Review

Nanocurcumin in cancer treatment: a comprehensive systematic review

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Abstract

Background Curcumin, a compound in turmeric, shows potential in cancer treatment but is hindered by low bioavailability and solubility. Nanocurcumin, enhanced through nanotechnology, addresses these limitations, offering potential in oncological applications. This review systematically examines the efficacy, bioavailability, and safety of nanocurcumin in cancer treatment, collating data from in vitro, in vivo, and clinical studies.

Methods A comprehensive systematic search was conducted across four major databases: PubMed (Medline), Scopus, Web of Science, and Embase (up to February 2024). The selection criteria were based on the PICOT structure, and studies were assessed for risk of bias using the Cochrane bias risk tool for clinical studies and related checklists for in vitro and in vivo studies. Statistical analyses were performed in STATA software version 17.

Results In total, 8403 articles were identified and assessed, and then only 61 articles were found eligible to be included. Nanocurcumin formulations, especially with Poly (lactic-co-glycolic acid) (PLGA), displayed superior solubility and therapeutic efficacy. In vitro studies highlighted its enhanced cellular uptake and anti-proliferative effects, particularly against cervical cancer cells. In vivo studies confirmed its chemopreventive efficacy and potential synergy with other cancer therapies. Though in early stages, clinical trials showed promise in reducing side effects and improving efficacy in cancer treatments.

Conclusion Nanocurcumin shows promise as an innovative approach in cancer therapy, potentially offering improved efficacy and reduced side effects compared to traditional treatments. Early clinical trials indicate its potential to enhance the quality of life for cancer patients by mitigating treatment-related toxicities and improving therapeutic outcomes. However, larger randomized controlled trials are necessary to definitively establish its clinical efficacy, optimal dosing regimens, and long-term safety profile across various cancer types. As research progresses, nanocurcumin could become a valuable addition to the oncologist's toolkit, particularly in combination therapies or for patients intolerant to conventional treatments. Future clinical studies should focus on optimizing treatment protocols, identifying responsive patient

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populations, and assessing long-term outcomes to facilitate the translation of these promising findings into standard clinical practice.

Abbreviations

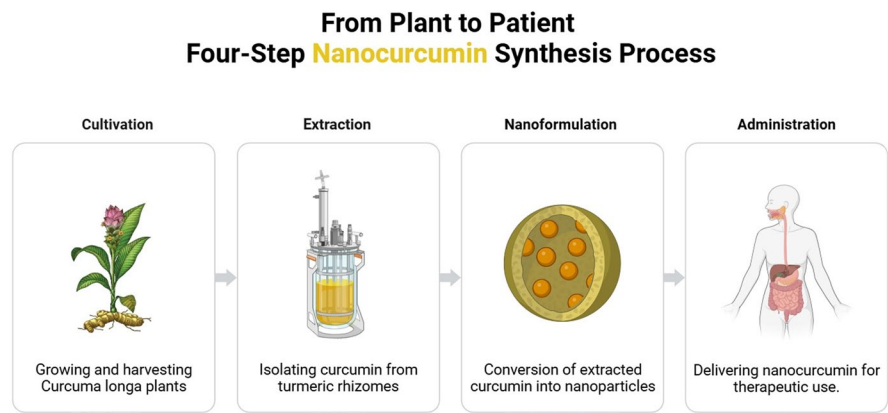|	
PLGA	Poly (lactic-co-glycolic acid)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyse
PEG	Poly (ethylene glycol)
MeSH	Medical Subject Headings
TEM	Transmission electron microscopy
PARP	Poly (ADP-ribose) polymerases
NGAL	Neutrophil gelatinase-associated lipocalin
MIBC	Muscle-invasive bladder cancer
NIPAAM	N-isopropyl acrylamide
AFM	Atomic force microscopy
EAC	Esophageal adenocarcinoma
HPLC	High-performance liquid chromatography
DSC	Differential scanning calorimetry
HCC	Hepatocellular carcinoma
NFC	Nanoparticle formulation of curcumin
DLS	Dynamic Light Scattering
DNC	Dendrosomal nanocurcumin
PCR	Polymerase chain reaction
TPP	Tripolyphosphate
XRD	X-ray diffraction
CsNPs	Chitosan nanoparticles
PVA	Polyvinyl alcohol
SEM	Scanning electron microscopy
FTIR	Fourier-transform infrared spectroscopy

1 Introduction

Cancer is characterized by uncontrolled cell growth, manifesting either as solid tumors or liquid cancers (such as those affecting blood or bone marrow). The main cancer treatment methods are surgery, chemotherapy, and radiotherapy. Although there have been notable improvements in cancer diagnosis and therapy, there is still an urgent want for the development of treatment methods that are both safe and effective. Traditional cancer treatments, such as chemotherapy and radiotherapy, frequently result in harmful side effects and the development of drug resistance. These constraints have stimulated the exploration of innovative therapeutic strategies specifically targeting cancer cells while limiting harm to normal tissues [1, 2]. Compared with previous standards of care (including chemotherapy, radiotherapy, and surgery), cancer immunotherapy has brought significant improvements for patients in terms of survival and quality of life. Immunotherapy has now firmly established itself as a novel pillar of cancer care, from the metastatic stage to the adjuvant and neoadjuvant settings in numerous cancer types [3].

Curcumin, a biologically active chemical extracted from the rhizome of Curcuma longa (turmeric), has attracted considerable interest due to its possible anti-cancer capabilities [4]. Multiple preclinical studies have shown that curcumin can influence various cellular pathways in cancer advancement, such as cell proliferation, apoptosis, angiogenesis, and metastasis [5, 6]. Nevertheless, the practical application of curcumin in medical settings has been impeded by its limited capacity to dissolve in water, its low rate of absorption into the body, and its quick breakdown by metabolic processes [7–9].

Nanotechnology has arisen as a viable approach to address the constraints of traditional medication delivery techniques [8]. Peptides and nanoparticles work synergistically in cancer treatment. Nanoparticles functionalized with peptides can target tumor cells better. Combining peptides and medicines can create self-assembled nanoparticles

Fig. 1 Nanocurcumin from cultivation to administration

From Plant to Patient
Four-Step Nanocurcumin Synthesis Process

Cultivation	Extraction	Nanoformulation	Administration
Growing and harvesting Curcuma longa plants	Isolating curcumin from turmeric rhizomes	Conversion of extracted curcumin into nanoparticles	Delivering nanocurcumin for therapeutic use.

for targeted cancer treatment[9]. Nanocurcumin, nanoformulations of curcumin, have been created to improve its solubility, stability, and bioavailability (Fig. 1) [10]. The nanoformulations consist of different platforms, including polymeric nanoparticles, liposomes, micelles, and nanoemulsions. Each platform has distinct physicochemical features and biological consequences [11].

The combination of nanotechnology and curcumin has created new possibilities for cancer treatment. Formulations of nanocurcumin have shown more bioavailability, enhanced absorption by cells, gradual release, and specific transport to tumor locations [12]. Furthermore, nanocurcumin has demonstrated superior effectiveness in inhibiting cancer growth than free curcumin in laboratory and animal studies [13, 14]. The positive results have generated enthusiasm for using nanocurcumin in clinical settings to treat cancer.

This systematic review offers a thorough assessment of the existing knowledge regarding using nanocurcumin in cancer treatment and compiling and examining data obtained from in vitro, in vivo, and clinical trials. We collected data from laboratory experiments, animal research, and experiments related to human patients, and we aim to investigate the effectiveness, ability to be absorbed by the body, and safety of nanocurcumin in different forms of cancer. In addition, we will review the obstacles and prospects of nanocurcumin as a promising therapeutic agent in oncology.

2 Method

2.1 Search strategy

A thorough and organized search followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Various electronic databases, namely PubMed (Medline), Scopus, Web of Science, and Embase, were examined to identify relevant studies published until February 2024. The search strategy utilized a combination of specific terms and Medical Subject Headings (MeSH) such as "nanocurcumin," "curcumin nano-formulation," "cancer," and "tumor." A manual search was performed to verify that no relevant studies were overlooked. This entailed reviewing the references and sources cited in the selected papers to locate additional studies that may not have been discovered during the electronic search.

The inclusion criteria for this review were as follows: [1] original research articles investigating the efficacy, bioavailability, or safety of nanocurcumin in cancer; [2] studies conducted in vitro, in vivo, or as clinical trials; [3] studies comparing nanocurcumin with free curcumin or other cancer therapies; and [4] articles published in English. Exclusion criteria included: [1] review articles, editorials, conference abstracts, and book chapters; [2] studies not related to cancer; and [3] studies using curcumin without nano-formulation. Table 1 shows the PICOT Framework and Eligibility Criteria for Study Selection.

2.2 Study selection and data extraction

Two independent reviewers (MB and AM) screened the titles and abstracts of the retrieved articles for eligibility. Full-text articles were then assessed for inclusion based on the predefined criteria. Any reviewer discrepancies were resolved through discussion or consultation with a third reviewer (RRD).

Table 1 PICOT framework and eligibility criteria for study selection

Population	Cells, animals, and humans with cancer diagnosis
Intervention	Nanocurcumin
Comparison	Other treatments
Outcomes	Apoptosis of cancer cells and prevention of disease progression
Search terms	Nanocurcumin, Cancer
Inclusion criteria	(1) original research articles investigating the efficacy, bio-availability, or safety of nanocurcumin in cancer; (2) studies conducted in vitro, in vivo, or as clinical trials; (3) studies comparing nanocurcumin with free curcumin or other cancer therapies; and (4) articles published in English
Exclusion criteria	(1) review articles, editorials, conference abstracts, and book chapters; (2) studies not related to cancer; and (3) studies using curcumin without nano-formulation
Research question	Is nanocurcumin effective for cancer treatment or not?

Data extraction was performed using a standardized form, which included the following information: first author, year of publication, study type (in vitro, in vivo, or clinical), cancer type, nanocurcumin formulation, comparison groups, outcome measures, and critical findings. For in vitro studies, additional data on cell lines, assays, and molecular mechanisms were extracted. In vivo studies were further characterized by animal models, tumor characteristics, and treatment regimens. Patient demographics, dosing schedules, and adverse events were recorded for clinical trials.

2.3 Quality assessment

The studies included in the analysis were evaluated for quality using suitable assessment tools corresponding to their respective study designs. Randomized controlled trials were assessed using the Cochrane Risk of Bias tool, while non-randomized studies were evaluated using the Newcastle–Ottawa Scale. In vitro studies underwent assessment using a modified version of the NIH National Cancer Institute's Framework for Assessing the Quality of In-Vitro Studies. The quality assessment was conducted independently by two reviewers (PH and NM), and any disagreements were resolved through consensus or by consulting a third reviewer (YM).

2.4 Data synthesis and analysis

The extracted data was qualitatively synthesized, explicitly focusing on assessing the efficacy, bioavailability, and safety of nanocurcumin in cancer. The studies were categorized based on their design (in vitro, in vivo, or clinical) and the type of cancer investigated. Subgroup analyses were conducted by considering different nanocurcumin formulations and comparison groups. Due to variations in study designs, outcome measures, and data reporting, performing a quantitative synthesis (meta-analysis) was not feasible. However, whenever possible, effect sizes and 95% confidence intervals were calculated for individual studies to provide a standardized measure of the observed effects' magnitude.

3 Result

3.1 Study selection

The initial search yielded 8403 records from the electronic databases. After removing duplicates, 5627 unique records were screened for eligibility based on their titles and abstracts. Of these, 5482 records were excluded as they did not meet the inclusion criteria. The remaining 190 articles were retrieved for full-text assessment, of which 129 were further excluded due to lack of relevant outcomes, use of curcumin without nano-formulation, or being review articles. Finally, 61 studies were included in the qualitative synthesis, comprising 47 in vitro, 12 in vivo, and two clinical trials. The PRISMA flow diagram depicting the study selection process is presented in Fig. 2.

Fig. 2 Identification of studies via databases and registers
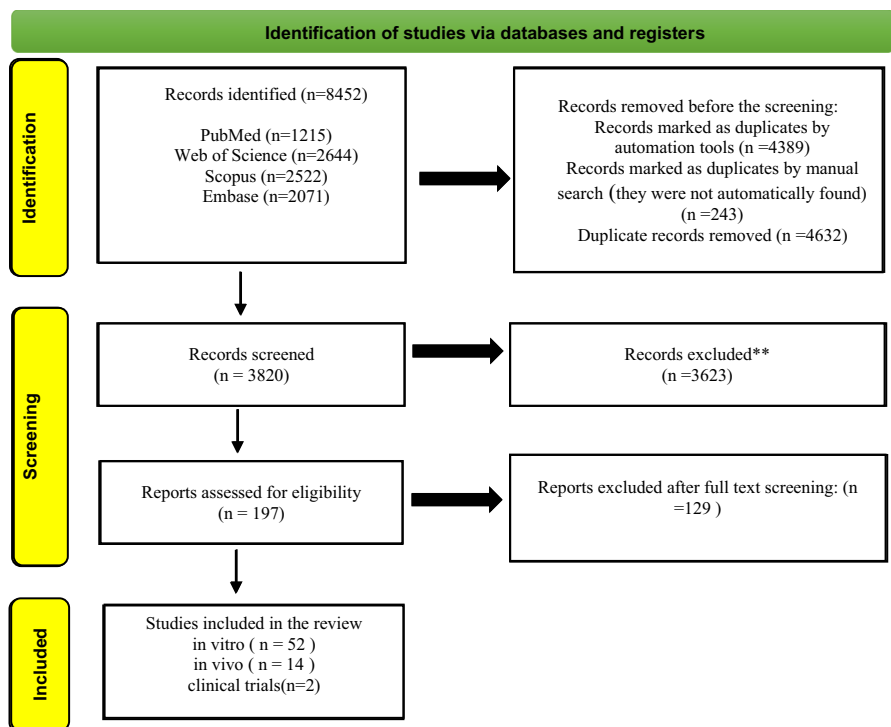
3.2 Characteristics of included studies

3.2.1 In vitro studies

The 47 in vitro studies (Table 2) utilized various cancer cell lines, including breast, colon, lung, prostate, and liver cancer. The most common nanocurcumin formulations were polymeric nanoparticles, such as PLGA, PEG, and chitosan. These studies employed techniques like MTT assay, flow cytometry, and Western blot to assess the anti-cancer effects of nanocurcumin.

Nanocurcumin demonstrated superior cellular uptake and anti-proliferative activity compared to free curcumin. For instance, in human cervical cancer cells (HeLa), nanocurcumin exhibited enhanced cytotoxicity, as evidenced by increased apoptosis and downregulation of clonogenic potential. Nanocurcumin also modulated vital signaling pathways, such as PI3K/Akt, JAK/STAT3, and NF-κB, and regulated the expression of apoptosis-related genes, including p53, Bcl-2, and caspases.

3.2.2 In vivo studies

The 12 in vivo studies (Table 3) investigated the efficacy of nanocurcumin in various animal cancer models. These studies predominantly used xenograft models and chemically-induced carcinogenesis models. The nanocurcumin formulations were administered through different routes, such as oral, intraperitoneal, and intratumoral.

Nanocurcumin demonstrated superior tumor growth inhibition and bioavailability compared to free curcumin. In a xenograft model of breast cancer, nanocurcumin significantly reduced tumor volume and increased survival. Additionally, nanocurcumin exhibited chemopreventive effects in a rat colon carcinogenesis model, reducing tumor incidence and multiplicity. Notably, nanocurcumin enhanced the efficacy of conventional chemotherapeutic agents, such as cisplatin and doxorubicin, in ovarian and breast cancer models.

3.3 Clinical trials

Two clinical trials (Table 4) investigated the safety and efficacy of nanocurcumin in cancer patients. Two phase II trials evaluated nanocurcumin as an adjunct therapy in prostate cancer patients undergoing radiotherapy and bladder cancer

Table 2 In vitro studies

	Authors name	Year	Source of cells	Analyze	Method synthesis
[15]	Bisht, S	2007	human pancreatic cancer cell	dynamic laser light scattering and TEM	
[16]	Lim, K.J., et al	2011	embryonal tumor-derived lines DAOY and D283Med, glioblastoma neurosphere lines HSR-GBM1 and JHH -GBM14		
[17]	Prasanth, R	2011	nasopharyngeal cancer cells	AFM	
[13]	Nair, K.L., et	2012	human epithelial cervical cancer cells (HeLa)	MTT, Annexin V/propidium iodide staining, cleavage of poly (ADP-ribose) polymerase (PARP), and reduction of clonogenic capacity	
[14]	Milano, F., et	2013	esophageal adenocarcinoma (EAC)		
[12]	Basniwal, R.K	2014			
[18]	Chaudhari, P.D	2015	breast cancer cell line culture, MCF-7	DSC, XRD, and TEM analyses were conducted. A study conducted in living organisms showed higher bioavailability in Wistar rats than in unprocessed curcumin, as determined by HPLC. Additionally, an MT assay was performed	
[19]	Dhivya, R. et al.,	2015	breast cancer cell line culture, MCF-7	DSC. XRD. TEM. In vivo, the study revealed increased bio-availability in Wistar rats compared to raw Curcumin by HPLC. MT assay	
[20]	Hossain, D.M., et al	2015	breast cancer		
[21]	Hu, B., et	2015	human hepatocellular carcinoma (HCC)		
[22]	Pillai, J.J., et	2015	The MTT assay depicted a high amount of cytotoxicity of PPF nanocurcumin in HeLa cells	Characterized by FT-IR and 1H-NMR techniques. TEM and DLS. DCS. The MTT AO/EB staining, DAPI staining, and clonogenic	
[23]	Xie, M. et	2015	Colorectal cancer cells (HCT116)		
[24]	Chamani, F., et	2016	Hepatocellular carcinomaHCC cell lines, HepG2 and Huh7	.MTT, PCR	
[25]	Keshavarz, R., et al	2016	Glioblastoma	PCR Annexin-V-FLUOS staining followed by flow cytometry and real-time	
[26]	Khan, M.A., et al	2016	Cervical cancer line SiHa, HeLa, CasKi, and C33A	(TEM), (DLS), HPLC, MALDI-TOF, FT-IR, XRD and UV–vis.Cell metabolic assay by MTT. Detection of apoptosis by DAP	tripolyphosphate (TPP) cross-linking method. drug entrapment efficiency was ≈85%
[27]	Khosropanah, M.H., et al	2016	Human breast adenocarcinoma cell line (MDA-MB231)	MTT) and dye exclusion assay. TEM(particle diameter was between 150 to 200 nm)	selfassembly
[28]	Paunovic, V., et al	2016	U251 glioma, B16 melanoma, and H460 lung cancer cells	Photoexcited nanocurcumin can trigger apoptosis independent of oxidative stress but relies on JNK and caspase pathways	tetrahydrofuran/water solvent exchange,

Table 2 (continued)

	Authors name	Year	Source of cells	Analyze	Method synthesis
[29]	Aldahoun, M.A., et al	2017	Prostate cancer cell line (PC3)	Nanocurcumin combined with the magnetic field (NANOCUR-MF) and control against PC3 was 35.93%, which is three times higher compared to curcumin combined with the magnetic field (CUR-MF)	Magnetic field
[30]	Dash, T.K. and VSB	2017	COLO205 cells		hydroxypropyl-β-cyclodextrin (HP-β-CD)
[31]	Mahjoub, M.A., et al	2017	MDA-MB-231 metastatic breast cancer cells	qRT-PCR. MTT assay, Annexin V-FITC staining. lowcytometry and wound healing assay	
[32]	Mishra, D. et al.,	2017	Breast cancer cell line (GILM2)	SEM.DLS	wet grinding method
[33]	Athira, G.K.,	2018	Anti-cancer potential to HeLa cells	FTIR), (SEM), (TEM), (DLS), (AFM), (XRD)	
[34]	Bagheri, R., Z. Sanaat, and N. Zarghami	2018	SW480 Colorectal Cancer Cell Line	(SEM) and FTIR Spectroscopy. MTT. qRT-PCR method	
[35]	Baghi, N., et al	2018	MDA-MB-231 breast cancer cells	MTT. real-time PCR. on DNC-related cytotoxicity. Annexin-V/PI staining followed by flow cytometry and wound healing assay	
[36]	Hashemzehi, M., et al	2018	Human breast cancer cell line MDA-MB-231	qRT-PCR and Western blotting. (MDA), (SOD), (CAT), (T-SH)	
[37]	Hosseini, S., et al	2018	Esophageal Squamous Cell Carcinoma (KYSE-30)		
[38]	Nguyen, N.T., et al	2018	MCF-7 breast cancer cell	(FT-IR), (TEM), DLS. Via HPLC along with AES-ICP to evaluate the high drug loading	
[39]	Shariati, M., et al	2018	Hepatocellular carcinoma cell line (Huh7)	MTT. RT-PCR	
[40]	Srivastava, S., et al	2018	OCC(oral cancer cells)		Employing homogenization with high-energy sonication
[41]	Dang, L.H., et al.,	2019		Transmission electron microscopy, variable UV–visible spectrophotometry, as well as fluorescence spectroscopy, DLS	Ultrasonication to control the self-assembly of phosphocasein
[42]	Harini, L., et al.,	2019	Breast cancer (MCF-7) cells	WST	Maximum of 23 μM was released from CUR-MSNAP at 96 h. CUR-MSNAP released 13 μM of drug, and then a sustained pattern of release was observed till 96 h
[43]	Hosseini, S., et al	2019	Breast cancer cells (MCF7)	MTT. PCR	
[44]	Seyed Hosseini, E., et al	2019	Ovarian cancer OVCAR3 SKOV3	MTT assay and flow cytometry. real-time PCR	

Table 2 (continued)

	Authors name	Year	Source of cells	Analyze	Method synthesis
[45]	Yang, R. et al	2019	MCF-7 cancer cells	Western blot.MTT. fluorescent image	The release of cumulative amounts of CUR after 72 h at pH 5.0 (58.2%) was also significantly higher than that at pH 7.0 (16.0%)
[46]	Cheng, T. et al	2020	Pancreatic adenocarcinoma cells. PDAC. Cell line 399.T3M4, MIA PaCa-2 and PANC-1	SEM, fluorescence microscopy, Fourier transform infrared spectroscopy, X-ray diffraction, and HPLC.MTT	
[47]	Hanna, D.H. and G.R. Saad,	2020	Human Hep-2 cancer cells	Fourier transform infrared spectroscopy, TEM, X-ray diffraction, and zeta potential analysis. Neutral red uptake.Flow cytometry. Real-time PCR. Annexin V/PI staining assay. LDH). AO/EB staining assay. Comet assay.Cell cycle arrest	sol-oil method
[48]	Kuo, I.M., et al	2020	CT26 colon cancer	Annexin V–fluorescein isothiocyanate (FITC) apoptosis detection (BD Biosciences).flow cytometer.Western blot. direct immunofluorescence	
[49]	Pandit, A.H., et al	2020	SUM149 human breast cancer	Zeta potential DLC, TEM, XTT assay Fluorescent microscopy Xenograft tumor growth assay	
[50]	Ghaderi, S., et al	2021	OVCAR-3 cells	Real-time PCR and western blotting	
[51]	Sadoughi, A., et al	2021	MCF-7, MDA-MB-231 breast cancer cells &human fibroblast cells	Spectrophotometry, SEM, MTT, and Annexin V.real-time PCR	
[52]	Wozniak, M. et al.,	2021	Melanoma (MugMel2), squamous cell carcinoma (SCC-25), and normal human keratinocytes (HaCaT) cell lines	MTT, healing assay, flow cytometry, and immunocytochemistry	
[53]	Alam, J., et al.,	2022	Gastric cancer AGS. PI/Cyto9 staining	MTT.HPLC.flow cytometry	
[54]	Atia, MM, et al	2022	Hepatic cancer HepG2 and Huh-seven cancer cell	TEM.DLS.Acridine orange/ethidium bromide (EB/AO) assays.Animal experiments and treatments.Western blot analysis. RT-PCR	
[55]	Essawy, M.M., et al.,	2022	Oral cancer squamous cell carcinoma cell line	Wound closure autofluorescence	
[56]	Mohammadi, H., et al	2022	HT29 and Hct116 Colon Cancer Cell Lines		
[57]	Mukherjee, D., et al	2022	Oral Squamous Cancer Cells. KB 3–1 cell)	Oral Squamous Cancer Cells. KB 3–1 cell)	
[58]	Sadeghi, R.V., et al	2022	Human cervical cancer cell line (HeLa cell line RRID: CVCL_003	MTT assay and flow cytometry real-time RT-PCR and western blot	

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Table 2 (continued)

	Authors name	Year	Source of cells	Analyze	Method synthesis
[59]	Krishnaveni P, et al	2023	DAL, A72 and HT29	Cell block technique, AO/PI staining, TUNEL assay, immunocytochemistry, immuno-fluorescence, and Real-time PCR. AO/PI staining and TUNEL assay	
[60]	Moawad, Mahmoud, et al	2023	Hep-G2	(qRT-PCR), flow cytometry	Ball milling
[61]	Subandi, Subandi, and Sigit Purbadi Purbadi S	2023	BeWo choriocarcinoma cell line (ATCC CCL-98)	Real-Time PCR, flow cytometry	
[62]	Seyed Hosseini, Elahe, et al	2023	SKOV3 and OVCAR3	Real-time PCR and Western blot	
[63]	Viraaj, V., et al	2023	KB-3–1 Cell line, oral cancer	AO assay, MTT Assay, Trypan blue assay (TB assay), Haemolytic assay	solvent-antisolvent method

	Authors name	Year	Carrier	Gen	Cellular result
[15]	Bisht, S	2007	N-isopropyl acryla-mide (NIPAAM) co-polymers, along with N-vinyl-2-pyrrolidone (VP) and poly(ethylene glycol)monoacrylate (PEG-A), are used in various applications		Triggering cell death, preventing NFκB activation, and reducing baseline levels of various inflammatory cytokines such as IL–6, IL–8, and TNFα
[16]	Lim, K.J., et al	2011			Combination of G 2/M arrest and apoptotic induction Downregulation of the insulin-like growth factor pathway in DAOY medulloblastoma cells. Levels of STAT3 were also attenuated
[17]	Prasanth, R	2011			
[13]	Nair, K.L., et	2012	Two PLGA combina-tions, 50:50 and 75:25, with varying ratios of lactide to glycolide, were utilized		
[14]	Milano, F., et	2013	Colloidal nanoparti-cles, named Thera-curmin		Up-regulated the expression of the co-stimulatory molecule CD86 in DCs
[12]	Basniwal, R.K	2014	Nanoparticles r2–40 nm and aque-ous solubility of up to a maximum of 3 mg/mL		Basic levels of T cell-induced cytotoxicity of 6.4 and 4.1% increased to 15 and 13%, respectively

Table 2 (continued)

	Authors name	Year	Carrier	Gen	Cellular result
[18]	Chaudhari, P.D	2015	Curcumin was formed into a stable micro-dispersion through melt granulation with Gelucire® 50/13, a hydrophilic carrier, and subsequent adsorption onto Aeroperl® 300 Pharma		
[19]	Dhivya, R. et al.,	2015	Nanocomposite of Curcumin with ZnO nanoparticle. The average particle size of ZnO nanoparticle and nanocomposite from XRD was 21.44 nm and 24.66 nm, respectively. Nanocomposite was found to have a narrow particle size of 53 nm		
[20]	Hossain, D.M., et al	2015		FoxP3	
[21]	Hu, B., et	2015	Polymeric nanoparticle formulation of Curcumin (NFC)	NFC and sorafenib synergistically down-regulated the expression of MMP9 via NF-κB/p65 signaling pathway	Decreased the population of CD133-positive HCC cells
[22]	Pillai, J.J., et	2015	Nanoparticles of PLGA-PEG co-polymer, which were conjugated with folic acid (PPF co-polymer)		
[23]	Xie, M. et	2015			Cell cycle arrest in G2/M phase. CM NPs exhibited reduced cytotoxicity on normal cells (NCM460) compared to CM-DMSO and 5-Fu
[24]	Chamani, F., et	2016	Dendrosomal nano-curcumin (DNC)	mir-34 family and DNA methyltransferases (DNMT1, DNMT3A and 3B)	
[25]	Keshavarz, R., et al	2016	Dendrosomal curcumin (DNC)	Enhanced expression of GADD45 and a reduced expression of NF-κB and c-Myc	Enhance the number of apoptotic cells (90%) compared with their application alone (15% and 38% for p53 overexpression and DNC, respectively)

Table 2 (continued)

	Authors name	Year	Carrier	Gen	Cellular result
[26]	Khan, M.A., et al	2016	Chitosan nanoparticles (CsNPs)		
[27]	Khosropanah, M.H., et al	2016	Myristic acid-chitosan (MA-chitosan) nanogels		
[28]	Paunovic, V., et al	2016	Curcumin nanoparticles. size of curcumin nanocrystals was approximately 250 nm		Mitochondrial depolarization, caspase-3 activation, and cleavage of poly (ADP-ribose) polymerase, indicating apoptotic cell death
[29]	Aldahoun, M.A., et al	2017			The IC50 of nanocurcumin in combination with the magnetic field (NANOCUR-MF) and the control group against PC3 was 35.93%, which was three times higher than curcumin combined with the magnetic field (CUR-MF), at 10.77%. However, their E% against HEK was insignificant, with 1.4% for NANOCUR-MF and 1.95% for CUR-MF
[30]	Dash, T.K. and VSB	2017	Optimizing organic solvent selection through freeze-drying enhanced encapsulation efficiency (60%) and a particle size of approximately 40 nm when acetone was used in PVA-stabilized dispersion		Curcumin reversed DOX resistance in COLO205 cells at low concentrations, and the presence of PVA enhanced curcumin encapsulation in HP-β-CD. Further, it was observed that prepared HP-β-CD-encapsulated Curcumin is equi-efficacious to nano-dispersed curcumin
[31]	Mahjoub, M.A., et al	2017	Dendrosomal nano-curcumin	CXCL12/CXCR4 axis and Hedgehog pathway genes	Lowcytometry and wound healing assay
[32]	Mishra, D. et al.,	2017	Silk fibroin, also known as SF, has an average diameter of 127.7 ± 6.8 nm and exhibits a bimodal distribution, with most particles ranging between 70 and 110 nm		Initial burst release within the first 24 h and continued release up to 7 days
[33]	Athira, G.K.,	2018	octenyl succinylated cassava starch-curcumin < 50 nm		C max of nanocurcumin (110.89 ± 0.921 ng/ml) was significantly higher when compared to that of native curcumin (82.94 ± 1.128 ng/ml)

Table 2 (continued)

	Authors name	Year	Carrier	Gen	Cellular result
[34]	Bagheri, R., Z. Sanaat, and N. Zarghami	2018	PLGA-PEG nanoparticles	telomerase gene.hTERT	
[35]	Baghi, N., et al	2018	Dendrosomal nano-curcumin	p53.EMT- ZEB1 and BMI1	When p53 overexpression and DNC are combined in treatment, the percentage of apoptotic cells significantly increases to 92%. Cells treated with a p53-expressing vector enhance 38%, while those treated with DNC enhance to 86%
[36]	Hashemzehi, M., et al	2018	Phytosomal-encapsulated	CyclinD1,GSK3a/b, P-AMPK, MMP9, and E-cadherin	Phytosomal-curcumin inhibits cell growth and movement triggered by thrombin via AMP-Kinase in breast cancer
[37]	Hosseini, S., et al	2018	nano-micelle	Cyclin D1	Cell proliferation in the KYSE-30 cell line decreased by 71.09%, a more significant reduction than Paclitaxel (61.30%) and Carboplatin (62.32%). The IC50 of nano-curcumin in KYSE-30 was notably lower at 1.87 mg/mL compared to free drugs (Paclitaxel 7.5 mg/mL and Carboplatin 40 mg/mL) in KYSE-30 and nano-curcumin (10 mg/mL) in normal cells
[38]	Nguyen, N.T., et al	2018	(nanogel)thermosensitive co-polymer heparin-Pluronic F127 (Hep-F127) co-delivering cisplatin (CDDP) and curcumins (Cur) (Hep-F127/CDDP/Cur). size:129.3±3.8 nm		The IC50 concentrations of each formulation showed that 100 ppm of Hep-F127/Cur resulted in a 63.10±1.91% reduction in cell growth. Treatment with Hep-F127/CDDP led to cell inhibition of 88.57±1.38%, while Hep-F127/Cur/CDDP treatment resulted in a notable 95.32±2.57% inhibition
[39]	Shariati, M., et al	2018		Smad3 and E2F1. Smad7	The best results were obtained from 72 h of experiments with 12.5 µM IC50
[40]	Srivastava, S., et al	2018	up to 200 nm	Blc2, and Bax	IC (50) value for growth inhibition was calculated as 47.89 and 26.19 µg/ml, respectively, for nano-CU and nano-FU
[41]	Dang, L.H., et al.,	2019	Micelles based on cationic amphiphilic block co-polymer		
[42]	Harini, L., et al.,	2019	Non-spherical mesoporous silica nanoparticles (MSNAs)	Activation of caspase 9, 6, 12, PARP, CHOP, and PTEN. protein Akt1	MSNAP causes more effective cell death at 30 µM curcumin than free curcumin. PEI-coated MSNA increased drug loading to 80%. The LD50 of MCM-41P was ten µg/mL, whereas the LD50 of MSNAP was 80 µg/mL
[43]	Hosseini, S., et al	2019	Nano-micelle	cyclinD1	Nano-curcumin decreased cell proliferation by 83.6%; at a curcumin concentration of 162.87 mmol/L, cell viability reduced to 16%

Table 2 (continued)

	Authors name	Year	Carrier	Gen	Cellular result
[44]	Seyed Hosseini, E., et al	2019	Dendrosomal nano-curcumin	LSINCT5. ABO73614	The DNC treatment showed an inhibitory effect at a 0.088-fold rate. The IC50 of DNC for SKOV3 cells was 25 μM at 24 h, reduced to 22 μM at 48 h, and decreased to 17.5 μM at 72 h. The concentrations were 20 μM at 24 h, 15 μM at 48 h, and ten μM at 72 h
[45]	Yang, R. et al	2019	A coral shaped nano-transporter DNA-FeS(2)-DA	PKM2 and FASN	Without NIR:CUR $IC_{50} = 250.6$ μg·mL^{-1}), CUR@DNA-FeS$_2$-DA ($IC_{50} = 222.0$ μg·mL^{-1}) with NIR:CUR@DNA-FeS$_2$-DA ($IC_{50} = 114.4$ μg·mL^{-1}). CUR ($IC_{50} = 229.3$ μg·mL^{-1})
[46]	Cheng, T. et al	2020	Curcumin/gelatin-blended nanofibrous	p-STAT3 Bip/PERK/elf2a	The colony number dropped by around 60% in the group that received a conditioned Cc/Glt NM (CM-Cc/Glt NM) medium. In comparison, DMEM vs. CM-Glt NM vs. CM-Cc/Glt NM showed 75.2 ± 7.7, 77.2 ± 13.3, and 29.6 ± 6.5, respectively
[47]	Hanna, D.H. and G.R. Saad,	2020	28 nm	P53, Bax, and Caspase-3, Bcl-XL	An IC50 value of 17 ± 0.31 μg ml − 1 was achieved after 48 h. This resulted in cell cycle arrest in the G2/M phase and a rise in apoptotic cells in the sub-G1 phase
[48]	Kuo, I.M., et al	2020		Cyclin D1 and Cyclin A.Hsp70	The IC50 values for curcumin, resveratrol, and their combined treatment on CT26 cells were determined to be 26.76 ± 1.06 and 88.76 ± 1.07 μM
[49]	Pandit, A.H., et al	2020	The size of nanocurcumin was < 100 nm		
[50]	Ghaderi, S., et al	2021		BAX/Bcl-2	
[51]	Sadoughi, A., et al	2021	Tri-polyphosphate chitosan nanoparticles 48 nm	TP53. VEGF	IC_{50} of nano Cur-chitosan-TPP vs free curcumin 15 μg/mL at 72 h vs 20 μg/mL at 48 h. led to an induction of apoptosis (79.93%) and cell cycle arrest (at S and G2M)
[52]	Wozniak, M. et al.,	2021			All subsequent biological studies chose curcumin in the concentration of 10 μM · Flow cytometry: The combination of liposomal Curcumin and PDT increased apoptosis to 40% and 30% in SCC-25 and MUG-Mel2

Table 2 (continued)

Authors name	Year	Carrier	Gen	Cellular result
[53] Alam, J., et al.,	2022	Emulsifier TPGS1000 in the PLGA based formulationCurcumin loaded diameter of ~175 nm,		Nano-curcumin significantly increased the inhibition rate from 7 to 69% after 24 h, from 11 to 87% after 48 h, and from 16 to 97% after 72 h. The IC50 values for Curcumin and Nano-curcumin were 24.20 µM and 18.78 µM, respectively, after 72 h. The sub-G0 population rose from 4.1% in the control group to 24.5% and 57.8% when treated with curcumin and nano-curcumin, respectively
[54] Atia, MM, et al	2022		YP2E1, P53, cleaved caspase-3, and COL1A1	Curcumin was reduced by 44.95% and 62.36%, respectively, while Niacin Curcumin was reduced by 66.21% and 47.85% compared to the AC group. Cleaved caspase-3 Niacin Curcumin showed a 57.5% reduction compared to the AC group. Retreatment with curcumin led to a 49.67% reduction in expression, and Niacin Curcumin was reduced by 65.29% compared to AC-treated mice
[55] Essawy, M.M., et al.,	2022			The 60.8 µg/mL concentration was more effective in inhibiting the migration of cancer cells by 25% compared to the native curcumin particle concentration of 212.4 µg/mL
[56] Mohammadi, H., et al	2022	Nano-micelle		IC50 values of Nanocurcumin in HT29, HCT116, and HGF were 70.63, 123.9, and 168.53 µg/ml, respectively
[57] Mukherjee, D., et al	2022	NC ~ 200 nm size		The nano-curcumin IC50 for the HeLa cell line after 48 h was approximately 15 µM. Flow cytometry data indicated a 46.5% result
[58] Sadeghi, R.V., et al	2022	Oleic acid-derived dendrosome nano-carrier(OA400 Nanoparticle)	E6, E7, P53, and Rb mRNA	The IC50 value of nano-curcumin for the HeLa cell line within 48 h was about 15 µM. Flow cytometry results showed that 46.5%
[59] Krishnaveni P, et al	2023	Curcumin solid lipid nanoparticles	Bax and Caspase 8,Bcl2, Cyclin D1 and PCNA, miR181a, pre-miR-182, miR155	solid lipid nanoparticles conveyed curcumin to cancer cells successfully and expanded the restorative impact by applying its capacities through miRNAs, acceptance of apoptosis as well as hindrance of metastasis
[60] Moawad, Mahmoud, et al	2023	Nanocapsules	p53, Bcl-2, Bax, and Bax	Curcumin nanocapsules significantly increased the apoptotic cell population in a dose- and time-dependent manner mRNA expression analysis showed that proapoptotic Bax, Caspase-3, and tumor suppressor gene p53 were up-regulated during the process initiated by curcumin nanocapsules and reduced the rate of Bcl-2/bax

Table 2 (continued)

	Authors name	Year	Carrier	Gen	Cellular result
[61]	Subandi, Subandi, and Sigit Purbadi Purbadi S	2023		NF-κB	Nanocurcumin and MTX reduced telomerase expression, NF-κB expression, and BrdU proliferation index in BeWo carcinoma cell line cultures more rapidly than MTX alone
[62]	Seyed Hos-seini, Elahe, et al	2023	Dendrosomal nano carrier	AKT, PI3K, PKC, JNK, P38 and MMPs mRNAs	The matrigel invasion, as well as cell viability of ovarian cancer cell lines SKOV3 and OVCAR3 by dendrosomal nano curcumin alone or in combination with oxalipl-atin, was inhibited significantly
[63]	Viraaj, V., et al	2023			The low proliferation index of the bulk is due to its large size and low permeability Furthermore, due to a threefold reduction in bulk, the chemically synthesized nanocurcumin exhibited a better proliferation index than the green synthetic nanocurcumin. This demonstrated improved uptake of nanocurcumin by the cell lines

Table 3 Invivo studies

	Authors	Title	Year	Objectives of study	Type of cancer	Duration of study	Sample size	Carcinogenic	Cell type of cancer
[64]	Alizadeh, A.M., et al.	Chemoprevention of azoxymethane-initiated colon cancer in rats by using a novel polymeric nanocarrier–curcumin	2012	Preventive effects of polymeric nanocarrier–curcumin on colon carcinogenesis in an AOM-induced rat tumor.	Normal colonic mucosa, mild to severe,dysplasia and colonic adenocarcinoma.	18 weeks	40Male Wistar rats (100–120 g)	azoxymethane(AOM).15 mg/kg, s.c- weekly for two consecutive weeks	
[65]	Chang, C.Z., et al.,	Curcumin, encapsulated in nano-sized PLGA, down-regulates nuclear factor κb (p65) and subarachnoid hemorrhage-induced early brain injury in a rat model.	2015	Examine the efficacy of nanocurcumin, a diarylheptanoid, on a SAH-induced EBI model.					FT-IR, DSC, and XRD-MT assay
[66]	Chaudhari, P.D. and P.N. Kendre	An emerging trend in addressing the challenges to oral nano-curcumin delivery is to improve the quality of life of cancer patients.	2015	Enhancement of solubility, bioavailability, and anti-cancer activity of curcumin	Breast cancer				
[67]	El-Azab, N.E.E., M.Y. Salem, and S. Abd El-Salam	A histological and immunohistochemical study of different therapeutic modalities for experimentally induced ulcerative colitis in rats.	2016		UC(Ulcerative colitis)	2 weeks	65adult male rats		
[68]	Mukerjee, A., A.P. Ranjan, and J.K. Vishwanatha	Targeted Nanocurcumin Therapy Using Annexin A2 Antibody Improves Tumor Accumulation and Therapeutic Efficacy Against Highly Metastatic Breast Cancer.	2016	Assess the in vivo targeting efficacy and examine the combined therapeutic effects of new Annexin A2 (AnxA2) antibody-linked curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (AnxA2-CPNP) for metastatic breast cancer through xenograft trials in mice.	Metastatic breast cancer				CF10A, MCF10AT and MCF10CA1

Table 3 (continued)

	Authors	Title	Year	Objectives of study	Type of cancer	Duration of study	Sample size	Carcinogenic	Cell type of cancer
[69]	Arozal, W., et al.	Pharmacokinetic Profile of Curcumin and Nanocurcumin in Plasma, Ovary, and Other Tissues.	2019		Ovary	15 days	10 Female Sprague Dawley rats 180–260 g		
[70]	Vijayakurup, V., et al.	Chitosan Encapsulation Enhances the Bio-availability and Tissue Retention of Curcumin and Improves its Efficacy in Preventing B a P-induced Lung Carcinogenesis	2019	Evaluate whether encapsulation of curcumin in chitosan nanoparticles can improve the cellular uptake and prolong the tissue retention of curcumin, yielding better chemoprevention	Lung Carcinogenesis				H1299
[71]	Abuelezz, N.Z., et al.,	Nanocurcumin alleviates insulin resistance and pancreatic deficits in polycystic ovary syndrome rats: Insights on PI3K/Akt/mTOR and TNF-α modulations.	2020	This study investigated TNF-α and pancreatic PI3K/AKT/mTOR levels in a PCOS animal model and evaluated their effects on developed pancreatic deficits. Secondly, we explored the impact of nanocurcumin as a potent anti-inflammatory supplement against these developed pancreatic pathologies	ovary	15 days	60 Virgin, adult female Wistar rats (7 weeks old and 160–200 g body weight) in 6 group		
[72]	Wang, G.N. and S. Sukumar	Characteristics and anti-tumor activity of polysorbate 80 curcumin micelles preparation by cloud point cooling.	2020	Xenografts in mice	breast cancer		Six-week-old female Nod/SCID/gamma strain of mice	Micell(polysorbate 80) 20nm	Utilizing the process of micelle formation that occurs during slow cooling below its cloud point

Table 3 (continued)

	Authors	Title	Year	Objectives of study	Type of cancer	Duration of study	Sample size	Carcinogenic	Cell type of cancer
[73]	immunological responses and anti-tumor effects of HPV16/18 L1-L2-E7 multiepitope fusion construct along with curcumin and nanocurcumin in C57BL/6 mouse model.	2021	Two multi-epitope DNA and peptide-based vaccine constructs (L1-L2-E7 and HSP70-L1-L2-E7) were used along with curcumin and nanocurcumin to evaluate immune responses and protective/therapeutic effects in tumor mouse mode				96C57BL/6 mice aged five to seven weeks(12group)		
[74]	Lakshmanan, A. et al.,	Nanocurcumin-Loaded UCNPs for Cancer Theranostics: Physicochemical Properties, In Vitro Toxicity, and In Vivo Imaging Studies	2021	UCNPs accumulate in the liver, lungs, intestines, and spleen four hours after administration.			Lewis Lung Cancer Mouse Model/ female BDF1 mice	Upconversion nanoparticles (UCNPs) using Poly (lactic-co-glycolic acid) (PLGA) 350nm	nanocarrier: reverse microemulsion/loading method:solvent-antisolvent method
[75]	Curcumin Nanoparticle Enhances the Anticancer Effect of Cisplatin by Inhibiting PI3K/AKT and JAK/STAT3 Pathway in Rat Ovarian Carcinoma Induced by DMBA	2021	Investigate the mechanism of curcumin nanoparticles given in combination with cisplatin in rat ovarian carcinoma	Ovarian carcinoma		25 female Wistar rats	dimethylbenz(a) anthracene (DMBA)		
[76]	Nanocurcumin preserves kidney function and hematology parameters in DMBA-induced ovarian cancer treated with cisplatin via its antioxidative and anti-inflammatory effect in rats	2023	Nanocurcumin, which has a good effect on kidney function in rats with ovarian cancer	Ovarian	4 weeks	20Wistar female rats aged eight weeks and weighing 150–200 g	Dimethylbenz(a) anthracene (DMBA)		Urea and creatinine colorimetric analysis at 534 nm,(TNF)-α,(NGAL) (FSH) ELISA Kit

Table 3 (continued)

	Authors	Title	Year	Objectives of study	Type of cancer	Duration of study	Sample size	Carcinogenic	Cell type of cancer
[77]	Abdelgawad LM,etal	Document details–Influence of Nanocurcumin and Photodynamic Therapy Using Nanocurcumin in Treatment of Rat Tongue Oral Squamous Cell Carcinoma Through Histological Examination and Gene Expression of BCL2 and Caspase-3	2023	comparing the effects of using Nanocurcumin and photodynamic therapy (PDT), alone or together, in treating OSCC in rats.	Tongue Oral Squamous Cell Carcinoma	Four months	Forty Wister male rats 8 weeks with a weight range of 120- 160 g	dimethylbenz anthracene 0.5 percent three times per week for four weeks	DAL, A72 and HT29 cell lines

	Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free	Reductions in tumor incidence by 33% compared to control
[64]	Alizadeh, A.M., et al.	Histological assay. Hematoxylin and eosin examinations-vidin–biotin immunoperoxidase	Two weeks before till 14 weeks after the last injection of AOM	0.2% and PNCC		Curcumin free	Reductions in tumor incidence 70 to 85 compared to control		
[65]	Chang, C.Z., et al.,	Western blot(, caspases) rt-PCR		75/150/300 µg/kg/day via osmotic mini-pump post-SAH					
[66]	Chaudhari, P.D. and P.N. Kendre			300 µg/kg	SAH-induced EBI model				Nanocurcumin treatment demonstrated neuroprotective effects by increasing NF-κB (p65) expression and decreasing caspase-9a expression related to mitochondria. These effects were observed in nanocurcumin nanoparticles, which may help mitigate EBI induced by SAH.

Table 3 (continued)

	Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free
[67]	El-Azab, N.E.E., M.Y. Salem, and S. Abd El-Salam	histological and immunohistochemical techniques	a daily oral dose of nanocurcumin starting three days after induction of colitis for two weeks;2		2 Weeks			Nanocurcumin is more effective than pentoxifylline in the treatment of UCin rats.
[68]	Mukerjee, A., A.P. Ranjan, and J.K. Vishwanatha						AnxA2-CPNPs effectively block cell proliferation, invasion, and migration, critical factors in cancer progression and spreading.	
[69]	Arozal, W., et al.	Cell viability, plasmin generation, and wound healing-Live animal imaging-angiogenesis assay		a single oral dose of 500 mg/kg				Curcumin concentrations in ovaries in the nanocurcumin group were 3.6 times higher than those in the curcumin group. They conclude that reducing curcumin's particle size did not alter its pharmacokinetic profile. However, it increased the distribution of curcumin in some tissues, although not optimal for use in ovarian cancer.

Table 3 (continued)

	Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free
[70]	Vijayakurup, V., et al.	chronic toxicity model in Swiss albino mice.MTT. Clonogenic assay/immunoassay. Western blotting. HOMA assessments and immunohistochemistry.	Oraly 25 mg/kg Aqueous suspension of chitosan nanocurcumin or free curcumin dissolved in corn oil					Free curcumin reduced tumor incidence by 22% and tumor multiplicity by 46.8%. In comparison, a quarter of the dose of chitosan nanocurcumin led to a 52% decrease in tumor incidence and a 71.4% decrease in tumor multiplicity compared to the B[a]P group.
[71]	Abuelezz, N.Z., et al.,	TEM.FTIR		HOMA.Western blotting. Histopathology. immunohistochemistry		100 mg and 200 mg/kg		
[72]	Wang, G.N. and S. Sukumar	U.V.TEM	SUM149 human breast cancer	MTT.Fluorescent microscopy and image analysis. Xenograft tumor growth assay			MC (100 mg/kg body weight), used at half the dose of FC (200 mg/kg body weight),	Achieved a statistically significant reduction in tumor size compared to vehicle-treated mice

Table 3 (continued)

Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free
[73] immunological responses and anti-tumor effects of HPV16/18 L1-L2-E7 multi-epitope fusion construct along with curcumin and nanocurcumin in C57BL/6 mouse model.		HEK-293 T cell line(normal). c3(tumor)	Granzyme B assay.Immunological assay.Monitoring tumor growth. Cytokine secretion. Antibody assay	three times with a two-week interval	20 µM		Curcumin and nanocurcumin inhibited the growth of C3 tumors in mice, resulting in 60% and 80% survival rates, respectively. Combining homologous multiepitope peptides and heterologous multiepitope DNA prime/multiepitope peptide boost regimens and curcumin and nanocurcumin provided complete protection against C3 tumors, leading to 100% tumor-free mice.
[74] Lakshmanan, A. et al.,	XRD.FTIR.	Rat glioma C6 cells.	MTT Assay.MTS Assay.Anti-Stokes Photo-luminescence Microscopy and Confocal Fluorescence Microscopy				PLGA-UCNPs showed 60–80% cell viability at 0.12–0.02 mg/mL in the rat C6 glioma cell medium.

Table 3 (continued)

	Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free
[75]	Curcumin Nanoparticle Enhances the Anti-cancer Effect of Cisplatin by Inhibiting PI3K/AKT and JAK/STAT3 Pathway in Rat Ovarian Carcinoma Induced by DMBA				ELISA, Western Blot Analysis, Quantitative RT-PCR Analysis	Administered for four weeks	Nanocurcumin (100 mg/kg BW every day), cisplatin (4 mg/kg BW every week)	Nanocurcumin improves the anti-cancer activity of cisplatin better than conventional curcumin. Cisplatin-curcumin and cisplatin-nanocurcumin showed a A remarkable increase in apoptotic markers, the ratio of Bax/BCl2 mRNA expressions of caspase-3 and caspase-9
[76]	Nanocurcumin preserves kidney function and hematology parameters in DMBA-induced ovarian cancer treated with cisplatin via its antioxidative and anti-inflammatory effect in rats	4weeks	Drug vehicle only, cisplatin only (4 mg/kg BW weekly), cisplatin (4 mg/kg BW weekly) with curcumin (100mg/kg BW daily), and cisplatin (4 mg/kg BW weekly) with nanocurcumin (100mg/kg BW daily)			Cisplatin and nanocurcumin in a rat model of ovarian cancer provide added benefits in preserving renal functio		

Table 3 (continued)

	Authors	Analyse of efficacy	Administration	Dosing	Duration of treatment	Control	Curcumin free	Compare nano with curcumin free
[77]	Abdelga-wad LM, et. al	Bcl2 and Caspase-3 expression levels measurements by ELISA, Body weight, Tumor volume, Histopathology observation		Nanocur-cumin200nm and 94% purity was given orally in distilled water with a concentration of 0.1-2 ml/mg/kg+A continuous 650 nm wavelength (6 mm diameter) was generated using gallium aluminum arsenide diode laser equipment				PDT using nanocurcumin photosensitizer was influential in the treatment of OSCC regarding clinical

Table 4 clinical trials

	Authors	Publication year	Title	Type of study	Cancer	Assay	Pat	Dose	Administrate	Efficacy
[78]	Saadipoor, A., et al	2019	Randomized, double-blind, placebo-controlled phase II trial of nanocurcumin in prostate cancer patients undergoing radiotherapy	Randomized, Double-blind	prostate cancer	CTCAE v.4.03 grading criteria	64	120 mg/day for	Three days before and during the RT course	Proctitis was observed in 18 out of 31 (58.1%) patients who received the placebo, compared to 15 out of 33 (45.5%) patients treated with nanocurcumin
[79]	Sandoughdaran, S., et al.,	2020	Randomized, Double-blind Pilot Study of Nanocurcumin in Bladder Cancer Patients Receiving Induction Chemotherapy	Randomized, Double-blind	muscle-invasive bladder cancer (MIBC)	26		180 mg/day	Clinical response rates were 30.8 and 50% in the placebo and nanocurcumin. No significant difference was found between the two groups concerning grade 3/4 renal and hematologic toxicities and hematologic nadirs	secondary: nephrotoxicity, hematologic nadirs, and toxicities	The entire clinical response assessment will be conducted up to four weeks after treatment completion

patients receiving chemotherapy [10, 11]. These trials reported improved clinical outcomes, such as reduced radiation-induced toxicities and enhanced tumor response rates, in the nanocurcumin-treated groups. However, the sample sizes in these trials were relatively small and more significant, well-designed studies are needed to validate the findings.

3.4 Synthesis of results

The collective evidence from in vitro, in vivo, and clinical studies suggests that nanocurcumin is a promising therapeutic agent for cancer treatment. Nanocurcumin consistently demonstrated enhanced bioavailability, cellular uptake, and anti-cancer efficacy compared to free curcumin. The improved physicochemical properties of nanocurcumin, such as increased solubility and stability, contribute to its superior performance.

Nanocurcumin exerts its anti-cancer effects through multiple mechanisms, including the induction of apoptosis, cell cycle arrest, and modulation of cancer-related signaling pathways. The ability of nanocurcumin to sensitize cancer cells to conventional therapies highlights its potential as an adjuvant treatment option.

However, it is essential to acknowledge the limitations of the current evidence. Most of the studies were preclinical, and the clinical trials had small sample sizes. The variability in nanocurcumin formulations, cancer types, and dosing regimens across studies makes direct comparisons challenging. Therefore, further research, particularly in large-scale, well-designed clinical trials, is necessary to establish the clinical efficacy and long-term safety of nanocurcumin in cancer treatment.

4 Discussion

The exploration of nanocurcumin in cancer therapy, as evidenced by the results of this systematic review, underscores its burgeoning role in oncological treatments. The distinctive physicochemical properties of nanocurcumin, notably in formulations using PLGA combinations (50:50 and 75:25), have been pivotal in enhancing its therapeutic efficacy. The 50:50 PLGA nanocurcumin, with its smaller particle size and higher encapsulation efficiency, demonstrates a favorable pharmacokinetic profile characterized by a more rapid release rate and sustained release over a week, thereby augmenting its anti-cancer capabilities [13].

In vitro studies have highlighted the superior cellular uptake and anti-proliferative activity of nanocurcumin compared to free curcumin, especially in human epithelial cervical cancer cells (HeLa). These research projects, using techniques such as MTT assay and Annexin V/propidium iodide staining, demonstrate the improved ability of nanocurcumin to fight tumors. This is supported by the findings of PARP cleavage and decreased clonogenic potential in HeLa cells [13]. Furthermore, the electrophoretic mobility shift assay and immunocytochemical analysis confirm the higher effectiveness of nanocurcumin, highlighting its potential in fighting different types of cancer. [14]. Mona M Atia and colleagues found that both curcumin and nanocurcumin decreased the viability of HepG2 and Huh-7 cancer cells and increased the occurrence of apoptosis, regardless of the presence or absence of acrylamide. Moreover, nanocurcumin exhibited superior anti-tumor effectiveness compared to curcumin. The administration of acrylamide in mice resulted in a significant rise in the expression of CYP2E1, p53, cleaved caspase-3, and COL1A1 in the liver, as well as elevated levels of blood alanine aminotransferase and aspartate aminotransferase activity. Nanocurcumin and curcumin successfully counteracted these effects, with nanocurcumin exhibiting a reduction in the histopathology and fibrosis resulting from acrylamide and effectively correcting the acrylamide-induced glycogen depletion. Using nanoparticle formulation can enhance the effectiveness of curcumin in fighting cancer and protecting the liver [54]. Another study has demonstrated that the combination of dendrosomal nanocurcumin and exogenous p53 work synergistically to provide anti-cancer effects on MDA-MB-231 breast cancer cells [6]. The nanocurcumin effectively inhibited the proliferation of Hep-2 cancer cells by causing cell cycle arrest in the G2/M phase and inducing apoptosis. This apoptotic process relied on the activation of caspase-3 and p53 [53].

In vivo studies complement these findings, illustrating nano curcumin's synergistic effect with other therapeutic agents, such as in the multiepitope HSP70-L1-L2-E7 vaccine construct against HPV-related C3 tumor cells. These studies also demonstrate the enhanced chemopreventive efficacy of curcumin-loaded chitosan nanoparticles compared to free curcumin in lung carcinogenesis models, suggesting broader applicability in different cancer types [18, 21]. Melva Louisa and colleagues showed that nanocurcumin mitigates the elevation of renal function indicators and alterations in hematological indices in rats subjected to cisplatin treatment. When comparing rats treated with cisplatin, plasma urea, creatinine, and neutrophil gelatinase-associated lipocalin (NGAL) levels were significantly reduced in the nano-curcumin-treated group. In addition, nanocurcumin resulted in an increase in glutathione activities, a decrease in lipid

peroxidation, and a reduction in plasma TNF-α levels. Combining nanocurcumin with cisplatin in a rat model of ovarian cancer may offer supplementary advantages as a prophylactic drug against renal dysfunction and the hematological damage caused by cisplatin [80]. Gemini nano-curcumin (Gemini-Cur) effectively reaches the cells and hinders cell division in a manner that is influenced by both time and dosage. Annexin V/FITC verified the apoptotic impact on 4T1 cells. Furthermore, in vivo experiments demonstrated that the growth of tumors in mice treated with Gemini-Cur was inhibited compared to the control group. Expression analyses revealed the regulation of genes associated with programmed cell death and the spread of cancer, such as Bax, Bcl-2, MMP-9, VEGF, and COX-2, in mice that received treatment. The studies presented here provide evidence of the potent anti-cancer effects of Gemini-Cur in mouse models. Nevertheless, additional molecular and cellular investigations are necessary to determine this therapeutic benefit [81] definitively. A study confirmed the targeting ability of a new Annexin A2 antibody-linked curcumin-filled poly (lactic-co-glycolic acid) (PLGA) nanoparticles (AnxA2-CPNP) against metastatic breast cancer in living organisms. The findings demonstrated that AnxA2-CPNPs successfully hindered cell growth, invasion, migration, tumor growth, and metastasis. Live imaging of animals illustrated that AnxA2-PNPs and AnxA2-CPNPs accurately aimed and gathered in the tumor. Experiments involving xenografts in mice displayed notable regression of breast tumors due to the precise targeting, gathering, and continual release of curcumin. [68].

Clinical trials, though limited, offer a glimpse into nanocurcumin's potential in actual patient settings. Studies involving patients undergoing radiotherapy for prostate cancer and chemotherapy for muscle-invasive bladder cancer indicate nanocurcumin's tolerability and efficacy. While not conclusively definitive, these trials emphasize nanocurcumin's role in improving clinical response rates and mitigating radiation-induced complications in cancer patients [15–17]. Saleh Sandoughdaran designed a study to assess the practicality and possible effectiveness of adding nanocurcumin supplements to the treatment of patients with localized muscle-invasive bladder cancer (MIBC) who are undergoing induction chemotherapy. Their data suggest that adding nanocurcumin as a supplemental therapy may be helpful for MIBC patients and provide justification for doing more extensive research in the future.

Furthermore, this study offers a significant translational understanding to bridge the gap between experimental research and clinical use in the field [79]. Researchers carried out an additional investigation to analyze the effects of nanocurcumin on prostate cancer patients undergoing radiotherapy. The study found no notable distinction between the two groups concerning radiation-induced cystitis, duration of radiation side effects, blood count lows, and tumor reaction. Nonetheless, these results provide valuable insights to bridge the divide between laboratory studies and practical clinical use [77]. Despite these positive indications, more significant, well-designed clinical trials are necessary to conclusively determine nanocurcumin's ability to effectively target and kill cancer cells in humans across various cancer types and stages. Future research should focus on optimizing dosing regimens, identifying responsive cancer types, and assessing long-term outcomes to establish nanocurcumin's clinical efficacy fully.

The convergence of these findings from various studies forms a compelling narrative for nanocurcumin's role in cancer therapy. It highlights nanocurcumin's ability to enhance curcumin's bioavailability and therapeutic efficacy, chiefly through improved solubility, stability, and targeted delivery. While preclinical studies paint a promising picture, the need for extensive clinical trials to ascertain nanocurcumin's safety and efficacy in humans is paramount.

The safety profile of nanocurcumin is a critical consideration in its development as a cancer therapeutic. While bulk curcumin has a well-established safety record, nanoformulations may exhibit different biological interactions and potential toxicities. Recent studies have shown promising results regarding nanocurcumin's safety. For instance, Saadipoor et al. (2019) reported no significant adverse effects in prostate cancer patients receiving nanocurcumin during radiotherapy [77]. Similarly, Sandoughdaran et al. (2020) observed no increased toxicity when combining nanocurcumin with chemotherapy in bladder cancer patients [78]. However, these studies had relatively small sample sizes and short durations. Preclinical research by Abuelezz et al. (2020) demonstrated the safety of nanocurcumin in animal models, with no observed toxicity at therapeutic doses [70]. Nevertheless, comprehensive long-term safety studies and more extensive clinical trials are essential to fully elucidate nanocurcumin's safety profile across various cancer types and treatment regimens before widespread clinical adoption.

The path to regulatory approval for nanocurcumin as a mainstream cancer treatment presents significant challenges. Nanoformulations, including nanocurcumin, face unique regulatory hurdles due to their complex nature and potential for novel biological interactions [81]. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have established specific guidelines for nanomedical products, requiring extensive characterization of physicochemical properties, biodistribution, and potential toxicity [82]. For nanocurcumin, demonstrating consistent manufacturing processes, stability, and batch-to-batch reproducibility is crucial [83]. Additionally, regulatory bodies demand robust clinical efficacy data from well-designed trials. While early-phase studies have shown promise [77, 78], more significant,

randomized controlled trials are necessary to meet regulatory standards. The regulatory landscape for nanomedicines is evolving, and nanocurcumin developers must navigate these changing requirements to achieve approval, a process that may take several years and substantial resources [84].

5 Conclusion

This systematic review demonstrates the immense potential of nanocurcumin as a promising therapeutic agent in cancer treatment. The findings from numerous in vitro, in vivo, and clinical studies consistently highlight nanocurcumin's superior bioavailability, enhanced anti-cancer efficacy, and favorable safety profile compared to native curcumin. Nanocurcumin formulations, particularly those involving PLGA polymers, exhibit distinct physicochemical properties that facilitate improved solubility, stability, and targeted delivery, thereby potentiating their therapeutic effects. The clinical implications of these findings are significant, suggesting that nanocurcumin could potentially improve treatment efficacy while reducing side effects commonly associated with traditional chemotherapies, thus enhancing the quality of life for cancer patients. The observed synergistic effects with conventional therapies indicate a potential for reducing drug dosages and minimizing toxicity. However, while certain limitations exist, such as variability in study designs and cancer types investigated and the need for larger-scale clinical trials to fully establish safety and efficacy, the collective evidence strongly advocates for the continued exploration of nanocurcumin in oncological applications. As research in nanotechnology and cancer biology advances, nanocurcumin holds immense promise to revolutionize cancer treatment strategies, offering improved outcomes and enhanced quality of life for patients. Extensive interdisciplinary collaborations and well-designed translational studies are crucial to fully harness nanocurcumin's therapeutic potential and facilitate its clinical implementation in cancer care, potentially making it a valuable addition to the oncologist's toolkit shortly.

5.1 Limitations and future directions

Despite the promising results observed in nanocurcumin research, future studies need to address several limitations and challenges. One significant limitation is the high cost of developing and producing nanocurcumin formulations. The complex manufacturing processes and specialized equipment required for nanoparticle synthesis contribute to increased production costs [85]. This economic barrier could potentially limit the accessibility of nanocurcumin-based treatments for patients. Future research should optimize production methods and explore cost-effective formulation strategies to make nanocurcumin more affordable and widely available.

Another critical area for future investigation is the potential development of resistance to nanocurcumin in cancer cells. While curcumin has shown promise in overcoming drug resistance in various cancer types [86], the long-term efficacy of nanocurcumin and its ability to prevent or delay resistance development needs further study. Research by Ghalandarlaki et al. (2014) suggests that nanocurcumin may have advantages in overcoming multidrug resistance due to its enhanced cellular uptake and retention [87]. However, more comprehensive studies are required to elucidate potential resistance mechanisms and develop strategies to counteract them.

Future directions should include:

Conducting large-scale, long-term clinical trials to establish the efficacy and safety profile of nanocurcumin across various cancer types.

Investigating combination therapies with nanocurcumin to enhance its anti-cancer effects and potentially overcome resistance.

Developing and evaluating cost-effective production methods for nanocurcumin to improve its economic viability.

Exploring the molecular mechanisms of nanocurcumin's action in different cancer types to optimize its use and predict potential resistance pathways.

Assessing the long-term effects of nanocurcumin treatment on cancer cell populations to understand and mitigate resistance development.

Investigating personalized nanocurcumin formulations based on individual patient characteristics and tumor profiles to maximize efficacy and minimize resistance.

Addressing these limitations and pursuing these research directions will be crucial in realizing the full potential of nanocurcumin as a mainstream cancer treatment option.

Declarations

Ethics approval and consent to participate This article reviews the existing literature and contains no studies with human participants or animals performed by authors. Therefore, no ethical approval was required for this work.

Competing interests The authors declare no competing interests.

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