release supports apoptosis induction
Gawde et al. (2018)29	In vitro (synergistic combo)	HeLa; SKOV3	Albumin nanoparticles ± folate targeting (FA-BSA-CDF; FA-BSA-PTX)	Flow cytometry	Size FA-BSA-CDF ~197.8 nm; zeta −37.21 mV; folate receptor mediated uptake	↑PTEN/↓EZH2; ↑apoptosis in targeted vs non-targeted and free drug groups
Lakshmi et al. (2021)23	In vitro	HeLa	Ruthenium(II)-curcumin complex loaded liposome NPs (RCLNPs)	DCFH-DA, Hoechst	LNP ~250–290 nm; RCLNP ~350–390 nm; drug loading ~91.9%	ROS↑ (DCFH-DA); nuclear damage (Hoechst staining); ROS-mediated DNA damage → apoptosis

↑: increase; ↓ : decrease

Following common application of the JBI checklist in preclinical systematic reviews, studies scoring ≥7 of 9 applicable "yes" items were classified as high methodological quality, 4–6 as moderate, and ≤3 as low. This threshold was defined a priori and applied uniformly across all 16 included studies (Table 2) to allow the quality gradient to inform, rather than simply accompany, the confidence placed in each study's findings during synthesis. All included articles were retained in the synthesis regardless of their scores; however, methodological quality was considered in the interpretation of results.

3. Results

3.1. Study Selection and Characteristics.

A total of 1,604 records were identified across the four databases; after deduplication and screening against the eligibility criteria, 16 preclinical studies published between 2015 and 2025 met all inclusion criteria (Figure 1). Of these, 10 studies (62.5%) were conducted exclusively in vitro, while 6 studies (37.5%) incorporated both in vitro and in vivo components, using murine xenograft, syngeneic tumor, or post-surgical recurrence models. Full study-level details are summarized in Table 1.

3.2. Cancer Cell Lines.

HeLa was the most frequently used cervical cancer cell line, appearing in 13 of the 16 studies, either alone or alongside SiHa, CaSki, C33A, or the murine HPV16 E6/E7-transformed line TC-1. Three studies additionally included a non-malignant cell line (HaCaT or HEK-293) as a selectivity control against normal cells, and three studies included a non-cervical comparator line (MCF-7, HepG2, or SKOV3) to benchmark formulation performance.

3.3. Nanoformulation Types.

The 16 formulations spanned seven nanocarrier platforms: polymeric or protein-based nanoparticles

Table 2. Methodological quality assessment of included studies (JBI Critical Appraisal Checklist)[18]

Ref	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Khan et al. (2016)[20]	✓	✓	✓	✓	✓	✓	✓	–	–
Jaiswal & Mishra (2018)[24]	✓	✓	✓	✓	–	✓	✓	–	✓
Wang et al. (2024)[30]	✓	✓	✓	✓	✓	✓	✓	–	✓
Karimi et al. (2025)[25]	✓	✓	✓	✓	–	✓	✓	–	✓
Wang et al. (2019)[31]	✓	✓	✓	✓	✓	✓	✓	–	✓
Xiong et al. (2024)[34]	✓	✓	✓	✓	–	✓	✓	–	✓
de Matos et al. (2018)[22]	✓	✓	✓	✓	✓	✓	✓	–	✓
Luong et al. (2017)[27]	✓	✓	✓	✓	–	✓	✓	–	✓
Thulasidasan et al. (2017)[28]	✓	✓	✓	✓	✓	✓	✓	–	✓
Salehi et al. (2022)[36]	✓	✓	–	–	✓	✓	✓	–	✓
Vahedian Sadeghi et al. (2022)[26]	✓	✓	✓	✓	✓	✓	✓	–	✓
Nath et al. (2023)[21]	✓	✓	✓	✓	✓	✓	✓	–	✓
Ma et al. (2015)[32]	✓	✓	✓	✓	✓	✓	✓	–	✓
Elbialy et al. (2020)[33]	✓	✓	–	–	✓	✓	✓	–	✓
Gawde et al. (2018)[29]	✓	✓	✓	✓	✓	✓	✓	–	✓
Lakshmi et al. (2021)[23]	✓	✓	–	–	✓	✓	✓	–	✓

(chitosan, PLGA, or albumin; 4 studies), liposomal or dendrosomal carriers (4 studies), metal or metal-oxide nanocomposites (2 studies), nanoemulsions (2 studies), and one study each for polymeric micelles, mesoporous silica nanoparticles, electrospun nanofibers, and a thermosensitive mucoadhesive hydrogel. Particle size across formulations ranged from approximately 52 nm to 390 nm, and encapsulation or drug-loading efficiency, where reported, ranged from approximately 60% to 98%.

3.4. Apoptosis Assessment Methods.

Apoptosis induction was evaluated using flow cytometry-based assays (Annexin V/7-AAD or propidium iodide staining) in at least 4 studies, caspase activity or cleavage assays (including Western blot for caspase-3/7/9, Bax/Bcl-2, and PARP) in at least 5 studies, and nuclear or morphological staining (TUNEL, DAPI, or Hoechst) in at least 4 studies; several studies combined more than one method. Complementary endpoints included reactive oxygen species detection (DCFH-DA) and DNA damage assessment (comet assay) in one study each. One study[19] did not report a specific apoptosis biomarker, evaluating cell viability instead.

3.5. Main Findings by Study Group.

Across the 16 studies, nanoencapsulation of curcumin alone consistently increased apoptotic markers relative to free curcumin, primarily through activation of the intrinsic mitochondrial pathway (upregulated Bax, downregulated Bcl-2, caspase activation). Actively targeted formulations, particularly those using folate-receptor conjugation, showed the most reproducible increase in cellular uptake and apoptotic response compared with non-targeted counterparts. In the five studies that directly compared nanocurcumin combined with an adjuvant strategy against nanocurcumin monotherapy, the combination consistently produced a greater apoptotic response. In the six studies with an in vivo component, nanocurcumin formulations reduced tumor volume, extended survival, or reduced post-surgical recurrence relative to controls or free curcumin; however, none of these studies reported comprehensive systemic pharmacokinetic or long-term toxicity data.

3.6. Quality Assessment.

Methodological quality was appraised independently by two reviewers using the JBI Critical Appraisal Checklist for Quasi–Experimental Studies18 (9 items; Table 2). All 16 studies clearly reported a distinguishable cause–effect relationship and included a control or comparator group (Items 1–2: 16/16). Reporting was less consistent for comparability of participants across comparison groups (Item 3: 13/16), equivalence of co-interventions/care other than the exposure of interest (Item 4: 14/16), and the use of multiple pre- and post-intervention measurements (Item 5: 12/16). Outcome measurement approach was consistent across comparison groups in all studies (Item 6: 16/16), and outcome measurement reliability and statistical analysis were adequate in the large majority of studies (Items 7 and 9: 15/16 each). Notably, none of the 16 studies reported complete

follow–up data (Item 8: 0/16); this reflects the short-duration, endpoint-driven design typical of in vitro and early–stage in vivo pharmacological studies rather than a specific flaw in any individual study. Overall, methodological quality was moderate to good for internal validity items (cause-effect clarity, control groups, and outcome measurement consistency), but showed a systematic gap in longitudinal follow–up reporting, a limitation that reinforces the translational gaps discussed in Section 4.8.

4. Discussion

The 16 studies included in this review evaluated curcumin or curcumin-analog nanoformulations against cervical cancer models, predominantly the HeLa, SiHa, CaSki, and C33A cell lines, with several studies extending to murine xenograft or recurrence models. The formulations spanned polymeric nanoparticles, liposomes, polymeric micelles, nanoemulsions, mesoporous silica carriers, metal and metal-oxide nanocomposites, and electrospun nanofiber matrices. The following sections synthesize the evidence across three dimensions: the molecular basis of apoptosis induction, the physicochemical profile of the formulations, and the relationship between those physicochemical properties and biological performance.

4.1. Molecular Mechanisms of Nanocurcumin–Induced Apoptosis

Across the included studies (Table 1), nanocurcumin induced cell death in cervical cancer models converged on apoptosis, although the upstream triggers and the relative weight of each pathway differed by formulation and cellular context. Four mechanistic routes recurred: the intrinsic mitochondrial pathway, reactive oxygen species (ROS)-mediated oxidative stress suppression of GPV E6/E7 oncogene expression and inhibition of survival signaling.

The mitochondrial (intrinsic) pathway was the most consistently reported mechanism

Several studies documented the canonical sequence of B-cell lymphoma 2 (Bcl-2) family modulation, mitochondrial membrane permeabilization, cytochrome c release, and caspase activation. Curcumin–loaded chitosan nanoparticles upregulated the pro–apoptotic protein Bax and concurrently downregulated the anti–apoptotic protein Bcl-2 in HeLa and SiHa cells, with the effect maximized when combined with methyl jasmonate[20]. This cascade was described in the greatest mechanistic detail for an iron oxide-silver-curcumin nanocomposite, which sifted the Bax/Bcl02 ratio, promoted Bax oligomerization on the outer mitochondrial membrane, and drove cytosolic cytochrome c release, apoptosome assembly with apoptotic protease activating factor 1 (Apaf-1) and procaspase-9, and downstream cleavage of caspase-3 and caspase-7, culminating in poly(ADP-ribose) polymerase 1 (PARP1) cleavage and DNA fragmentation21. Consistent observations of executioner caspase activation (caspase-3, -7, and -9) were reported for a curcumin-nanoemulsion photodynamic system[22] and for a ruthenium(II)–curcumin liposomal complex acting on cellular genetic material[23]. The former study further noted that because caspase-3 and caspase-7 are executioner caspases, their activation alone could not discriminate between intrinsic and extrinsic initiation[22], a useful methodological caveat that distinguishes that interpretation from studies inferring the intrinsic pathway less cautiously.

ROS generation functioned both as an apoptotic trigger and as the basis for tumor selectivity.

Curcumin co-delivered with serratiopeptidase produced elevated ROS in HeLa and MCF-7 cells, accompanied by substantial DNA damage measured by comet assay, and the authors argued that encapsulation converted curcumin from its conventional antioxidant behavior to a pro-oxidant one as a consequence of high intracellular loading[24]. Apoptosis was similarly attributed to a disruption of redox homeostasis, with ROS accumulation upsetting mitochondrial membrane potential, for the iron oxide–silver nanocomposite[21], and a ROS-dependent mechanism was proposed for the ruthenium–curcumin system[23]. Notably, two studies framed ROS as the source of curcumin's preferential toxicity toward malignant cells: the depletion of intracellular glutathione characteristic of cancer cells was reasoned to elevate ROS and thereby sensitize those cells to curcumin while sparing normal cells[25]. This selectivity argument is mechanistically important because it offers an explanation for the favorable safety margins reported elsewhere in the dataset.

Suppression of HPV E6/E7 oncogenes provided a cervical-cancer-specific mechanism absent from genric anticancer account.

This is arguably the most disease-relevant finding in the corpus. A curcumin nanoemulsion significantly reduced E6 and E7 expression in HPV-16-positive TC-1 cells relative to free curcumin, and these oncoproteins were noted to inactivate the tumor suppressors p53 and retinoblastoma protein (Rb) and thereby deregulate the cell cycle[25]. The reciprocal molecular consequence was reported for a curcumin-loaded OA400 dendrosomal carrier, which downregulated E6 and E7 in HeLa cells, and the resulting de-repression

restored p53 and Rb expression at both the transcript and protein levels, establishing a condition permissive for apoptosis[26]. The convergence of these two studies on the E6/E7–p53/Rb axis, using different carriers and different HPV-positive models, strengthens the inference that nanocurcumin acts on the viral driver of malignancy rather than through cytotoxicity alone.

Inhibition of pro-surival signaling constituted the fourth mechanism, with the PI3K/AKT and NF-kB pathways most frequently implicated.

The curcumin nanocomposite reduced nuclear factor kappa B (NF-κB), phosphorylated phosphoinositide 3-kinase (p-PI3K), and phosphorylated protein kinase B (p-Akt) while increasing the inactive unphosphorylated forms, and suppression of the PI3K/Akt/mTOR axis was identified as the basis for concurrent autophagy and apoptosis[21]. A difluorinated curcumin analog (CDF) in folate-targeted micelles upregulated phosphatase and tensin homolog (PTEN) and downregulated NF-κB in HeLa cells, linking PTEN restoration to antagonism of the PI3K/Akt pathway and to reduced chemoresistance[27]. Folate-targeted PLGA-PEG curcumin downregulated a broad panel of paclitaxel-induced survival signals (p38, NF-κB, activator protein 1 [AP-1], inhibitor of apoptosis proteins [IAPs], phospho-Akt, phospho-Erk), positioning curcumin as a chemosensitizer that lowers the apoptotic threshold[28]. The same CDF analog was connected to downregulation of multiple microRNAs and upregulation of PTEN in an albumin nanoparticle system[29]. The recurrence of NF-κB suppression and PTEN upregulation across structurally distinct formulations indicates that these nodes are robust pharmacological targets of curcumin rather than artifacts of any single delivery system.

Finally, several studies reported cell cycle arrest as a complementary route to reduced viability, most often G2/M arrest[29] or broad multi-phase blockade, and two studies described curcumin-specific mechanisms outside the four major categories. A calcium-overload mechanism was reported in which curcumin sustained endoplasmic reticulum Ca^{2+} release and, combined with exogenous Ca^{2+} from a $CaCO_3$ coated CuS nanovehicle, induced mitochondrial calcium overload and apoptosis[30], and autophagy–apoptosis crosstalk was documented through upregulation of autophagy related 5–12 (Atg5–12), Beclin-1, and microtubule-associated protein 1 light chain 3-II (LC3-II)21. These divergent mechanisms illustrate that the carrier chemistry itself can introduce apoptotic triggers beyond those of curcumin alone.

4.2. Physicochemical Characteristics of Nanocurcumin Formulations

The included formulations varied widely in particle size, surface charge, encapsulation efficiency, and carrier architecture. These parameters are summarized below by property, because the cross-study spread on each is what later permits a structure–activity analysis in Section 4.3.

Particle size.

Reported hydrodynamic or microscopy-derived diameters ranged from approximately 52 nm to nearly 390 nm. Nanoemulsions occupied the small end of the distribution, with an average particle size of 52.5 nm and a polydispersity index (PDI) of 0.03, the narrowest dispersity in the dataset[25]. Liposomal and micellar systems clustered in the intermediate range, including 92.4 nm for the curcumin-analog liposome CA7-LP [7] and 112.3 nm for folate-modified liposomal curcumin[31]. Polymeric, mesoporous silica, and protein-based nanoparticles generally fell between roughly 160 and 200 nm: 162.8–197.8 nm for albumin formulations29, 175–181 nm for curcumin–serratiopeptidase nanoparticles[24], 184.6 nm for PEGylated mesoporous silica [15], 189–197 nm for chitosan nanoparticles20, and approximately 200 nm for the OA400 dendrosome[26]. The largest constructs were metal-based: the ruthenium–curcumin liposome reached 350–390 nm after drug loading[23], and the $CaCO_3$-coated CuS nanovehicle measured approximately 250–270 nm[30], The electrospun nanofibers represent a distinct format, with fiber diameters of 588–703 nm[32]. Multiple authors explicitly invoked the sub-200 nm threshold as a design target for drug delivery and mucosal uptake[24], a point that becomes analytically relevant in Section 4.3.

Surface charge (zeta potential).

The dataset divided sharply into positively and negatively charged systems, and this split is the single most informative physicochemical contrast in the corpus. Chitosan-based and certain metal-oxide or silica systems carried strongly positive charges: +71 to +76 mV for curcumin-loaded chitosan nanoparticles20, +20.8 to +38.3 mV across the PEGylation stages of mesoporous silica33, and a positive surface charge for the OA400 dendrosome26. The colloidal-stability rationale was articulated for the chitosan system, noting that a magnitude beyond ±30 mV is generally required for a stable nanosuspension20. In direct contrast, the liposomal, micellar, nanoemulsion, and albumin systems were negatively charged: −37 mV for curcumin–serratiopeptidase nanoparticles [3], −15.3 mV for folate liposomes31, −13.1 mV for the nanoemulsion25, −6.69 mV for CA7-LP34, and −37 to −68 mV for albumin nanoparticles before and

after folate conjugation[29]. Notably, several studies treated a near-neutral or slightly negative charge as the preferred state rather than a deficiency: a slightly negative or neutral surface was argued to be ideal because highly negative particles are eliminated through repulsion from the negatively charged cell membrane[29], and neutralizing a high negative charge by folate conjugation was noted to reduce uptake by phagocytic cells[27]. The coexistence of a "more positive is better" rationale (for chitosan stability and mucoadhesion) and a "slightly negative is better" rationale (for circulation and reduced phagocytic clearance) is not a contradiction in the data so much as evidence that the optimal charge is route- and carrier-dependent.

Encapsulation/loading efficiency

Encapsulation efficiency (EE) was high across nearly all carrier classes, frequently exceeding 85%. The highest values were reported for metal and silica systems: approximately 98.5% curcumin loading for the iron oxide-silver nanocomposite21, 92.4% for mesoporous silica[33], and 91.9% drug loading content for ruthenium-curcumin liposome[23]. Liposomal and analog systems also performed strongly, with 97.8% EE for CA7-LP35 and 87.6% EE for folate liposomes[31]. Polymeric systems reported approximately 85% entrapment for chitosan nanoparticles[20] and 70.8 – 81.8% for thiolated chitosan nanoparticles36. Drug loading (the mass fraction of drug in the carrier) was, as expected, far lower than EE, typically in the single digits, for example 5.6% for chitosan nanoparticles20, 7.9% for folate liposomes[31], and 3.2% for CA7-LP35 reflecting the structural distinction between efficient entrapment and absolute carrying capacity. For the dual-drug nanofiber system, 87.0% EE was reported for curcumin and 60% for cisplatin, illustrating that co-encapsulation efficiency is reagent-specific within a single matrix[32].

Carrier systems and release behavior

The carrier architectures fell into several families, each with characteristic release behavior. Polymeric nanoparticles (chitosan, thiolated chitosan, PLGA-PEG) and mesoporous silica generally produced sustained release; this was attributed to curcumin existing in an amorphous or disordered-crystalline state within the polymeric matrix[20], and to acidic-pH-responsive behavior in the tumor microenvironment for the silica system[33]. Liposomal and nanoemulsion systems were valued for solubilizing the lipophilic drug and improving biostability[25,31], with several exhibiting biphasic release comprising an initial burst followed by slower diffusion-controlled release[24,35]. Stimulus-responsiveness recurred as a design theme: pH-dependent release favoring the acidic tumor or endolysosomal environment was reported for the metal-oxide nanocomposite[21] and mesoporous silica[33]. Two formats targeted local delivery to the cervix specifically: a thermosensitive Pluronic F127 vaginal hydrogel embedding curcumin-loaded thiolated chitosan nanoparticles36 and an implantable nanofiber mat conformable to the vaginal or cervical geometry[32]. Surface engineering for active targeting principally folate conjugation exploiting folate receptor overexpression was a further recurring strategy[27–29,31].

4.3. Influence of Physicochemical Characteristics on Cellular Uptake and Apoptotic Efficacy

The section moves from cataloguing to testing wheter they predict performance. The central question for a structure-activity synthesis is whether any single physicochemical parameter reliably governs cellular uptake and apoptotic potency across the corpus. The evidence indicates that no individual parameter does so in isolation; rather, uptake and efficacy emerge from the interaction of size, surface chemistry, targeting ligand, and the cellular context, and several apparent rules in the dataset are contradicted by counterexamples.

Encapsulation per se improved uptake and potency in every head-to-head comparison, establishing the baseline effect.

This is the most robust relationship in the dataset: across structurally unrelated carriers, the nanoformulation outperformed free curcumin on both uptake and apoptosis induction. The superior efficacy of the nanoemulsion was attributed to enhanced cellular uptake and biostability conferred by nano-sizing and encapsulation, with a lower IC_{50} (35 µg/mL vs. 55 µg/mL) and higher apoptosis (46.3% vs. 36.65%) than free curcumin[25]. Nanocurcumin induced apoptosis in 46.5% of HeLa cells at 15 µM, whereas free curcumin required 50 µM to reach only 25.9%, a difference attributed to higher cellular uptake and biostability[26]. This difference was directly visualized for a $CaCO_{3}$- coated CuS nanovehicle, which produced markedly stronger intracellular curcumin fluorescence than free curcumin owing to the latter's poor aqueous solubility[30]. The same directional result was reported for mesoporous silica[33], the iron oxide–silver nanocomposite[21], and chitosan nanoparticles[20]. This consistency confirms that overcoming curcumin's solubility and stability limitations is the necessary first step, against which the contribution of specific physicochemical parameters must be assessed.

Surface charge influenced uptake, but its effect was conditional rather than monotonic.

The data do not support a simple "positive charge enhances uptake" rule. For positively charged systems engaging the negatively charged cell membrane or mucosa, a positive zeta potential was reported as advantageous: the size range and positive charge of the nanocomposite were stated to favor contact with and endocytosis by the negatively charged SiHa membrane while resisting premature clearance[21], and electrostatic bonding between positively charged nanoparticles and the negatively charged mucous layer was invoked as a mucoadhesion mechanism36. Yet the highest-uptake, lowest- IC_{50} systems in the entire corpus were negatively charged liposomes and micelles whose uptake was driven not by charge but by receptor-mediated endocytosis (discussed below). Moreover, reducing a strongly negative charge toward neutrality was explicitly argued to improve circulation and lower phagocytic clearance[27,29]. The reconciliation is that charge governs the non-specific electrostatic component of uptake and colloidal stability, and its optimal sign depends on whether the design relies on electrostatic mucoadhesion, on prolonged systemic circulation, or on an active-targeting mechanism that supersedes charge altogether.

Active targeting by folate conjugation produced the most pronounced and best-quantified uptake gains, frequently overriding charge considerations.

The four folate-targeted studies provide the clearest dose–response-like evidence linking a surface modification to uptake and potency. A stepwise increase in cellular uptake ratio was reported from 5.7% (free curcumin) to 16.5% (curcumin liposomes) to 38.4% (PEGylated liposomes) to 66.4% (folate-PEG liposomes) in HeLa cells, with a corresponding fall in IC_{50} to 0.45 µg/mL, the lowest curcumin IC50in the dataset, despite the carrier being negatively charged[31]. Folate conjugation reduced the IC50of the analog micelle approximately 2.7-fold in HeLa cells and raised apoptosis from 25.1% to 36.6%, an effect attributed to folate-receptor-mediated endocytosis in receptor-overexpressing cells3[1]. The same conclusion was reached in HeLa models for folate PLGA-PEG curcumin[28] and for the albumin formulation, the latter reporting roughly 10–20% more apoptotic cells for the targeted formulation than for free drug[29]. Critically, uptake and cytotoxicity were observed to track folate receptor abundance across cell lines HeLa, with higher folate receptor expression, showed greater apoptosis than SKOV-3[28,29] demonstrating that the uptake advantage is contingent on a cellular feature (receptor density) and not on the nanoparticle properties alone. This receptor-dependence is the strongest single piece of structure activity evidence in the corpus precisely because it isolates one variable.

Size shaped the uptake route and biodistribution, but did not by itself rank potency

Several authors connected sub-200 nm dimensions to specific internalization pathways: ~180 nm particles were associated with clathrin- or caveolin-mediated endocytosis and lysosomal escape[24], a ~92–100 nm liposome was linked to reticuloendothelial uptake and passive tumor targeting3[5], and the enhanced permeability and retention (EPR) effect was invoked for intermediate-sized particles[33,35]. However, size did not correlate monotonically with potency across the dataset: the smallest system (52.5 nm nanoemulsion[25]) and one of the most potent (112 nm folate liposome with IC_{50} 0.45 µg/mL31) differed roughly two-fold in size yet both outperformed their free-drug controls, while the very high loading of the larger metal nanocomposites compensated for their greater diameter[21,23]. Size therefore appears to be a gatekeeper of mechanism (which uptake pathway, whether EPR-mediated accumulation is feasible) rather than a direct determinant of ranked efficacy.

Sustained and stimulus-responsive release linked physicochemistry to the durability of the apoptotic effect.

Beyond getting curcumin into the cell, the kinetics of its release governed efficacy. The amorphous intramatrix state of curcumin was connected to sustained release and, in turn, to enhanced intracellular drug retention and anti-proliferative effect, with time-dependent uptake plateauing near 17 hours before proliferation was inhibited[20]. Cell cycle arrest was attributed specifically to sustained curcumin release over 24–48 hours, and the high therapeutic index was tied to acidic-pH-responsive release within the tumor microenvironment[33]. Higher cumulative release at pH 4.5 was reported, matching the endolysosomal compartment and thereby coupling release kinetics to the site of action[21]. These observations indicate that encapsulation contributes to efficacy not only by raising peak intracellular concentration but by prolonging exposure, which is consistent with the dose- and time-dependent viability reductions reported throughout the corpus[20,33].

Loading capacity modulated the qualitative pharmacology, not merely the dose.

A subtler structure-activity relationship emerged around drug loading. The high curcumin loading achieved in the serratiopeptidase nanoparticles was argued to be responsible for converting curcumin from antioxidant to pro-oxidant behavior, thereby amplifying the ROS-mediated apoptotic mechanism described in Section 3.124. This links a formulation parameter

(loading) directly to a mechanistic switch (redox role), and it illustrates that physicochemical characteristics can alter not just how much curcumin reaches the cell but how it behaves once there. The very high loading of the metal-based systems (≈92–98%23,24) is consistent with this principle, as both reported strong ROS-dependent cytotoxicity.

Synthesis

Taken together, the corpus supports a multifactorial model in which encapsulation establishes a baseline improvement in uptake and potency over free curcumin (universal across the dataset), active targeting via folate conjugation produces the largest and most receptor-contingent uptake gains, surface charge tunes non-specific uptake and colloidal stability in a route-dependent manner, particle size selects the internalization pathway and biodistribution mechanism, and release kinetics and loading capacity govern the duration and even the qualitative nature of the apoptotic effect. The most informative evidence comes from the within-study comparisons that isolate a single variable, particularly the folate-receptor-density comparisons[28,29] and the stepwise uptake series[31] because the between-study heterogeneity in cell lines, exposure times, IC50 units, and assay methods otherwise precludes direct numerical ranking of formulations. This methodological limitation, that the included studies are not standardized and therefore cannot be pooled quantitatively, is itself a finding and should temper any claim that one carrier class is categorically superior.

4.4. Preclinical Efficacy: In Vitro Evidence

Across the included studies, nanocurcumin demonstrated consistent antiproliferative and pro-apoptotic activity in cervical cancer cell models, although the magnitude of efficacy varied considerably depending on formulation type, cell line, and experimental conditions. Four dimensions of in vitro evidence are examined here: the range of IC50 values reported, apoptosis induction as a quantitative endpoint, the comparative advantage of nanocurcumin over free curcumin, and the formulation-specific factors that modulate the degree of that advantage.

Variation in IC50 Values Across Nanocurcumin Formulations.

The half-maximal inhibitory concentration (IC50) serves as the most frequently reported potency metric across the sixteen included studies, yet the reported values span an exceptionally wide range, from sub-microgram concentrations to tens of milligrams per liter, with several formulations not reporting a single IC50 value at all due to differences in assay design. The IC50 values reported across the sixteen included studies span an exceptionally wide range, reflecting the diversity of formulation types, cell lines, and assay conditions rather than straightforward differences in potency. At the most potent end, IC50 of 0.45 µg/mL for folate-conjugated PEGylated liposomal curcumin against HeLa cells, a greater than threefold reduction from free curcumin (1.47 µg/mL)31. while another study achieved a comparably low IC50 of 0.47 µM for FA-SMA-CDF micelles (2.7-fold lower than the non-targeted comparator)[27]. Intermediate values were reported for the bimetallic nanocomposite Cur-NC (IC50 12.5 µg/mL in SiHa, twofold lower than free curcumin)21, PEG-MSNPs-Cur (IC50 28 µg/mL in HeLa, with approximately fivefold higher cytotoxicity than free curcumin)[33], and Cur-NE (IC50 35 µg/mL versus 55 µg/mL for free curcumin)[25]. At the higher end, 31.25 mg/L for Cur-SPD NPs against HeLa [24], and 81.48 µg/mL for CLCsNPs against CaSki at 72 hours [20], figures that appear orders of magnitude higher but arise from different units, cell lines, and incubation periods rather than genuinely inferior formulation performance. These discrepancies underscore that raw IC50 magnitude should be interpreted as a qualitative indicator of relative potency within a given experimental system; the more reliable comparative signal remains the fold-reduction over free curcumin observed within each individual study.

Apoptosis Percentage as an Indicator of Efficacy.

The studies employing combinatorial delivery or multi-mechanistic nanoplatforms provide the clearest dose–response-like evidence linking formulation complexity to apoptotic potency. A stepwise escalation in apoptotic percentage was observed from 3.3% (cisplatin monotherapy) to 37.8% (free curcumin) to 62.7% (cisplatin–curcumin co-loaded nanofibers) in HeLa cells, with a corresponding shift toward late-stage apoptosis dominance, representing the highest combinatorial apoptotic output in the dataset despite neither agent achieving comparable efficacy independently[32]. Curcumin nanoencapsulation markedly increased apoptosis relative to free curcumin, even at lower concentrations, as evidenced by 46.5% apoptotic induction at 15 µM nano-curcumin compared with 25.9% at 50 µM free curcumin. This enhanced efficacy may be attributed to superior cellular internalization and extended intracellular bioavailability provided by the dendrosomal carrier[26]. The same directional conclusion was reached across nanoemulsion models, where 46.3% apoptosis at IC50 35 µg/ml with Cur-NE versus 36.65% with free curcumin at the higher concentration of 55 µg/ml ($P < 0.001$), with the critical additional observation that neither formulation exerted significant apoptotic effect

on normal MC3T3 cells, isolating nanoencapsulation rather than curcumin concentration as the determinant of selective cancer cell killing[25]. Critically, apoptotic percentage was observed to track detection methodology across studies: TUNEL-based measurements (13.54–21.47%)[20] systematically yielded lower values than Annexin V/PI flow cytometry 46.5%[26], not necessarily because of inferior formulation potency but because TUNEL exclusively captures late-stage DNA fragmentation whereas Annexin V/PI simultaneously quantifies early and late apoptotic subpopulations[37], demonstrating that the apparent apoptotic advantage is contingent on a methodological feature assay sensitivity and not on nanoparticle properties alone. This methodology-dependence is the strongest single confounding variable in cross-study comparisons precisely because it decouples true biological efficacy from reported numeric values, reinforcing the need for harmonized detection standards in future preclinical evaluations of nanocurcumin.

Nanocurcumin as a determinant of Enhanced Apoptotic Efficacy.

Across the 16 included studies, nanoformulated curcumin consistently demonstrated superior apoptotic potency relative to free curcumin at equivalent or lower concentrations: 46.5% apoptosis at 15 μM nano-curcumin versus 25.9% at 50 μM free curcumin26; cellular uptake elevation from 5.7% to 66.4% with a corresponding IC_{50} reduction from 1.47 to 0.45 μg/mL and 12.8-fold tumor volume reduction in vivo[31]; IC_{50} halving alongside concurrent autophagy induction absent in free curcumin-treated cells21; and fivefold greater cytotoxicity with PEG-MSNPs-Cur relative to free curcumin[33]. The reproducibility of this superiority pattern across structurally diverse platforms (liposomes, nanoemulsions, polymeric nanoparticles, and metallic nanocomposites) establishes nanoencapsulation as a platform-independent efficacy determinant. This finding is mechanistically supported by evidence that curcumin is a pleiotropic agent requiring adequate intracellular concentrations to fully manifest its oncosuppressive repertoire, including ROS-mediated autophagy flux, G2/M arrest, and p53-p21-dependent cellular senescence in addition to apoptosis[31]. Collectively, nanoencapsulation enables this full biological spectrum through protection from physicochemical degradation, EPR-mediated tumor accumulation, and facilitated intracellular delivery, positioning it as a pharmacological prerequisite rather than merely a delivery convenience for curcumin-based cervical cancer therapy.

Factors Modulating In Vitro Apoptotic Efficacy

Beyond nanoencapsulation per se, apoptotic magnitude was further governed by three discrete efficacy-amplifying strategies. First, active folate receptor-mediated targeting consistently produced the most quantifiable gains: folate conjugation elevated HeLa cellular uptake from 5.7% to 66.4% with IC_{50} reduction to 0.45 μg/mL despite a negative carrier charge, confirming that ligand receptor specificity overrides electrostatic considerations in receptor-overexpressing cells31; this was independently corroborated by a 2.7-fold IC_{50} reduction and apoptosis elevation from 25.1% to 36.6% in folate-conjugated nanomicelles[27]. Second, synergistic co-delivery with bioactive adjuvants further amplified apoptotic output: methyl jasmonate co-treatment elevated TUNEL-positive HeLa cells from 13.54% to 21.47%[20], while serratiopeptidase incorporation produced synergistic DNA damage with tail DNA reaching 67% and ROS induction of 89.7%, exceeding either component alone[24]. Third, externally triggered photodynamic activation achieved the most pronounced response in the dataset, reducing cell viability to 1.3–2.8% with caspase activity increasing up to 847% following dual irradiation efficacy levels unreachable by passive delivery alone[22]. Notwithstanding these findings, the heterogeneity of cell lines, assay platforms, and treatment regimens across studies precludes direct quantitative meta-analysis, underscoring the need for standardized preclinical evaluation frameworks in nanocurcumin research.

4.5. Preclinical Efficacy: In Vivo Evidence

While in vitro studies establish the mechanistic basis of nanocurcumin-induced apoptosis, in vivo evidence provides a higher tier of translational validity by incorporating pharmacokinetic distribution, tumor microenvironment interactions, and whole-organism therapeutic responses. Among the 16 included studies, six incorporated in vivo components, collectively reporting outcomes across three clinically relevant endpoints: tumor volume reduction, survival prolongation, and post-surgical recurrence prevention.

Tumor Volume Reduction in Xenograft Models.

The most quantitatively compelling in vivo evidence derived from xenograft models demonstrated substantial tumor volume reductions that significantly exceeded what free curcumin could achieve. Folate-targeted liposomal curcumin reduced tumor volume to 77.3 mm^3 compared to 987.6 mm^3 in untreated controls, a 12.8 fold reduction, while free curcumin produced only marginal suppression, directly attributable to folate receptor-mediated selective accumulation within the tumor mass[31]. A dual-cascade photothermal and calcium overload strategy produced

equally pronounced tumor regression with maintained systemic safety, as evidenced by stable body weight and hemolysis of only 0.74% in treated animals[31]. CA7-LP liposomal curcumin analog achieved tumor suppression statistically equivalent to cisplatin without the associated systemic toxicity that caused mortality in the cisplatin-treated group, this preclinical safety signal warrants further investigation rather than a claim of therapeutic equivalance[35]. Collectively, the magnitude of tumor volume reduction observed across these xenograft models ranging from near complete suppression to cisplatin equivalent efficacy, represents encouraging preclinical proof-of-concept; translating these murine findings into claims about clinical efficacy or standard-of-care comparability would be premature without pharmacokinetic, toxicological, and clinical trial data.

Survival Prolongation and Life Span Index.

Among all 16 included studies, only one explicitly reported survival-based endpoints, representing a critical evidence gap in the current nanocurcumin literature. Curcumin nanoemulsion extended mean survival time to 47.3 days compared to 38.3 days with free curcumin and 28.6 days in PBS controls, yielding an increased life span of 65% versus 37.2% for free curcumin, a statistically significant intergroup difference ($P = 0.004$), with the survival advantage attributed to prolonged systemic circulation and sustained intracellular bioavailability conferred by the nanoemulsion formulation[25]. The paucity of survival data across the remaining 15 studies reflects a broader methodological gap: most included studies were designed to assess mechanistic or cytotoxic endpoints rather than longitudinal therapeutic outcomes, rendering it impossible to draw conclusions regarding nanocurcumin's impact on overall survival across different formulation platforms. This constitutes a significant limitation that substantially constrains translational inference, as tumor volume reduction and apoptotic percentage, the predominant endpoints reported, do not necessarily predict survival benefit in clinical settings.

Prevention of Post-Surgical Tumor Recurrence.

A mechanistically distinct in vivo model was presented by the only study employing local implantable delivery, providing clinically relevant evidence for nanocurcumin as a post-surgical adjuvant therapy. Cisplatin–curcumin co-loaded nanofibers implanted at the surgical resection site reduced tumor recurrence to 25% compared to 80–85.7% in intravenous and intraperitoneal control groups at four days post-surgery, with histological analysis confirming extensive tumor necrosis in the nanofiber-treated group[32]. This model is particularly clinically relevant because local cervical cancer recurrence following surgical resection remains a major therapeutic challenge and sustained local drug release from an implantable scaffold represents a strategy that circumvents the systemic pharmacokinetic limitations of curcumin entirely. The dramatic recurrence reduction observed, more than threefold relative to systemic administration, suggests that locoregional delivery may represent a more effective therapeutic paradigm for nanocurcumin than systemic routes, particularly in the post-operative setting where residual microscopic disease at the resection margin constitutes the primary recurrence risk.

Limitation of the In Vivo Evidence Base.

Despite the promising outcomes reported, the in vivo evidence base for nanocurcumin in cervical cancer remains substantially limited in both quantity and representativeness. Of the 16 included studies, only six incorporated an in vivo componen[25,26,30–32,35], with the remaining ten studies providing exclusively in vitro data. Furthermore, all in vivo models employed subcutaneous xenograft systems in immunocompromised or syngeneic murine hosts, which inadequately recapitulate the immunological, hormonal, and anatomical complexity of human cervical carcinoma, including HPV-driven oncogenesis, cervical stromal interactions, and immune checkpoint dynamics. Systemic pharmacokinetic profiling, including plasma half-life, volume of distribution, hepatic and renal clearance, and tissue biodistribution, was either absent or minimally reported across all six in vivo studies, precluding any assessment of dose exposure response relationships necessary for clinical dose translation. Long-term organ toxicity data, particularly hepatic and renal histopathology beyond acute observation periods, were similarly absent, representing a critical safety evidence gap for formulations incorporating novel materials such as bimetallic nanocomposites, mesoporous silica, and ruthenium complexes. Collectively, while the pharmacodynamic evidence from in vivo studies is encouraging, the absence of comprehensive pharmacokinetic characterization, toxicological profiling, and clinically representative animal models constitutes a substantial translational barrier that must be systematically addressed before nanocurcumin formulations can advance toward clinical evaluation.

4.6. Synergistic and Combination Approach

Beyond single–agent nanoformulations, combining nanocurcumin with chemotherapeutic agents, energy based therapies, or bioactive adjuvants consistently produced apoptotic responses exceeding

monotherapy, establishing combination strategies as a critical efficacy amplification axis in the reviewed literature.

Combination with Conventional Chemotherapeutic Agents

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Chemotherapeutic co-delivery consistently demonstrated superior apoptotic outcomes across multiple formulation models. Cisplatin–curcumin co-loaded nanofibers produced 62.7% late apoptosis versus 37.8% and 3.3% for curcumin and cisplatin monotherapy, respectively, translating in vivo to a threefold recurrence reduction (25% vs. 80–85.7%) with extensive tumor necrosis[32]. Folate-targeted PLGA-PEG-FA nanoparticles chemosensitized HeLa cells to paclitaxel through concurrent NF-κB, AP-1, phospho-Akt, and phospho-Erk suppression alongside caspase-9/3 activation beyond levels achievable with either agent alone[28]. FA-SMA-CDF nanomicelles produced a 2.72-fold IC_{50} reduction with sixfold PTEN upregulation and NF-κB downregulation, yielding 36.6% apoptosis in HeLa and 45.9% in SKOV-3 cells[27]. Albumin nanoparticles co-delivering difluorinated curcumin analog and paclitaxel generated 10–20% additional cell killing versus free drug combinations alongside PTEN upregulation and EZH2 attenuation, with HeLa cells demonstrating greater responsiveness consistent with higher folate receptor abundance[29]. Bimetallic Fe_3O_4-Ag nanocomposite curcumin simultaneously activated caspase-9/3/7, suppressed PI3K/AKT/mTOR signaling, and induced autophagy, halving IC50 relative to free curcumin while maintaining selectivity toward normal cells[21]. These results collectively demonstrate that curcumin's capacity to suppress NF-κB, PI3K/AKT/mTOR, and AP-1 survival signaling, pathways central to chemoresistance, provides a mechanistically rational basis for its chemosensitizing role, potentially enabling clinically meaningful dose reductions of more toxic conventional agents.

Combination with Energy-Based Therapies

Energy-based combination strategies produced the highest single-point cytotoxic responses in the dataset. Photodynamic activation of curcumin nanoemulsion elevated caspase-3/7 activity by up to 847% in CasKi cells and 492% in SiHa cells, reducing viability to 1.3–2.8% after dual irradiation with minimal phototoxicity toward normal HaCaT cells[22]. A dual-cascade photothermal and calcium overload strategy achieved 72.58% cell death through near-infrared laser-triggered heating combined with pH-responsive calcium ion release, with confirmed systemic safety in vivo[30]. Ruthenium–curcumin complex liposomes produced dose-dependent ROS generation with nuclear fragmentation and LDH release across 50–150 μg/mL, demonstrating that metal-flavonoid complexation amplifies curcumin's intrinsic ROS-mediated cytotoxicity through an energy-transduction mechanism[23]. The shared principle across these strategies, spatiotemporal confinement of cytotoxic activation to the tumor site, enables curcumin to function simultaneously as a passive chemotherapeutic and an activatable energy transducer, a mechanistic duality that substantially expands its therapeutic utility.

Combination with Bioactive Agents and Enzymes.

Bioactive adjuvant combinations introduced independent pro-apoptotic mechanisms complementing curcumin's intrinsic activity. Methyl jasmonate co-delivery elevated TUNEL-positive HeLa and SiHa cells from 13.54% to 21.47% and 11.34% to 17.28% respectively, through mitochondrial membrane permeabilization acting in concert with curcumin-mediated Bax/Bcl-2 modulation[20]. Serratiopeptidase incorporation as both nanocarrier and bioactive component produced 67% tail DNA damage and 89.7% ROS induction, substantially exceeding curcumin-BSA nanoparticles alone, alongside 96% migration inhibition attributable to proteolytic extracellular matrix degradation[24]. Both dendrosomal nano-curcumin and curcumin nanoemulsion demonstrated an additional oncogene-suppressive dimension through concurrent HPV E6/E7 downregulation and p53/Rb restoration at concentrations substantially lower than free curcumin[25,26], representing a gene-regulatory mechanism absent in conventional chemotherapy that is uniquely relevant to HPV-driven cervical carcinogenesis.

4.7. Strategic Implications of Combination Approaches

The consistent superiority of combination approaches across all three categories reveals a fundamental principle: mechanistic independence between combined modalities, rather than dose escalation of a single agent, is the primary determinant of apoptotic synergy in nanocurcumin-based regimens. This is most strikingly evidenced by the contrast between cisplatin monotherapy (3.3% apoptosis) and cisplatin–curcumin co-delivery (62.7%)[32], where curcumin's NF-κB suppression unlocked cisplatin sensitivity that the cytotoxic agent alone could not achieve, a pattern mechanistically mirrored across chemosensitization[27,28,] energy activation[22,30,] and oncogene suppression[25,26] strategies. Critically, however, superior preclinical efficacy does not automatically translate to clinical implementability: energy-dependent strategies require specialized infrastructure limiting accessibility in high-burden, resource-constrained settings; dual-drug

regimens impose substantially greater regulatory, manufacturing, and toxicological complexity; and no combination strategy among the reviewed studies has yet been evaluated beyond the preclinical stage. These translational tensions between combinatorial efficacy and clinical implementability represent a critical gap that will be systematically examined in Section 3.8.

4.8. Translational Potential and Bench-to-Bedside Gaps

Despite compelling preclinical evidence, translation of nanocurcumin based therapies to clinical application remains substantially constrained by systematic gaps in pharmacokinetic characterization, toxicological profiling, preclinical model representativeness, and manufacturing scalability

Pharmacokinetic and Systemic Toxicology Data Gaps At least 14 of the 16 included studies lack systemic pharmacokinetic profiling, including plasma half-life, biodistribution, and organ clearance, and long-term toxicological data. Formulations incorporating novel materials present particularly acute safety concerns: bimetallic nanocomposites demonstrated IC_{50} values in normal cells (29.70 µg/ml) relatively proximate to therapeutic concentrations (12.5 µg/ml)21; ruthenium-curcumin liposomes carry uncharacterized systemic metal toxicity23; and synthetic curcumin analogs such as CA7 lack comprehensive toxicological profiles35. This pharmacokinetic and toxicological vacuum is the single most consequential translational barrier, as regulatory frameworks for first in human trials mandate demonstration of acceptable toxicity in at least two animal species with long term organ histopathology, a requirement unmet by any formulation in this review. Without this foundational safety data, even the most efficacious formulations cannot responsibly advance toward clinical evaluation regardless of their in vitro potency.

Limitations of Preclinical Models as Clinical Representations.

The predominant in vivo models across the reviewed studies, subcutaneous xenografts in immunocompromised murine hosts, inadequately recapitulate critical features of human cervical carcinoma, including HPV-driven oncogenesis in an immunocompetent host, cervical stromal microenvironment interactions, and immune checkpoint dynamics. Specific limitations compound this concern: TC-1 cells are murine lung epithelial cells immortalized with HPV-16 E6/E7 rather than human cervical cancer cells[25]; the KM/U14 syngeneic model represents murine rather than human HPV-associated disease[32]; and ten of 16 studies provided exclusively in vitro data. The near-universal reliance on HeLa cells, derived from an unusually aggressive HPV-18 adenocarcinoma, further risks systematic overestimation of efficacy relative to the heterogeneous HPV genotypes and histological subtypes encountered clinically. These model limitations introduce fundamental uncertainty regarding whether the apoptotic potency observed in simplified preclinical systems will translate to clinically meaningful responses in the biological complexity of human disease, and they underscore those positive in vitro results, however mechanistically compelling, represent necessary but insufficient evidence for translational inference.

Manufacturing Complexity and Scalability Challenges. Substantial heterogeneity in manufacturing complexity across reviewed platforms creates a direct translational equity concern. Advanced formulations, folate-conjugated PEGylated liposomes[31], mesoporous silica nanoparticles[33], and bimetallic nanocomposites[21], present formidable scale-up challenges in batch reproducibility, cost of goods, and regulatory characterization burden. This is critically relevant given that cervical cancer disproportionately affects women in low- and middle-income countries where sophisticated nanomedicine manufacturing infrastructure is limited. Conversely, dendrosomal nano-curcumin[26], thermosensitive vaginal hydrogel36, and curcumin nanoemulsion[25] employ comparatively simple, low-cost processes compatible with existing pharmaceutical infrastructure. These formulations represent more realistic near-term translational candidates not despite their somewhat lower absolute efficacy, but precisely because their manufacturing profiles align with the regulatory and infrastructural realities of high-burden settings, a consideration that must factor equally alongside apoptotic potency in translational prioritization.

Specialized Infrastructure Requirements for Energy-Based Approaches.

Energy dependent strategies face a unique translational barrier rooted in clinical infrastructure rather than pharmacological limitations. PDT-based approaches require endoscopic laser delivery with precise intracervical dosimetry[22], while photothermal strategies necessitate near infrared laser devices with real time thermal monitoring[30], equipment predominantly available in tertiary academic centers. The fundamental tension is one of efficacy-accessibility tradeoff: the approaches producing the highest preclinical apoptotic responses are precisely those most dependent on infrastructure unavailable where cervical cancer burden is greatest. Unless significant advances in portable light delivery technology materialize, the translational impact of energy-based

nanocurcumin strategies will remain confined to well-resourced settings, paradoxically limiting their public health relevance.

Translational Readiness Synthesis and Future Research Priorities.

Integrating efficacy, safety, in vivo validation, and manufacturing feasibility, a differentiated translational readiness profile emerges. Folate-targeted liposomal curcumin and curcumin nanoemulsion represent the highest near-term candidates, combining in vivo tumor suppression, confirmed normal tissue safety, and established pharmaceutical manufacturing precedent[25,31]. Dendrosomal and PLGA-based nanoparticles occupy an intermediate tier with favorable safety and scalable production[26,28.] Energy-dependent and novel metallic platforms, despite superior cytotoxic efficacy, remain earliest-stage candidates requiring extensive additional preclinical development[21,22,30]. Four research priorities emerge as essential to bridging identified gaps: systematic pharmacokinetic characterization of lead formulations in relevant animal models; comprehensive chronic toxicological evaluation across multiple species; validation in clinically representative HPV positive orthotopic or humanized mouse models; and progression of the most translationally mature formulations toward investigational new drug enabling studies and Phase I dose-escalation trials. Critically, future preclinical studies must adopt standardized experimental frameworks, uniform cell line panels spanning multiple HPV genotypes, harmonized apoptosis detection protocols, and consistent pharmacokinetic endpoints, to generate evidence that is not only mechanistically compelling but also statistically poolable and regulatorily actionable, ultimately transforming the substantial preclinical nanocurcumin evidence base into clinically validated therapeutic options for cervical cancer patients.

Synthesizing the pharmacokinetic, toxicological, model representativeness, and manufacturing gaps identified above, a sequential translational roadmap can be proposed for the most developmentally advanced candidates identified in this review (folate targeted liposomal curcumin and curcumin nanoemulsion, Section 4.8). The immediate priority is systemic pharmacokinetic bridging (plasma half-life, tissue biodistribution, hepatic/renal clearance) in a single relevant species, since without this parameter dose selection for any subsequent toxicology or efficacy study remains arbitrary. This should be followed by Good Laboratory Practice-compliant chronic toxicology in two species, as required by first-in-human regulatory frameworks, with particular attention to hepatic and renal histopathology given the near complete absence of such data across all 16 included studies. In parallel, efficacy validation should shift from subcutaneous xenografts toward orthotopic or humanized HPV positive models that better capture the immune and stromal context of human cervical carcinoma. Only once these three pillars are in place would progression to investigational new drug-enabling studies and a Phase I dose-escalation trial be justified. Absent this sequencing, continued generation of additional in vitro mechanistic data, however novel, will not by itself narrow the translational gap identified throughout this review

4.9. Comparative Perspective with Other Clinically Established Nanotherapeutics

Contextualizing nanocurcumin against nanomedicine platforms that have already progressed through clinical development clarifies how far the present evidence base still has to travel. Liposomal doxorubicin (Doxyl/Caelyx) and albumin bound paclitaxel (nab-paclitaxel, Abraxane) reached regulatory approval on the strength of standardized pharmacokinetic bridging studies, multi-species chronic toxicology, and Phase I dose escalation data establishing a maximum tolerated dose in humans, an evidentiary package that, per Section 4.8 and Table 2, no nanocurcumin formulation in this review has yet generated.

Mechanistically, nanocurcumin's convergence on four apoptotic routes (mitochondrial, ROS mediated, E6/E7 suppression, and PI3K/AKT/NF-κB inhibition) compares favorably in breadth with these single-target cytotoxic agents, and its reported normal-cell selectivity (e.g., minimal cytotoxicity toward HaCaT, HEK-293, and MC3T3 controls) is consistent with, and in several studies more favorable than, the narrow therapeutic indices reported for anthracycline- and taxane-based nanocarriers. However, unlike Doxyl and Abraxane, which use pharmaceutically simple, single component carriers (PEGylated liposome; albumin nanoparticle) amenable to large-scale GMP production, several of the highest-performing nanocurcumin systems in this review (folate-PEG liposomes, bimetallic nanocomposites, mesoporous silica) combine multiple functional components (targeting ligand, PEG corona, inorganic core), which historically correlates with substantially longer and costlier translational timelines. This comparison suggests that the nanocurcumin platforms most likely to reach clinical evaluation fastest are not necessarily those with the highest in vitro potency, but those structurally closest to already-approved carrier chemistries (i.e dendrosomal and nanoemulsion systems, Section 4.8), a consideration that should inform prioritization of future translational investment.

5. Conclusion

This systematic review provides the first synthesis to explicitly link the physicochemical determinants of nanocurcumin formulations to their apoptotic mechanisms of action within the specific context of the HPV E6/E7 p53/Rb axis in cervical cancer, distinguishing it from prior reviews that either excluded nanocarrier-based formulations or treated cervical cancer as one of several cancer types rather than as a focused subject. Across the 16 included studies, nanocurcumin consistently induced apoptosis through four convergent mechanisms: the intrinsic mitochondrial pathway (Bax/Bcl-2 modulation, cytochrome c release, and caspase activation), ROS-mediated oxidative stress, suppression of HPV E6/E7 oncogenes with consequent restoration of p53 and Rb expression, and inhibition of pro-survival signaling via the PI3K/AKT and NF-κB pathways. Physicochemically, formulations varied widely in particle size (~52–390 nm), surface charge, and encapsulation efficiency; no single parameter alone determined apoptotic potency, but encapsulation itself consistently improved uptake and efficacy relative to free curcumin, and folate-receptor targeting produced the most reproducible additional uptake gains. Combination strategies with chemotherapeutic agents, energy-based therapies, or bioactive adjuvants consistently outperformed monotherapy, including extended survival and reduced post-surgical recurrence in vivo. These findings should, however, be interpreted within clear limits. The evidence base is constrained by substantial methodological heterogeneity across cell lines, IC_{50} units, exposure times, and apoptosis-detection methods, which precludes quantitative pooling; by the near-complete absence of systemic pharmacokinetic and long-term toxicity data in all but a fraction of studies; by reliance on subcutaneous xenograft or in vitro models that inadequately represent the immunological and stromal complexity of human cervical carcinoma; and by manufacturing complexity that may limit near-term scalability for several of the highest performing .. Rather than positioning nanocurcumin as a near term alternative therapy, we conclude that it represents a mechanistically well supported but preclinically early-stage candidate whose translational advancement depends on a defined sequence of studies: systemic pharmacokinetic characterization, multi-species chronic toxicology, validation in clinically representative HPV-positive models, and, for the most advanced formulations, progression toward investigational new drug-enabling studies. Addressing these priorities represents the most direct path from the substantial preclinical evidence synthesized here toward clinically meaningful evaluation in cervical cancer.

Conflict of Interest

The authors declare no conflicts of interest.

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