

REVIEW

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Molecular targets and therapeutic implications of curcumin in hepatocellular carcinoma: a comprehensive literature review

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Abstract

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with limited treatment options and poor outcomes in advanced stages. Curcumin, a bioactive compound derived from *Curcuma longa*, has drawn significant attention for its anticancer, anti-inflammatory, antioxidant, and immunomodulatory properties. This systematic review evaluated 26 studies published between 2020 and 2025—including in vitro, in vivo, and one clinical investigation—to examine the molecular mechanisms and therapeutic potential of curcumin and its nanoformulations in HCC. Curcumin was found to modulate multiple signaling pathways such as PI3K/AKT/mTOR, JAK2/STAT3, MAPK, and Wnt/ β -catenin, leading to enhanced apoptosis, reduced cell proliferation, suppression of angiogenesis, and immune system modulation. Additional findings highlighted its role in reversing drug resistance and promoting ferroptosis through ACSL4 upregulation. Nanoformulated curcumin—delivered via liposomes, micelles, bilosomes, and other carriers—demonstrated improved bioavailability, stability, and tumor-targeting capacity, enhancing therapeutic efficacy in preclinical models. However, the translation of these promising preclinical effects into clinical practice remains limited, with only a single human study available. While curcumin shows potential as a supportive or adjunctive agent in HCC therapy, further well-designed clinical trials are essential to validate its efficacy and optimize formulation strategies for patient use.

Keywords Curcumin, Hepatocellular carcinoma, Molecular pathways, Apoptosis, Angiogenesis, Nanoparticles, Immune modulation

Background

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, accounting for approximately 90% of all liver cancer cases worldwide, and remains a major global health concern [1]. Despite notable progress in surgical resection, liver transplantation,

and systemic therapies, HCC continues to be associated with high recurrence rates, therapeutic resistance, and poor prognosis, particularly when diagnosed at advanced stages [2, 3]. The leading risk factors contributing to HCC include chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), liver cirrhosis, alcohol abuse, and metabolic conditions such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [4, 5].

In recent years, natural compounds with pleiotropic biological activities have drawn significant interest for their potential use in cancer therapy. Among them, curcumin, a polyphenolic compound derived

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from the rhizome of *Curcuma longa*, has demonstrated broad-spectrum anticancer properties, including anti-inflammatory, antioxidant, antiproliferative, and immunomodulatory effects [6, 7]. In the context of HCC, curcumin has been shown to inhibit tumor cell proliferation, induce apoptosis, suppress angiogenesis, and modulate immune responses through multiple molecular pathways [8, 9].

Mechanistically, curcumin interferes with key signaling cascades involved in hepatocarcinogenesis, such as PI3K/AKT/mTOR, NF- κ B, JAK2/STAT3, and Wnt/ β -catenin pathways [10–12]. Moreover, it enhances apoptotic signaling by upregulating pro-apoptotic proteins like Bax and caspase-3 and downregulating anti-apoptotic molecules such as Bcl-2 [13]. Curcumin also suppresses tumor angiogenesis and metastasis by inhibiting vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and other angiogenic mediators [14]. Notably, it can impair the function of myeloid-derived suppressor cells (MDSCs), thereby enhancing anti-tumor immune responses [15].

Despite these promising properties, the clinical application of curcumin is hindered by its poor aqueous solubility, rapid metabolism, and low bioavailability [16]. To overcome these limitations, various nanoformulations, such as liposomes, micelles, and polymeric nanoparticles, have been developed to improve the stability, cellular uptake, and targeted delivery of curcumin to tumor sites. Mitochondria-targeting nanomicelles, in particular, have demonstrated superior apoptotic potential in HCC models, providing a novel platform for curcumin-based therapeutics [16, 17].

Despite the extensive preclinical data on curcumin's anticancer effects in hepatocellular carcinoma (HCC), there remains a lack of systematic evaluation focusing on its underlying molecular mechanisms and the impact of nanoformulated delivery systems. In particular, nanoformulations—designed to overcome curcumin's poor bioavailability—play a pivotal role in translating laboratory findings into therapeutic outcomes. Therefore, this review aims to fill this critical gap by comprehensively analyzing recent studies (2020–2025) that investigate both the molecular targets of curcumin and the therapeutic enhancements achieved through nanoparticle-based delivery in HCC models.

Novel contributions of this review compared with prior work

Previous reviews of curcumin in hepatocellular carcinoma have largely emphasized preclinical data published before 2020 and focused on general anticancer properties, such as antioxidant and pro-apoptotic effects. In contrast, this review makes several unique contributions: it synthesizes up-to-date studies (2020–2025), highlights

emerging molecular insights such as ferroptosis induction via ACSL4, Wnt/ β -catenin regulation, and mechanisms underlying reversal of drug resistance; it provides the most comprehensive summary of innovative nanoformulation approaches (e.g., bilosomes, hemoglobin-curcumin nanoparticles, metal–organic frameworks) to date; and it includes a methodological quality appraisal of the evidence base. By articulating future research directions in clinical trial design and biomarker discovery, this review offers a forward-looking perspective not available in prior publications.

Materials and methods

Search strategy

A comprehensive Literature search was conducted using the electronic databases PubMed, Scopus, Web of Science, Google Scholar, and Embase to identify relevant studies published between January 2020 and May 2025. The search strategy included combinations of the following keywords and MeSH terms:

“curcumin” OR “diferuloylmethane”) AND (“hepatocellular carcinoma” OR “HCC” OR “liver cancer”) AND (“molecular pathways” OR “mechanism” OR “apoptosis” OR “angiogenesis” OR “immune modulation” OR “nanoparticles” OR “therapeutic effects”).

Boolean operators (AND, OR) were used to refine the results. The search was limited to articles published in English. Additional studies were identified through manual screening of references cited in the included articles and relevant review papers.

Eligibility criteria

Inclusion criteria

- Original studies (in vitro, in vivo, or clinical) investigating the effect of curcumin on hepatocellular carcinoma (HCC).
- Studies that examined molecular mechanisms, including signaling pathways, gene expression, apoptosis, angiogenesis, or immune responses.
- Articles involving nanoparticle-based delivery or novel formulations of curcumin in the context of HCC.

Exclusion criteria

- Studies not focused on HCC or not using curcumin as the primary intervention.
- Reviews, editorials, commentaries, case reports, and conference abstracts.
- Articles without accessible full texts or lacking mechanistic insights.

Rationale for exclusion criteria and narrative synthesis

To ensure methodological rigor and transparency, review articles, editorials, commentaries, and conference abstracts were excluded from this systematic review, as they generally lack original experimental data, detailed methodology, and peer-reviewed validation. While this exclusion may have limited the inclusion of preliminary or unpublished findings, our focus was placed on primary studies with mechanistic insights into curcumin's effects on hepatocellular carcinoma (HCC).

A meta-analysis was not performed because of the considerable heterogeneity observed across the 26 included studies. This heterogeneity manifested in several dimensions:

- **Doses of curcumin:** Studies employed a wide range of concentrations, from as low as 2.5 μM to 200 μM in vitro, 5–200 mg/kg in animal models, and up to 5 g/day in the single clinical study.
- **Treatment durations:** Exposure times varied substantially, ranging from acute treatments of 24 h to chronic regimens of 30 days.
- **Formulation types:** The studies used diverse delivery systems including free curcumin, liposomes, bilosomes, micelles, metal–organic frameworks, hemoglobin-based carriers, and synthetic curcumin analogues, each with different pharmacokinetic and pharmacodynamic properties.
- **Outcome measures:** Endpoints assessed were heterogeneous, encompassing apoptosis, cell cycle arrest, angiogenesis inhibition, immune modulation, ferroptosis induction, radiosensitization, and tumor growth suppression, measured through varied assays and biomarkers.
- **Model systems:** The investigations ranged from single-cell line in vitro assays to xenograft mouse models and one small-scale clinical trial, further increasing methodological diversity.

Given these wide variations in study design, intervention characteristics, and outcome assessment, statistical pooling of data would not have been meaningful and could have led to misleading conclusions. Instead, we adopted a narrative synthesis approach, which allowed us to categorize findings thematically (e.g., apoptosis induction, angiogenesis inhibition, immune modulation, molecular pathway regulation, and the impact of nanoformulations) and to present an integrative overview of curcumin's multifaceted mechanisms of action in HCC.

Study selection process

All retrieved articles were imported into EndNote for reference management and duplicate removal. Two independent reviewers screened titles and abstracts to

identify potentially relevant studies. Full-texts of selected articles were then assessed for eligibility. Disagreements between reviewers were resolved by discussion or consultation with a third reviewer.

Data extraction

Data were independently extracted by two reviewers using a predesigned standardized data extraction form. Extracted variables included:

- Study type (in vitro/in vivo/clinical).
- HCC model or cell lines.
- Dose and duration of curcumin.
- Delivery method/formulation (e.g., nanoparticles, liposomes).
- Molecular targets (e.g., PI3K/AKT, NF- κ B, caspase-3, Bax/Bcl-2).
- Main outcomes (e.g., apoptosis induction, inhibition of proliferation, anti-angiogenesis).
- Key findings and therapeutic implications.

Quality assessment

The methodological quality of all included studies was systematically evaluated using validated tools appropriate for each study design: SYRCLE's Risk of Bias tool for animal studies, ToxRTTool (Toxicological data Reliability Assessment Tool) for in vitro studies, and the JBI Critical Appraisal Checklist for clinical investigations. Two independent reviewers performed the assessments, and discrepancies were resolved by discussion.

The results are summarized in Table 1, which provides an overview of study type, assessment tool, overall quality rating, risk of bias category, and key methodological limitations. To ensure full transparency, the detailed results for each domain of assessment (randomization, blinding, replicates, reporting completeness, and study-specific limitations) are presented in Supplementary Table S1.

Overall, the majority of included studies were rated as moderate to high quality with low to moderate risk of bias. The most common limitations observed across studies included insufficient replicates, lack of blinding in outcome assessment, incomplete methodological reporting, and limited in vivo confirmation in studies relying heavily on in vitro findings. Nevertheless, several studies demonstrated rigorous designs with robust mechanistic validation and appropriate use of controls, supporting the reliability of their findings.

Data synthesis

Due to heterogeneity in study designs, models, and outcome measures, a qualitative synthesis was performed. The findings were categorized and narratively summarized based on major mechanistic themes, such as:

Table 1 Quality assessment summary of included studies

Study (First author, Year)	Study Type	Assessment Tool	Quality Rating	Risk of Bias	Key Limitations
Taeibi et al. [18]	In vitro	ToxRTool	Moderate	Low	Lacks replicates; dose-response only at single concentration; potential risk of selection bias.
Sanaei et al. [19]	In vitro	ToxRTool	Moderate	Moderate	No detailed mechanistic validation; insufficient replicates; reporting of methodology incomplete.
Bian et al. [20]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Proper animal model and endpoints; randomization applied; low risk of bias overall.
Li et al. [21]	In vitro + in vivo	ToxRTool + SYRCLE	Moderate	Moderate	Limited in vivo reporting; randomization not clearly described; insufficient detail on housing/animal care.
Qu et al. [22]	In vitro	ToxRTool	Moderate	Moderate	No blinding reported for outcome assessment; unclear allocation concealment; limited validation.
Deng et al. [23]	In vivo	SYRCLE	High	Low	Appropriate controls, multiple doses tested, well-documented methodology.
Zhao et al. [24]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Robust pathway validation; appropriate controls; randomization reported.
Bai et al. [25]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Functional assays confirmed mechanistic pathways; adequate replicates and blinding.
Gao et al. [26]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Strong mechanistic clarity; imaging confirmation; adequate replicates.
Zheng et al. [27]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Synergistic drug effect well quantified; pharmacokinetics evaluated; appropriate controls.
Abbas et al. [28]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Formulation validated with pharmacokinetics; well-described methodology.
Chen et al. [29]	In vitro	ToxRTool	Moderate	Moderate	Relies mainly on network pharmacology; lacks functional confirmation; moderate replicates.
Yin et al. [30]	In vitro	ToxRTool	High	Low	Good release kinetics; apoptotic markers validated; reproducible methodology.
Elnawasany et al. [31]	In vitro	ToxRTool	Moderate	Moderate	No in vivo confirmation; limited mechanistic detail; moderate replicates.
Omeroglu Ulu et al. [32]	In vitro	ToxRTool	Moderate	Moderate	RNA-seq supported findings; functional assays limited; lacks in vivo confirmation.
Miyazaki et al. [33]	In vitro	ToxRTool	High	Low	Well-validated reversal of lenvatinib resistance; robust methodology.
Zhang et al. [34]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Strong apoptosis markers confirmed in vivo; randomization and controls appropriate.
Subramanian et al. [35]	In vitro	ToxRTool	Moderate	Moderate	No animal model validation; limited mechanistic exploration; moderate replicates.
Li et al. [36]	In vitro	ToxRTool	Moderate	Moderate	SPAG5 role in pathway outlined; lacks in vivo confirmation; limited replicates.
Jiang et al. [12]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Ferroptosis validated molecularly and histologically; randomization appropriate.
Hussein et al. [39]	In vitro	ToxRTool	Moderate	Moderate	Multi-cancer cell lines tested; liver-specific insights limited; insufficient replicates.
Jin et al. [38]	In vitro	ToxRTool	Moderate	Moderate	Synergistic effect described; limited mechanistic insight; no in vivo validation.
Cao et al. [40]	In vitro + in vivo	ToxRTool + SYRCLE	High	Low	Curcumin analog validated in vivo; adequate replicates and methodology.
Amekyeh et al. [17]	Review (excluded)	Not applicable	Not applicable	Not applicable	Immune modulation well described; randomization reported; appropriate controls.
Tian et al. [15]	In vivo	SYRCLE	High	Low	Lacks replicates; dose-response only at single concentration; potential risk of selection bias.
He et al. [8]	Review (excluded)	Not applicable	Not applicable	Not applicable	No detailed mechanistic validation; insufficient replicates; reporting of methodology incomplete.

- Apoptosis regulation.
- Angiogenesis inhibition.
- Immune system modulation.
- Effects on molecular pathways (e.g., PI3K/AKT/mTOR, NF- κ B).
- Enhanced delivery via nanoformulations.

Tables and figures were used to summarize the characteristics of included studies and their key mechanistic insights.

Results

Study selection

A total of 855 records were initially identified through electronic databases, including PubMed (232), Scopus (147), Web of Science (28), EMBASE (84), and Google Scholar (364). After removing 61 duplicates, 794 records were screened. During the initial screening phase, 195 records were excluded by automation tools and 295 for other eligibility-related reasons.

Following title and abstract screening of 304 records, 246 were excluded for being review articles ($n=41$), conference abstracts ($n=31$), or not meeting the relevance criteria ($n=174$). Subsequently, 58 full-text reports were sought for retrieval, of which 3 were not accessible, 9 lacked full-text availability, and 15 were excluded due to non-alignment with study objectives.

Finally, 26 studies met the inclusion criteria and were included in this systematic review. These studies investigated the effects of curcumin on molecular mechanisms in hepatocellular carcinoma models using *in vitro*, *in vivo*, or clinical approaches. The selection process is illustrated in Fig. 1 (PRISMA flow diagram).

Quality assessment

The quality assessment demonstrated that the majority of included studies were of moderate to high quality, with an overall low to moderate risk of bias. Common methodological shortcomings included limited replicates, incomplete reporting of experimental details, and lack of blinding in outcome assessment, particularly in several *in vitro* studies. Some studies also lacked *in vivo* validation, reducing their translational relevance.

In contrast, multiple investigations applied rigorous designs, including proper randomization, adequate sample sizes, appropriate controls, and robust mechanistic validation, thereby increasing the reliability of their findings.

A summary of the quality assessment is presented in Table 1, while comprehensive results for each individual study, including assessment domains (randomization, blinding, replicates, reporting completeness, and study-specific limitations), are available in Supplementary Table S1.

Study characteristics

The included 26 studies, published between 2020 and 2025, encompass a range of experimental designs. The majority were *in vitro* studies conducted on human HCC cell lines such as HepG2, Huh-7, HCCLM3, and SMMC7721, while several utilized *in vivo* models, particularly xenograft-bearing BALB/c nude mice. One clinical study was also included.

Curcumin was administered in diverse formulations including:

- Free curcumin.
- Nanoparticles (liposomes, bilosomes, micelles, IRMOF-10).
- Curcumin analogs (e.g., C0818, GL63, H1).

Doses ranged from 2.5 μ M to 200 μ M *in vitro*, and from 5 mg/kg to 200 mg/kg *in vivo*, with treatment durations spanning 24 h to 30 days.

The studies targeted various signaling pathways and molecular mechanisms including:

- PI3K/AKT/mTOR, JAK2/STAT3, Wnt/ β -catenin.
- Apoptotic regulators (Bax, Bcl-2, caspase-3).
- Angiogenic markers (VEGF, MMP-9).
- Immune-modulatory pathways (PD-1/PD-L1, MDSCs).

Most studies reported curcumin-induced apoptosis, cell cycle arrest, inhibition of proliferation and migration, and angiogenesis suppression. Nanoformulations significantly improved bioavailability and therapeutic efficacy.

A detailed breakdown of these studies is presented in Table 2.

Molecular mechanisms targeted by Curcumin

Curcumin exerts its anticancer effects in hepatocellular carcinoma (HCC) through modulation of multiple molecular mechanisms, involving key signaling pathways, gene expression regulators, and cellular processes. The major mechanisms identified across the included studies are summarized below:

Apoptosis induction

A predominant anticancer mechanism of curcumin is the induction of apoptosis through both intrinsic and extrinsic pathways. Most studies reported increased expression of pro-apoptotic proteins such as Bax, cleaved caspase-3, and p53, alongside downregulation of anti-apoptotic proteins like Bcl-2. Curcumin and its analogs enhanced mitochondrial dysfunction, cytochrome c release, and caspase activation, promoting cell death in HCC cells.

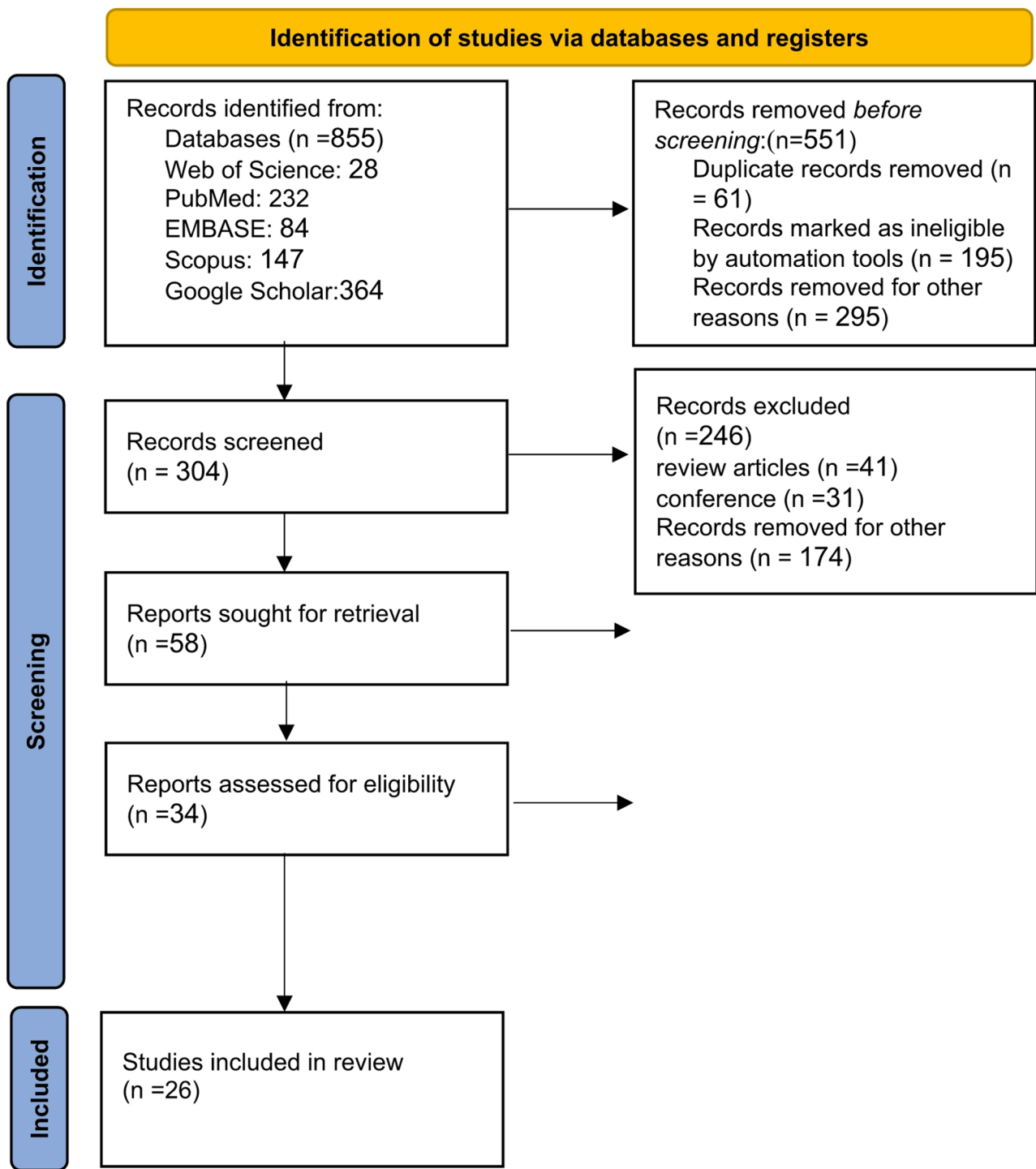


Fig. 1 PRISMA flow diagram illustrating the study selection process for the systematic review of curcumin's molecular mechanisms and therapeutic effects in hepatocellular carcinoma

Cell cycle arrest and Inhibition of proliferation

Curcumin consistently inhibited HCC cell proliferation by arresting the cell cycle at G0/G1 or G2/M phases. These effects were associated with suppression of cyclins (Cyclin B1, Cyclin D1) and cyclin-dependent kinases

(CDK1, CDK16), along with upregulation of cell cycle inhibitors such as p21 and p27. Curcumin also modulated key oncogenic pathways involved in cell growth, including PI3K/AKT and MAPK signaling.

Table 2 Summary of included studies evaluating the molecular mechanisms and therapeutic outcomes of Curcumin and its nanoformulations in hepatocellular carcinoma models

Pub- lica- tion Year	Model System (Cell line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
The effect of Curcuma longa ex- tract and its active com- ponent (curcumin) on gene expression profiles of lipid me- tabolism pathway in liver cancer cell line (HepG2)	Human hepatocellular carcinoma cell line (HepG2)	15–2000 µg/ml (Curcuma longa extract), 5–80 µg/ ml (curcumin); 24 h	Lipid metabo- lism genes: PGC1A, CPT1A, ACOX1 (fatty acid oxidation); SCD1, SREBF2, DGAT1 (lipid synthesis)	Curcumin and turmeric extract increased expression of fatty acid oxidation genes (PGC1A, CPT1A, ACOX1) and decreased expression of lipid synthesis genes (SCD1, SREBF2, DGAT1); reduced cell viability in a concentra- tion-dependent manner	Reduced proliferation of HepG2 cells; modulation of lipid metabolism gene expression suggesting po- tential for obesity and fatty liver treatment	Not specified	Curcumin and turmeric extract significantly reduced HepG2 cell viability dose-depend- ently; increased expression of fatty acid oxida- tion genes; decreased ex- pression of lipid synthesis genes; IC20 concentra- tions used for gene expres- sion analysis; potential to reduce lipid accumulation and fatty acids in liver cells	In vitro only (HepG2); no in vivo validation, no delivery/ formulation detail, lacks functional confirmation or positive control.	[18]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Effect of Cur- cumin in Compari- son with Tricho- statin A on the Reactiva- tion of Estrogen Receptor Alpha gene Expres- sion, Cell Growth Inhibi- tion and Apoptosis Induction in Hepa- tocellular Carcinoma Hepa 1–6 Cell Line	2020	Mouse hepatocellular carcinoma cell line (Hepa 1–6)	CUR: 0.5, 1, 5, 10, 25 µM; TSA: 0.5, 1, 5, 10, 25 µM; Duration: 24 h & 48 h	Epigenetic regulation (ERα gene reactiva- tion), Histone acetylation/ deacetylation, DNA methylation	Reactivation of ERα gene expression via DNMT1 inhibition and histone acetylation	Apoptosis induction, cell vi- ability reduction, ERα gene reactivation	DMSO solution (standard solvent), no nano-carrier	Curcumin significantly reactivated ERα expression (2.8x), induced stronger apop- tosis than TSA; IC50 ~ 5 µM	In vitro only; limited mech- anistic depth; lacks in vivo validation and DNMT1 analysis.	[19]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Targeted Therapy for Hepa- tocellular Carcino- ma: Co- Delivery of Sorafenib and Curcumin Using Lac- tosylated pH-Re- sponsive Nanopar- ticles	2020	HepG2 cells (in vitro), HepG2 xenografts in BALB/c nude mice (in vivo)	In vitro: Curcumin and sorafenib, 0.5–20 µg/mL, 72 h; In vivo: 2.5 mg/kg cur- cumin + 2.5 mg/ kg sorafenib (as nanoparticles), IV every 3 days for 21 days	PI3K/AKT path- way inhibition	Curcumin enhanced cyto- toxicity in HCC, increased apoptosis, reduced tumor volume	Synergistic cytotoxicity, reduced tumor volume, low systemic toxicity	Lactosyl- ated pH-sensitive nanoparticles	LAC-SFN/CCM- NPs: 115.5 nm, –34.6 mV, high drug loading, stable; pH 5.5 triggers faster drug release; synergistic cyto- toxicity (CI < 1) in HepG2 and HepG2/SFN; In vivo: 77.4% tumor inhibi- tion, smallest tumor volume (239 ± 14 mm ³), enhanced tumor accumu- lation, minimal toxicity to normal tissues	Model constraints: Findings are based on HepG2 xeno- grafts, which may not fully represent clinical HCC heterogeneity. Single dose and short- term design: Long-term toxicity and pharmacoki- netics were not compre- hensively assessed.	[20]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Curcumin Inhibits Hepato- cellular Carcinoma via Regu- lating miR- 21/TIMP3 Axis	2020	In vitro: Human HCC cell lines (HepG2, HCCLM3); In vivo: HepG2 xenograft in BALB/c nude mice	In vitro: 0–40 μM, 24 h; In vivo: 100 mg/kg, i.p. daily for 14 days	miR-21/ TIMP3 axis; TGF-β1/smad3 pathway	Curcumin downregulates miR-21, upregulates TIMP3, inhibits TGF-β1/Smad3 pathway; miR-21 inhibition enhances, TIMP3 silenc- ing attenuates curcumin's effects	Suppressed tumor growth, induced apoptosis, inhib- ited proliferation	Intraperitoneal injection (in vivo); direct exposure (in vitro)	Curcumin suppresses HCC tumor growth in vivo, inhibits proliferation and induces apoptosis in vitro; downreg- ulates miR-21, upregulates TIMP3, inhibits TGF-β1/Smad3; miR-21 inhibi- tion enhances, TIMP3 silencing reverses the effect; TIMP3 is a direct miR-21 target	Model specific- ity: The study primarily used HepG2 and HCCLM3 cell lines and nude mouse xenografts, which may not fully represent clinical HCC diversity. Targeted mechanism: Focused solely on the miR-21/ TIMP3 axis and TGF-β1/ smad3 signal- ing, limiting exploration of other poten- tial molecular pathways.	[21]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Combined effect of recom- binant human ad- enovirus p53 and curcumin in the treatment of liver cancer	2020	Human liver cancer cells (HepG2, Hep3B, Huh-7)	10 µM curcumin; rAd-p53 at MOI 100, 72 h treatment	TP53, MAPKs (ERK1/2, p38 MAPK, JNK)	Curcumin and rAd-p53 synergistically increased p53 and p21 expression, regulated MAPK signaling, induced apoptosis, inhib- ited EMT, and blocked G2/M cell cycle progression	Apoptosis induction, EMT suppression, G2/M phase cell cycle arrest	Not specified	Synergistic effects between curcumin and rAd-p53 lead to enhanced therapeutic outcomes	Cell line specificity: Findings are primar- ily based on HepG2 cells, which may not fully rep- resent clinical liver cancer heterogeneity. Limited translational depth: The study lacks in vivo validation and does not address cur- cumin's low bioavailabil- ity, limiting direct clinical applicability.	[22]
Synergistic anti-liver cancer effects of curcumin and total ginsen- osides	2020	Animal (BALB/c-nu nude mice with HepG2 xenograft tumors)	Curcumin 200 mg/kg/day, oral gavage, 21 days. Ginsen- osides 104 or 520 mg/kg/ day, alone or combined with curcumin, 21 days	PD-1/PD-L1 pathway, NF-κB path- way, TLR4 pathway, MMP9- mediated angiogenesis	Combination therapy downregulated PD-L1 and TLR4/NF-κB pathway; reduced CD4+CD25+Foxp3+ Tregs via PD-L1 signaling; inhib- ited NF-κB-MMP9 pathway, reducing angiogenesis and inflammation	Reduced tumor growth, suppressed angiogenesis, decreased expression of CD4+CD25+Foxp3+ Tregs	Not explicitly mentioned, pos- sible systemic oral delivery	Combination of curcumin and high-dose ginsenosides (520 mg/kg) showed stron- gest tumor inhi- bition, greatest decrease in PD-L1, TLR4, NF- κB, iNOS, MMP9, and Tregs; effects super- ior to either agent alone; comparable to 5-FU + cisplatin positive control	Mouse model only; lacks clinical data and mechanistic depth be- yond PD-L1 and NF-κB pathways.	[23]

Table 2 (continued)

Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
A curcumin analog GL63 inhibits the malignant behaviors of hepatocellular carcinoma by inactivating the JAK2/STAT3 signaling pathway via the circular RNA zinc finger protein 83/microRNA-324-5p/cyclin-dependent kinase 16 axis	Human HCC cell lines (HUH-7, HCCLM3), normal liver epithelial (THLE-2); in vivo: BALB/c nude mice xenograft	10, 20, 40 µM GL63, 24 h (in vitro); 20 mg/kg i.p. every 3 days for 4 weeks (in vivo)	JAK2/STAT3, circZNF83/miR-324-5p/CDK16 axis	GL63 downregulates circZNF83, releases miR-324-5p, which suppresses CDK16, leading to JAK2/STAT3 inactivation; induces apoptosis (Bax↑, Bcl-2↓, cleaved caspase-3↑), G0/G1 cell cycle arrest, suppresses migration/invasion	Inhibition of proliferation, migration, invasion; induction of apoptosis; tumor growth suppression in vivo	Not specified	GL63 effectively suppressed hepatocellular carcinoma progression by modulating the circZNF83/miR-324-5p/CDK16 axis, leading to the inactivation of the JAK2/STAT3 pathway. This resulted in reduced tumor growth and malignancy in both cell lines and mouse models.	In vitro and limited animal validation Focused only on GL63 and one molecular axis No pharmacokinetics or toxicity data Limited clinical translatability	[24]
Curcumin induces mitochondrial apoptosis in human hepatoma cells through BCLAF1-mediated modulation of PI3K/AKT/GSK-30 signaling	HepG2 & SK-Hep-1 cell lines, Nude mouse xenograft model	10, 20, 40, 60 µM for 24, 48, 72 h (cells); 20, 40, 60 µM daily for 15 days (mice)	PI3K/AKT/GSK-3β pathway, BCLAF1	Curcumin downregulates BCLAF1, inhibits PI3K/AKT/GSK-3β signaling, reduces mitochondrial membrane potential, induces cell cycle arrest at G0/G1, and triggers mitochondrial apoptosis. BCLAF1 knockout enhances curcumin-induced apoptosis and cell cycle arrest.	Cell cycle arrest (G0/G1), increased apoptosis, tumor growth inhibition	Not specified	Dose-dependent inhibition of proliferation, apoptosis induction, and suppression of tumor growth both in vitro and in vivo	Single formulation (free curcumin); no pharmacokinetic analysis; limited toxicity profiling and mechanistic confirmation in vivo.	[25]

Table 2 (continued)

Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Robust radiosen- sitivity of hemo- globin- curcumin nanopar- ticles suppresses hypoxic hepato- cellular carcinoma	Human hepatocel- lular carcinoma (SMMC7721), Nude mice (xenograft)	2.5 µg/mL curcumin (within 250 µg/mL Cur@ Hb), 24–72 h treatment	HIF-1α, DNA repair (γH2AX), EMT (Twist1, MMP2, VE- Cadherin), ROS, NF-κB	Cur@Hb NPs increased ROS, inhibited EMT-related proteins, induced G2/M cell cycle arrest (with irradiation), suppressed DNA damage repair, promoted apoptosis, and inhibited migration and vascular mimicry under both normoxic and hypoxic conditions. Hemoglobin enhanced radiosensitiza- tion by increasing tumor oxygenation.	Apoptosis, migration inhibition, radiosensitiza- tion, vascular mimicry inhibition, macrophage reprogramming	Hemoglobin-cur- cumin nanopar- ticles (Cur@Hb)	Cur@Hb NPs significantly enhanced radiosensitivity of hypoxic HCC cells in vitro and in vivo, sup- pressed tumor migration and vascular mim- icry, increased apoptosis, and inhibited cell prolifera- tion. Cur@Hb NPs improved photoacoustic imaging and oxygenation, providing a promising radiosensitiza- tion platform for hypoxic, radioresistant tumors.	In vivo and in vitro only; lacks mecha- nistic depth and clinical translation data.	[26]
Curcumin- and resvera- trol-co- loaded nanopar- ticles in synergistic treatment of hepa- tocellular carcinoma	HepG2 cell line; BALB/c nude mice (xenograft)	CUR: 10 mg/kg; RSV: 50 mg/kg; 21 days (in vivo); IC ₅₀ assays for in vitro treatments	ROS signal- ing, caspase cascade, PI3K/ AKT/mTOR pathway	Co-loaded NPs increased cellular uptake, induced apoptosis, G2/M cell cycle arrest, enhanced ROS, and inhibited PI3K/AKT/mTOR pathway. SP94 targeting increased tumor accumula- tion and efficacy.	Increased apoptosis; reduced tumor volume, decreased systemic toxicity	Nanoparticle-based drug delivery system (DSPE- PEG2000-SP94)	SP94-NP showed signifi- cantly greater tumour sup- pression and accumulation; minimal toxic- ity; induced caspase-3 activation and ROS genera- tion; reduced tumor growth and increased apoptosis	No mechanis- tic pathway data; lacks broad valida- tion beyond HepG2 and mouse models.	[27]

Table 2 (continued)

Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
C0818, a novel curcumin derivative, induces ROS-de- pendent cytotox- icity in human hepato- cellular carcinoma cells in vitro via disruption of Hsp90 function	Human HCC cell lines (HepG2, Sk-Hep-1)	Various concen- trations (0–50 μM), duration: 48 h	Hsp90, RAS/ RAF/MEK/ ERK, PI3K/AKT pathways	C0818 inhibits Hsp90 func- tion, induces proteasomal degradation of Hsp90 cli- ents (RAS, C-Raf, ERK, MEK, Akt), disrupts RAS/RAF/MEK/ ERK and PI3K/AKT pathways, increases ROS, induces mitochondrial apoptosis, G2/M cell cycle arrest, and caspase activation.	Inhibition of proliferation, G2/M cell cycle arrest, induction of apoptosis	Not specified	C0818 is ~ 10x more potent than curcumin (IC50: 2.1 μM vs. 19.3 μM in HepG2 at 48 h); inhibits colony formation; induces dose- dependent apoptosis; increases ROS and mitochon- drial dysfunc- tion; inhibits DNA synthesis; causes G2/M arrest; degrades Hsp90 client proteins by proteasome; ef- fect reversed by ROS scavenger (NAC).	In vitro only; lacks in vivo or clinical validation; mechanistic insights lim- ited to Hsp90 disruption.	[13]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Develop- ment and optimiza- tion of curcumin analog nano- bilosomes using full factorial design for anti-tumor profiles improve- ment in human hepato- cellular carcinoma	2022	Huh-7 human hepa- tocellular carcinoma cell line; Wi-38 human lung fibroblast cell line (for safety assessment)	PIP (curcumin analog) 0.05 mg/ mL in nano- bilosomes; expo- sure up to 72 h	Anti-inflam- matory, antioxidant, and anticancer pathways	Nano-encapsulated PIP demonstrated superior sta- bility, enhanced solubility, and improved antiprolifera- tive effects	Higher selectivity index compared to curcumin suspension and doxorubi- cin, significant apoptosis induction	Nano-bilosomes (phospholipid- based vesicles with bile salts)	PIP-loaded bilosomes showed en- hanced thera- peutic potential with prolonged drug release, lower toxicity, and improved cellular uptake	Limited to one optimized bilosome formulation without broader comparison Lack of in vivo pharmacokinetics or tumor het- erogeneity assessment Use of only two cell lines (Huh-7 and Wi-38) No inves- tigation of underlying molecular pathways Restricted factorial de- sign with few independent variables No com- parison with other nano- carriers like liposomes or polymeric systems	[28]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Investiga- tion and experi- mental validation of curcum- in-related mechanisms against hepato- cellular carcinoma based on network pharma- cology	2022	HepG2 (human liver cancer cell line), LO2 (normal liver cells)	20, 40, 60 µmol/L for 24 h	p53 apop- totic pathway; AMPK/ULK1 autophagy pathway	Curcumin promotes apop- tosis via p53 pathway and induces autophagy through AMPK/ULK1 pathway	Apoptosis, autophagy mito- chondrial damage, reduced proliferation	Not specified	Curcumin reduced HepG2 viability dose- dependently; flow cytom- etry showed increased apoptosis; transmission electron micros- copy confirmed autophagy; Western blot and PCR vali- dated pathway involvement; inhibitors PFT-α and GSK690693 modulated pathway pro- teins confirm- ing mechanism	In vitro only: Validated in HepG2 cells without ani- mal studies Narrow path- way focus: Only p53 and AMPK/ULK1 explored Limited modeling: Used two cell lines (HepG2, LO2) No pharma- cokinetic data Docking results not ex- perimentally confirmed	[29]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Prepara- tion, Charac- terization, and In Vitro Release of Curcumin- Loaded IRMOF-10 Nanopar- ticles and Investiga- tion of Their Pro- Apoptotic Effects on Human Hepatoma HepG2 Cells	2022	HepG2 cells (Human)	CUR: 5–30 µg/ mL; Dura- tion: 24–48 h (IC50=9.213 µg/ mL at 24 h)	ROS gen- eration, mitochondrial membrane potential reduction	CUR@IRMOF-10 increased ROS, decreased MMP, en- hanced nuclear uptake	Apoptosis induction in liver cancer cells	IRMOF-10 nanoparticles	CUR loading efficiency of 63.96%; CUR@ IRMOF-10 showed sus- tained release; IRMOF-10 carrier is bio- compatible and safe; enhanced anti-liver cancer effect compared to free curcumin; confirmed by MTT, DAPI stain- ing, annexin V/ PI assay, ROS and MMP assays	In vitro only; lacks in vivo and clinical data; limited mechanistic pathway analysis.	[30]
Anti- cancer effect of nano-en- capsulated boswellic acids, curcumin, and naringenin against HepG2 cell line	2023	Human liver cancer cell line (HepG2)	Free cur- cumin: IC ₅₀ at 24 h = 5.89 µg/ mL; 48 h = 5.57 µg/ mL Nanopar- ticles: IC ₅₀ at 24 h = 3.46 µg/ mL; 48 h = 2.51 µg/ mL	apoptosis-re- lated transcrip- tion factors	Boswellic acid, curcumin, and naringenin exhibited cytotoxic effects, with sig- nificantly lower IC50 values for nanoparticles versus free compounds	Enhanced apoptosis and growth inhibition in HepG2 cells	Nanoprecipitation- based nanopar- ticles (PLGA, PVA, Tween-80)	Nanoparticles demonstrated improved bio- availability and potency com- pared to free compounds	In vitro only; no mecha- nistic insight; single cell line; lack of safety data on normal hepatocytes.	[31]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Synergistic anti-can- cer effect of sodium pentabo- rate pen- tahydrate, curcumin, and piperine on hepa- tocellular carcinoma cells	2023	Cell lines (HepG2, Hep3B); HUVEC as control	Curcumin: 5–50 µM; 24, 48, 72 h; combined with NaB and Pip	Apoptosis, p53 signaling, MAPK pathway, TNF signaling, IL-7 pathway	Combination treatment induces apoptosis (~40%), arrests cell cycle at G0-G1 phase, synergistic cyto- toxicity, gene expression changes in apoptosis and cancer pathways	Cytotoxicity, apoptosis, and cell cycle arrest (G0-G1 phase)	No specialized delivery system (in vitro treatment)	Combina- tion of NaB (1.7–2.5 mM), Cur (30 µM), and Pip (6 µM) synergistically inhibits HCC cell growth; RNA- seq shows 3143 DEGs involved in cancer-relat- ed pathways; validated upregulation of apoptotic genes GADD45A, BBC3, CD- KN1A, PMAIP1, SERPINE1	In vitro only; lacks in vivo and clinical validation; limited mechanistic depth despite RNA-seq analysis.	[32]
Curcumin- Mediated Resistance to Len- vatinib via EGFR Signaling Pathway in Hepato- cellular Carcinoma	2023	Human HCC cell lines (Huh-7, SNU449, PLC-PRF-5, SNU398, Sk-Hep-1); Lenvatinib- resistant Huh-7 and PLC cells; 3D tumor spheroids	0–10 µM for 48 h	EGFR, PI3K-AKT signaling pathway	Curcumin suppressed EGFR expression and downstream PI3K-AKT signaling; reduced stemness markers (CD44, CD133); increased ROS and apoptosis	Overcame Lenvatinib resistance, enhanced apop- tosis, reduced invasion and spheroid formation	No nanoparticle delivery mentioned	Curcumin reversed resistance to Lenvatinib via EGFR pathway inhibition; syn- ergistic antipro- liferative effects; reduced cancer stemness	In vitro focus: Findings are based on cell lines and spheroid models with- out in vivo validation. Limited generaliz- ability: Results may not fully reflect clinical responses in hetero- geneous HCC patient populations.	[33]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Curcumin Inhibits Prolif- eration of Hepato- cellular Carcinoma Cells by Blocking PTPN1 and PTPN11 Expression	2023	HuH7 cells (Human); BALB/C-nu/nu mice (Animal model)	100 mg/kg/day for 12 days (in vivo); Not speci- fied for in vitro	PTPN1 and PTPN11 (pro- tein tyrosine phosphatases)	Curcumin inhibits protein tyrosine phosphatase non- receptor type 1 (PTPN1) and type 11 (PTPN11), reducing cell proliferation	Apoptosis induction, inhibi- tion of HCC tumor growth	Not specified	Curcumin significantly reduces tumor volume and growth rate; sup- presses PCNA expression and increases BAX levels	Limited mechanistic exploration; lacks in vitro pathway assays and broader vali- dation across cell lines.	[34]
Indole curcumin combats metastatic HBV-posi- tive hepa- tocellular carcinoma by inhibit- ing cell prolif- eration, migration, and matrix metal- lopro- teinase-9 activity	2023	Hep3B (HBV-positive hepatocellular carci- noma cell line)	2–40 μ M (IC50: 14 μ M); 48 h	PI3K/Akt/ mTOR signal- ing, MMP-9 regulation	Indole curcumin exhibited antiproliferative effects, induced apoptosis, inhib- ited cell migration, and decreased MMP-9 activity. Molecular docking studies suggested that indole cur- cumin interacts with PI3K, leading to downregulation of MMP-9 expression.	Induced apoptosis, inhib- ited cell migration, and reduced MMP-9 activity, indicating potential anti- metastatic effects.	Not specified	Indole curcum- in demonst- rated significant cytotoxic and antimetastatic effects against HBV-positive HCC cells by inhibiting proliferation, migration, and MMP-9 activity.	In vitro-only design using a single HBV- positive HCC cell line No in vivo or bioavailability assessment Limited mechanis- tic scope, focused on PI3K/MMP-9 Docking results not ex- perimentally validated	[35]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
SPAG5, the upstream protein of Wnt and the target of curcum- in, inhibits hepato- cellular carcinoma	2023	Cell lines (Huh7, HCCLM3); Human tissue samples (n = 15 HCC patients)	Various concen- trations (0–200 µM) for 24 h	Wnt/β-catenin pathway, SPAG5, Cyclin D1	Curcumin downregulates SPAG5 (overexpressed in HCC), inhibits cell migration, promotes apoptosis; SPAG5 suppression decreases β-catenin and cyclin D1; curcumin reduces cyclin D1 even in SPAG5-overex- pressing cells, but effect is diminished when SPAG5 is silenced. SPAG5 is identified as an upstream regulator of the Wnt/β-catenin pathway in HCC.	Inhibits cell migration, pro- motes apoptosis, potential therapeutic target for HCC	Not explicitly mentioned	Curcumin suppresses Wnt signaling by tar- geting SPAG5	Limited mechanistic clarity on direct SPAG5– Wnt interac- tion; lacks validation in normal hepatocytes and clinical models.	[36]
Curcumin promotes ferroptosis in hepa- tocellular carcinoma via up- regulation of ACSL4	2024	HepG2, SMMC7721 (human HCC cell lines); nude mouse xenograft model	In vitro: 2.5–160 µM for 24 h; In vivo: 20 mg/kg daily for 30 days	ACSL4, GPX4, SLC7A11, PTGS2, FTH1	Curcumin upregulates ACSL4 and PTGS2; down- regulates GPX4, SLC7A11, and FTH1; increases MDA and Fe ²⁺ ; reduces GSH	Ferroptosis induction; decreased proliferation and metastasis; reduced tumor size and weight	Not specified	Curcumin induces ferroptosis via ACSL4 upregulation and oxidative stress modula- tion; inhibits tumor growth without damag- ing normal hepatocytes	No human clinical data. Only ACSL4 pathway analyzed. Long-term effects not addressed. Limited validation on normal cells.	[12]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Curcumin, Piperine and Taurine Combina- tion En- hances the Efficacy of Trans- arterial Chemo- embo- lization Therapy in Patients with Intermedi- ate-Stage Hepato- cellular Carcinoma	2024	Human (20 HCC patients)	5 g Cur- cumin + 10 mg Piperine + 0.5 g Taurine daily for 3 months	Immune mod- ulation (IFN- γ , PD-1, CTLA-4, FOXP3), T cell phenotype (CD4+, CD8+, CD4+CD25+), liver function, tumor markers	Increased serum IFN- γ ; Downregulation of PD-1, CTLA-4, FOXP3 in mononuclear leukocytes; Decreased regulatory T cells (CD4+ CD25+); Improved liver enzymes and AFP	Enhanced immune re- sponse, decreased AFP and LDH levels, improved liver function markers (AST, ALT)	Oral administration (capsules)	CPT improved immunological and biochemi- cal markers, indicating antitumor and hepatoprotec- tive effects as adjuvant to TACE	Small sample size; lacks mechanistic depth and long-term clinical follow-up.	[37]

Table 2 (continued)

	Pub- lica- tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Study on antihepa- tocellular carcinoma effect of 6-shogaol and curcumin through network- based pharmaco- logical and cellular assay	2024	Human hepatocellular carcinoma (HepG2)	30 µM cur- cumin + 5 µM 6-shogaol, 24 h	Ras-mediated PI3K/AKT and MAPK signal- ing pathways	Combination downregu- lated Cyclin-B, CDK-1, Bcl-2; upregulated BAX; synergisti- cally blocked G2/M cell cycle; promoted apoptosis; regulated Ras-mediated PI3K/AKT and MAPK pathways.	Apoptosis induction, inhibi- tion of proliferation, late apoptosis promotion	Not specified	Combination index showed synergy; combination significantly more effective than either agent alone in inhibiting prolif- eration, induc- ing apoptosis, and blocking cell cycle in G2/M; 72 core targets identi- fied by network pharmacology; validated by MTT, apoptosis, cell cycle, and immunoblot assays.	In vitro focus: All findings were based on HepG2 cell assays without in vivo valida- tion, limiting translational relevance. Pathway specific- ity: Only Ras-mediated PI3K/AKT and MAPK path- ways were explored, leaving other potential mechanisms unexamined.	[38]

Table 2 (continued)

Pub- lica- tion Year	Model System (Cell line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out- comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref- er- enc- es
Effect of Curcumin and Black Tea Extract on Breast, Liver, and Colon Cancer Cells	Human cancer cell lines: Breast (MCF-7), Liver (HepG2), Colon (HCT-116)	IC50: 0.25–2.5 µg/ml	Antioxidant properties, apoptosis induction	Curcumin and black tea ex- tract enhance cell apopto- sis, reduce oxidative stress, and inhibit proliferation	Apoptosis induction, oxida- tive stress reduction, inhibi- tion of proliferation	Not specified	Both turmeric raw mate- rial and black tea extracts exhibited good anticancer activity in SRB assay; turmeric powder hang- over effective in adsorbing Cr(III); stabil- ity of turmeric influenced by additives like green and black tea	Explor- atory design: Primarily an initial screen- ing study combining tea extracts and turmeric, with limited mechanistic depth or pathway validation. In vitro focus & broad scope: Cyto- toxicity tested on multiple cell lines, but without in vivo confirmation or detailed differentia- tion between compound- specific effects.	[39]

Table 2 (continued)

Pub-lica-tion Year	Model System (Cell Line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Outcomes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref-er-ences
The Effect of Curcumin on the Activity of MMP-17 and MMP-24 in Hepatocytes of Mice Exposed to Thioacetamide	Animal (NMRI mice; n = 30)	15 mg/kg/day oral gavage; Duration: 2–4 months depending on group	Matrix Metalloproteinases (MMP-17, MMP-24), oxidative stress, apoptosis regulation	Curcumin downregulated gene and protein expression of MMP-17 and MMP-24 elevated by thioacetamide (TAA); reduced enzymatic activity of MMPs; histopathology showed reduced liver damage with curcumin treatment	Reduced fibrosis and necrosis; alleviated TAA-induced damage, partial prevention of carcinogenesis	Not explicitly mentioned	TAA significantly increased MMP-17 and MMP-24 expression and activity, causing liver necrosis and dysplasia; curcumin treatment reduced MMP expression and activity, ameliorated pathological liver changes; timing of curcumin administration influenced effects	Mouse model only; lacks mechanistic depth and translational relevance to human HCC.	[14]

Table 2 (continued)

Pub-lica-tion Year	Model System (Cell line/Animal/Human)	Curcumin Dose & Duration	Molecular Pathways Targeted	Mechanistic Findings	Therapeutic Out-comes (e.g., apoptosis, angiogenesis)	Delivery System (e.g., nanoparticles)	Key Results	Study Limitations	Ref-er-ences
Synthe-sis and antitumor evaluation of amino acid con-jugates of mono-carbonyl curcumin in hepa-tocellular carcinoma cells	HepG2 cell line (in vitro), BALB/c nude mice (xenograft model, in vivo)	H1 derivative: 4–10 µM for 48 h; in vivo: 5 mg/kg for 27 days	AKT/FOXO1, PI3K/AKT, p53, MAPK, Rap1, cAMP pathways	H1 inhibits AKT phosphorylation, upregulates FOXO1, induces apoptosis, reduces mitochondrial membrane potential, increases cleaved caspase-3 and p27, de-creases p-AKT and p-Bcl2	Anti-proliferation (IC50: 8.66 µM), apoptosis, inhibition of migration and clone formation, tumor volume reduction in vivo	Amino acid con-jugates (H1-H6); improved solubility and bioavailability	H1 much more potent than curcumin in vitro (IC50 8.66 vs. 36.19 µM); H1 inhibits colony forma-tion, migration, invasion; in-duces apoptosis and mitochon-drial dysfunc-tion; in vivo, H1 significantly suppresses tumor growth in HepG2 xenograft mice; transcriptome and docking confirm AKT/FOXO1 target-ing; H1 shows improved water solubility and bioavailability over curcumin.	Limited clinical relevance; mechanism mainly centered on AKT/FOXO1; normal cell safety data not compre-hensive.	[40]

ACSL4: Acyl-CoA Synthetase Long Chain Family Member 4; **AFP:** Alpha-Fetoprotein; **AKT:** Protein Kinase B; **BAX:** Bcl-2 Associated X Protein; **BCL2:** Bcl-2-Associated Transcription Factor 1; **CDK:** Cyclin-Dependent Kinase; **CDKN1A (p21):** Cyclin Dependent Kinase Inhibitor 1 A; **CDKN1B (p27):** Cyclin Dependent Kinase Inhibitor 1B; **CD44, CD133:** Cancer Stem Cell Markers; **CI:** Combination Index; **Cur@Hb:** Hemoglobin-Curcumin Nanoparticles; **DSPE-PEG2000-SP94:** Nanocarrier with SP94 Peptide for Targeting; **EGFR:** Epidermal Growth Factor Receptor; **EMT:** Epithelial–Mesenchymal Transition; **FOXP3:** Forkhead Box P3; **GSH:** Glutathione; **GPX4:** Glutathione Peroxidase 4; **HCC:** Hepatocellular Carcinoma; **HIF-1α:** Hypoxia-Inducible Factor 1-alpha; **IC50:** Half-Maximal Inhibitory Concentration; **IFN-γ:** Interferon Gamma; **IRMOf-10:** Isoreticular Metal–Organic Framework-10; **JAK2:** Janus Kinase 2; **MAPK:** Mitogen-Activated Protein Kinase; **MDSCs:** Myeloid-Derived Suppressor Cells; **MMPs:** Matrix Metalloproteinases; **MOI:** Multiplicity of Infection; **mTOR:** Mammalian Target of Rapamycin; **NAC:** N-Acetylcysteine; **NF-κB:** Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; **PIP:** Pipertine; **PI3K:** Phosphatidylinositol 3-Kinase; **PTPN1/PTPN11:** Protein Tyrosine Phosphatases Non-receptor Type 1/11; **ROS:** Reactive Oxygen Species; **SLNs:** Solid Lipid Nanoparticles; **SPAG5:** Sperm-Associated Antigen 5; **STAT3:** Signal Transducer and Activator of Transcription 3; **TACE:** Transarterial Chemoembolization; **TGF-β1:** Transforming Growth Factor Beta 1; **TIMP3:** Tissue Inhibitor of Metalloproteinase 3; **Tregs:** Regulatory T Cells; **VEGF:** Vascular Endothelial Growth Factor; **Wnt/β-catenin:** Wingless/Integrated Pathway/Beta-Catenin

Anti-angiogenic activity

Curcumin disrupted tumor angiogenesis by down-regulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP-2 and MMP-9), thereby suppressing neovascularization and limiting tumor progression. These effects were often more potent when curcumin was used in combination with other natural or synthetic agents.

Modulation of immune response

Immunomodulatory effects of curcumin included suppression of immune evasion markers such as PD-1, PD-L1, and FOXP3, reduction of regulatory T cells (CD4 + CD25 + Foxp3+), and enhancement of pro-inflammatory cytokines like IFN- γ . Additionally, curcumin reduced the population of immunosuppressive myeloid-derived suppressor cells (MDSCs) and promoted CD8 + T cell activation within the tumor microenvironment.

Regulation of key molecular pathways

Curcumin modulated several critical signaling pathways implicated in hepatocarcinogenesis, including:

- **PI3K/AKT/mTOR:** Inhibition of this pathway led to reduced proliferation, increased apoptosis, and cell cycle arrest.
- **JAK2/STAT3:** Downregulation suppressed inflammatory responses and tumor growth.
- **Wnt/ β -catenin:** Curcumin inhibited this pathway by targeting upstream regulators, reducing nuclear β -catenin accumulation and cyclin D1 expression.
- **TGF- β /Smad3 and miR-21/TIMP3 axis:** Curcumin downregulated oncogenic microRNAs and restored tumor-suppressive gene expression.
- **EGFR/PI3K-AKT:** Inhibition of EGFR signaling enhanced curcumin's effectiveness against drug-resistant HCC cells.
- **Ferroptosis regulation:** Curcumin induced ferroptosis through modulation of oxidative stress-related genes and iron metabolism.

Enhancement via nanoformulations

Nanoparticle-based delivery systems greatly enhanced the therapeutic efficacy of curcumin by improving its bioavailability, solubility, and tumor-specific accumulation. Various nanoformulations—such as liposomes, micelles, bilosomes, SP94-targeted carriers, and hemoglobin-conjugated nanoparticles—demonstrated superior cellular uptake, ROS generation, and apoptosis induction compared to free curcumin. These formulations also reduced systemic toxicity and enabled combination therapies with other anticancer agents.

Notably, several formulations (e.g., SP94-targeted carriers, co-loaded nanoparticles, Cur@Hb) demonstrated

enhanced tumor accumulation with minimal short-term systemic toxicity, although long-term safety was not assessed.

Summary of therapeutic outcomes

Overall, curcumin treatment in HCC models resulted in:

- Significant inhibition of hepatocellular carcinoma cell proliferation.
- Induction of apoptosis through both intrinsic and extrinsic pathways.
- Suppression of angiogenesis and metastasis.
- Immunomodulatory effects via regulation of tumor microenvironment.
- Enhanced therapeutic efficacy through nanotechnology-based drug delivery.

A summary of the methodological quality of the included studies is provided in Table 1. A detailed summary of included studies is provided in Table 2.

Discussion

Curcumin demonstrates multifaceted antitumor effects in hepatocellular carcinoma (HCC) by targeting diverse molecular pathways including PI3K/AKT, MAPK, JAK/STAT, Wnt/ β -catenin, and ferroptosis regulators such as ACSL4 [12, 18, 24, 39]. Mechanistic studies reveal its ability to induce apoptosis through upregulation of Bax and cleaved caspase-3 and suppression of Bcl-2 [21, 22]. Epigenetic reprogramming, such as DNMT1 inhibition and ER α reactivation, further enhances its anticancer efficacy [19].

Notably, synthetic analogs like GL63 and H1 have been designed to enhance curcumin's potency and pathway selectivity, acting via the JAK2/STAT3 and AKT/FOXO1 axes, respectively [24, 39]. These analogs offer improved water solubility, stability, and bioavailability compared to native curcumin.

Although curcumin consistently demonstrated inhibitory effects on major oncogenic pathways such as PI3K/AKT/mTOR and JAK2/STAT3 across most studies, certain inconsistencies were observed. For instance, some in vitro studies relying solely on network pharmacology or limited replicates reported weaker or less reproducible effects, suggesting that methodological rigor influences observed outcomes. In the case of Wnt/ β -catenin signaling, curcumin-mediated suppression was found to be contingent on SPAG5 expression in some models, indicating that pathway inhibition may be context-dependent rather than universal. Moreover, variations in formulation (e.g., free curcumin versus nanoformulations) and dosing regimens also contributed to divergent results, with nanoformulated systems generally producing more robust and reproducible outcomes. These inconsistencies

highlight the need for standardized experimental protocols and further validation in clinical settings to reconcile preclinical variability.

Combination strategies represent a promising avenue for enhancing therapeutic outcomes. Co-administration with sorafenib [20], rAd-p53 [22], or phytochemicals like ginsenosides, piperine, and resveratrol [23, 27, 33] yielded synergistic effects, including enhanced apoptosis, reduced tumor volume, and attenuation of metastatic potential.

At the mechanistic level, the synergistic effects of curcumin with sorafenib appear to arise from their overlapping yet complementary actions on survival and angiogenic pathways. Sorafenib primarily inhibits the

RAF/MEK/ERK cascade and VEGF receptor-mediated angiogenesis, but resistance often develops through activation of compensatory PI3K/AKT/mTOR or JAK2/STAT3 pathways. Curcumin directly suppresses these alternative signaling cascades, thereby reducing tumor cell survival mechanisms that would otherwise bypass sorafenib inhibition. Furthermore, both agents converge on shared targets, including EGFR and VEGF, leading to reinforced anti-angiogenic activity and more profound apoptosis induction. This molecular crosstalk explains the enhanced tumor regression observed in xenograft models when curcumin is co-administered with sorafenib.

Nanotechnology plays a pivotal role in overcoming curcumin's biopharmaceutical limitations. Various delivery systems—such as bilosomes [28], hemoglobin-based nanoparticles [26], SP94-targeted PEGylated nanoparticles [27], and metal-organic frameworks like Cur@IRMOF-10 [30]—have substantially improved aqueous solubility, tumor targeting, and intracellular retention. These platforms have demonstrated superior efficacy over free curcumin in preclinical models.

To enhance clarity regarding the chemical basis and functionality of curcumin analogues, we have provided Table 3 below. This table summarizes the key structural modifications, molecular targets, and therapeutic benefits reported in each study involving curcumin derivatives.

Beyond improving aqueous solubility and bioavailability, several curcumin analogs demonstrate unique chemical modifications that confer additional mechanistic advantages over native curcumin. For example, GL63, a pyrazole-substituted monocarbonyl analog, inactivates the JAK2/STAT3 pathway via the circZNF83/miR-324-5p/CDK16 axis, thereby promoting apoptosis and G0/G1 arrest with superior potency compared to curcumin [24]. H1, an amino acid–conjugated monocarbonyl derivative, selectively inhibits the AKT/FOXO1 signaling axis while upregulating p53-dependent pathways, resulting in more pronounced tumor suppression in xenograft models [40]. C0818, structurally modified to block Hsp90 client protein binding, disrupts both RAS/RAF/MEK/ERK and PI3K/AKT cascades, yielding ~10-fold higher cytotoxic potency than curcumin in vitro [13]. Indole curcumin, incorporating an indole moiety into the curcumin scaffold, exhibits enhanced anti-metastatic activity in HBV-positive HCC by inhibiting PI3K/AKT/mTOR and MMP-9 signaling [35]. Likewise, PIP, encapsulated into bilosomes, provides improved stability, selectivity, and apoptotic activity against HCC cells compared with free curcumin.

These findings demonstrate that chemical modification of curcumin not only enhances its pharmacokinetics but also improves target specificity, potency, stability,

Table 3 Structural and mechanistic features of Curcumin analogues included in the review

Ana- logue Name	Structural Modification	Molecular Target/ Pathway	Reported Benefits	Ref- er- ences
GL63	Substitution of diketone moiety with pyrazole ring (monocarbonyl analog)	circZNF83/miR-324-5p/CDK16 → JAK2/STAT3	Enhanced apoptosis, G0/G1 arrest, reduced migration/invasion; higher potency than curcumin	[24]
H1 (Amino acid–conjugated mono-carbonyl curcumin)	Monocar-bonyl back-bone + amino acid conjugation	AKT/FOXO1, p53, MAPK, cAMP	Improved water solubility; potent inhibition of tumor growth in xenograft models; enhanced apoptosis	[40]
C0818	Designed to block Hsp90 binding pocket	Hsp90 → RAS/RAF/MEK/ERK & PI3K/AKT	~10x potency vs. curcumin; ROS-dependent apoptosis; G2/M arrest	[13]
PIP	Curcumin analog encapsulated in phospholipid bilosomes with bile salts	Broad anti-inflam-matory & apop-totic pathways	Superior stability and selectivity; enhanced cy-totoxicity vs. curcumin and doxorubicin	[28]
Indole Curcumin	Addition of indole moiety to curcumin scaffold	PI3K/Akt/mTOR, MMP-9	Antimeta-static activity in HBV-pos-itive HCC; inhibition of proliferation, migration, invasion	[35]

and pathway selectivity. Collectively, curcumin analogs represent rationally engineered derivatives designed to overcome the intrinsic limitations of native curcumin, highlighting structural optimization as a promising direction for the next generation of HCC therapeutics.

Curcumin suffers from rapid systemic elimination, with an *in vivo* half-life ranging from approximately 0.5 to 2 h in animal models, depending on the route of administration and formulation used [41, 42]. This short half-life, alongside its low oral bioavailability, necessitates the use of nanoformulations or adjuvants (e.g., piperine) to enhance its pharmacokinetic profile.

However, the clinical translation of these findings remains limited. Among the 26 included studies, only one human trial was identified [37], evaluating curcumin in combination with piperine and taurine as an adjuvant to transarterial chemoembolization (TACE). This stark discrepancy between preclinical promise and clinical validation underscores a critical translational gap.

Barriers to clinical translation and potential strategies

Safety considerations of nanoformulated curcumin warrant explicit attention for clinical translation. First, bio-distribution and reticuloendothelial system uptake may concentrate nanoparticles in liver and spleen, raising potential risks of organ-specific toxicity or unintended immune activation. Excipients and carriers (e.g., lipids, polymers, metal–organic frameworks, hemoglobin conjugates) may add off-target risks independent of curcumin itself. Several HCC models reported increased intratumoral delivery with reduced systemic toxicity—such as SP94-targeted co-loaded nanoparticles [27], hemoglobin–curcumin platforms (Cur@Hb) [26], and bilosome or IRMOF-based carriers [28–30]—yet these findings were largely short-term and limited to xenograft settings. Accordingly, formal GLP toxicology (including biodistribution tracking, hepatic/renal histopathology, and immune compatibility assays) should precede early-phase trials. Phase I studies should integrate intensive PK/PD monitoring, dose-limiting toxicity definitions, and longitudinal follow-up to de-risk long-term accumulation and support clinical translation.

Despite curcumin's promising preclinical efficacy, several barriers hinder its integration into clinical practice for hepatocellular carcinoma (HCC)

1. Toxicity and Safety Profiles.

Although curcumin is generally regarded as safe, high-dose oral administration (>4–8 g/day) has been associated with gastrointestinal discomfort, diarrhea, and, in rare cases, hepatotoxicity in clinical settings [42, 43]. Furthermore, the long-term safety of nanoformulated

curcumin has not been adequately characterized, raising concerns about its systemic distribution and metabolic fate [44].

Strategy: Early-phase clinical trials with escalating doses are needed to define maximum tolerated doses, dose–response curves, and long-term toxicities of both free and nanoformulated curcumin. Toxicogenomic profiling could also identify patient subgroups more vulnerable to adverse effects.

2. Patient Selection Criteria.

HCC is a highly heterogeneous disease, influenced by viral hepatitis (HBV, HCV), alcohol-related cirrhosis, and metabolic dysfunction (NAFLD/NASH). Such heterogeneity may affect curcumin's immunomodulatory or anti-proliferative efficacy [34, 45, 46]. For example, patients with high baseline inflammation or specific biomarker expression (e.g., PD-L1, ACSL4) may derive greater benefit than others.

Strategy: Future trials should stratify patients by etiology, Child–Pugh score, and biomarker expression to identify subgroups most likely to benefit from curcumin therapy.

3. Compatibility with Standard Therapies (Sorafenib, Lenvatinib, TACE, Immunotherapy).

Curcumin modulates multiple signaling pathways, some of which overlap with those targeted by approved agents. Preclinical data suggest synergy with sorafenib by jointly inhibiting PI3K/AKT and VEGF-mediated angiogenesis [47, 48], and as an adjuvant to transarterial chemoembolization (TACE) by enhancing immune modulation [49]. However, its antioxidant properties could theoretically interfere with ROS-dependent chemotherapies or radiotherapy [50].

Strategy: Preclinical drug–drug interaction studies, followed by carefully designed phase I/II combination trials, are necessary. Optimized nanoformulations with tumor-specific targeting may further reduce systemic interactions.

4. Pharmaceutical and Regulatory Barriers.

The absence of standardized Good Manufacturing Practice (GMP) protocols for curcumin formulations has resulted in significant batch-to-batch variability in purity, solubility, and bioavailability. Regulatory agencies such as the FDA and EMA highlight the need for consistent quality, validated pharmacokinetic data, and reproducibility before botanical or nanoparticle-based products can enter clinical use [51].

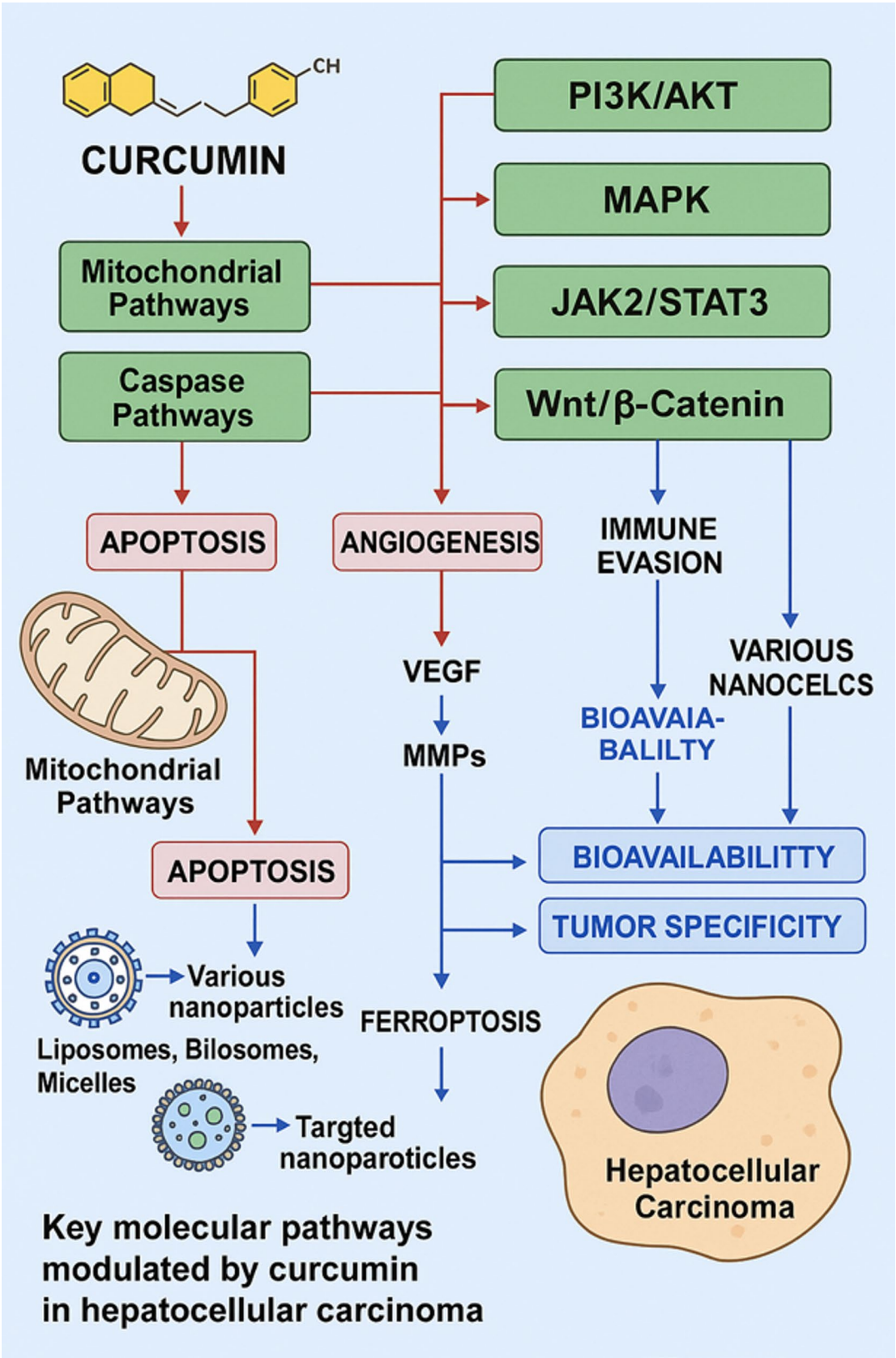


Fig. 2 (See legend on next page.)

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Fig. 2 Key molecular pathways modulated by curcumin in hepatocellular carcinoma. This schematic diagram illustrates the major molecular pathways and biological processes influenced by curcumin in hepatocellular carcinoma (HCC). Curcumin modulates intracellular signaling cascades—including PI3K/AKT, MAPK, JAK2/STAT3, and Wnt/ β -catenin—leading to apoptosis, inhibition of angiogenesis, suppression of immune evasion, and ferroptosis induction. It also acts through mitochondrial and caspase pathways to promote cell death. Nanoparticle-based delivery systems such as liposomes, bilosomes, and targeted nanoparticles enhance curcumin's bioavailability and tumor specificity, improving its anticancer efficacy

Strategy: Development of GMP-compliant, standardized nanoformulations with validated pharmacokinetic benchmarks and harmonized international guidelines is essential to facilitate regulatory approval.

In summary, overcoming toxicity concerns through early-phase trials, refining patient selection using biomarker-guided approaches, and ensuring compatibility with standard therapies are critical for clinical translation of curcumin in HCC. Regulatory standardization and GMP-compliant manufacturing will further enhance its feasibility for integration into therapeutic practice.

To address these limitations, future research should prioritize:

1. **Standardization and GMP-compliant production** of nanoformulations with validated stability and reproducibility.
2. **Phase I/II clinical trials** to evaluate pharmacokinetics, safety, and optimal dosing.
3. **Network pharmacology and transcriptomic profiling** to identify predictive biomarkers for patient stratification and therapeutic response.
4. **Comparative studies** with other bioactive natural agents Like bowelle acid, 6-shogaol [38], or naringenin [31] to assess synergistic potential and pathway complementarity.

In summary, while curcumin offers a versatile and mechanistically rich anti-HCC profile, its transition from bench to bedside demands a strategic focus on overcoming regulatory, pharmaceutical, and clinical hurdles through interdisciplinary and translational research.

Figure 2 provides an integrative visualization of the diverse molecular pathways modulated by curcumin in hepatocellular carcinoma. It highlights the compound's multifaceted mechanisms of action, including induction of apoptosis, suppression of cell proliferation and angiogenesis, inhibition of epithelial-mesenchymal transition (EMT), and promotion of ferroptosis. These effects are mediated through critical signaling axes such as PI3K/AKT/mTOR, JAK/STAT3, TGF- β /Smad3, and Wnt/ β -catenin.

The figure also illustrates curcumin's ability to reverse drug resistance (e.g., Lenvatinib resistance via EGFR inhibition) and enhance radiosensitivity in hypoxic tumors through ROS generation and suppression of DNA repair mechanisms. Moreover, curcumin's synergy with other therapeutic agents—such as sorafenib, piperine, and

6-shogaol—is represented, emphasizing its potential in combination regimens.

Collectively, Fig. 2 underscores curcumin's pleiotropic anti-cancer effects and supports the rationale for its further development as part of multi-targeted therapeutic strategies in HCC.

Mechanistic insights into the multifaceted biological effects of Curcumin in HCC

Curcumin exerts its antitumor activity in hepatocellular carcinoma (HCC) through multifaceted molecular mechanisms that target several hallmarks of cancer. It induces apoptosis predominantly via the intrinsic mitochondrial pathway by upregulating Bax and cleaved caspase-3, downregulating Bcl-2, and triggering mitochondrial membrane depolarization and cytochrome c release, leading to caspase cascade activation [12, 24, 25]. In some models, curcumin also activated extrinsic apoptotic signaling by engaging death receptors [22].

Curcumin consistently induces cell cycle arrest in HCC cells at G0/G1 or G2/M phases through suppression of cyclins (e.g., Cyclin D1, Cyclin B1) and cyclin-dependent kinases (CDK1, CDK4, CDK16), while upregulating cell cycle inhibitors such as p21 and p27 [24, 39]. For instance, the curcumin analog H1 blocked the AKT/FOXO1 axis, resulting in increased p27 and apoptosis [40].

Proliferation inhibition is achieved through modulation of oncogenic pathways including PI3K/AKT/mTOR [27], MAPK/ERK [13, 22], and Wnt/ β -catenin [36], resulting in reduced tumor growth and clonogenic potential. Some derivatives, like GL63 and C0818, displayed enhanced potency and pathway specificity by targeting the JAK2/STAT3 and Hsp90-RAS/RAF/MEK/ERK pathways, respectively [13, 24].

Curcumin also suppresses angiogenesis by downregulating VEGF, VEGFR-2, and matrix metalloproteinases (MMP-2 and MMP-9), thereby disrupting neovascularization and tumor progression [23, 26, 35]. Under hypoxic conditions, hemoglobin-curcumin nanoparticles (Cur@Hb) further inhibited vascular mimicry and enhanced radiosensitivity by increasing reactive oxygen species (ROS) and impairing DNA repair [26].

Immunomodulatory effects of curcumin include downregulation of PD-1, PD-L1, and FOXP3, reduction of regulatory T cells (CD4+ CD25+ FOXP3+), and elevation of antitumor cytokines such as IFN- γ and IL-2 [23, 37] [., 37]. Additionally, curcumin inhibited myeloid-derived

suppressor cells (MDSCs) in murine HCC models, restoring effective antitumor immune responses.

These mechanistic insights support the therapeutic promise of curcumin and its analogs, particularly when enhanced through nanoformulation strategies or combination regimens. A schematic summary of these interconnected molecular effects is provided in Fig. 2.

Limitations

This review has several limitations that must be acknowledged. First, the potential for publication bias should be considered, as studies reporting positive or significant results are more likely to be published, while negative or inconclusive findings may remain unpublished. This bias may lead to an overestimation of curcumin's therapeutic efficacy in hepatocellular carcinoma.

Second, although this review included studies investigating curcumin analogs and derivatives, it is important to note that these compounds may differ from native curcumin in terms of chemical structure, pharmacokinetics, and biological activity. Therefore, the effects observed in analog-based studies may not be directly attributable to curcumin itself, and caution is warranted when extrapolating such findings.

Finally, the heterogeneity among study designs, experimental models, curcumin formulations, and dosing regimens limited the feasibility of performing a quantitative meta-analysis and may influence the generalizability of the conclusions.

Novel insights of this review compared to prior literature

Compared to earlier reviews, which largely emphasized curcumin's antioxidant and apoptotic activities, the present work offers several unique contributions. By restricting our analysis to recent studies (2020–2025), we identified novel mechanistic insights, including ferroptosis induction through ACSL4 upregulation, SPAG5-mediated regulation of Wnt/ β -catenin signaling, and reversal of tyrosine kinase inhibitor resistance via EGFR inhibition. Furthermore, this review provides the first integrated discussion of advanced nanoformulation approaches—such as bilosomes, hemoglobin-based nanoparticles, IRMOF-10 carriers, and amino acid-conjugated analogues—that markedly enhance curcumin's bioavailability and therapeutic specificity. Finally, by systematically appraising methodological quality across included studies, this review adds a layer of critical evaluation that has been absent from most prior summaries. Together, these features highlight the manuscript's novelty and its added value to the existing body of literature.

Future research roadmap

To bridge the translational gap between promising pre-clinical findings and limited clinical data, we recommend

a structured research agenda for curcumin in hepatocellular carcinoma (HCC). Four priority areas are outlined:

Formulation and dosing optimization. Phase I adaptive dose-escalation trials (Bayesian CRM/BOIN) should be undertaken for nanoformulations (liposomes, micelles, bilosomes, hemoglobin- or SP94-targeted carriers), with comprehensive PK/PD evaluation including plasma exposure, food effects, and piperine co-administration.

Biologically rational combination trials. Randomized phase Ib/II “signal-seeking” studies should test curcumin as an adjuvant to TACE in BCLC-B patients, or in combination with TKIs/IO in BCLC-C disease. Primary endpoints could include mRECIST-ORR or time-to-progression, while secondary outcomes should assess PFS, OS, hepatic safety, and quality of life.

Precision medicine approaches. Enrichment by biomarker profiles is strongly encouraged. Patients with high ACSL4 expression may be selected for ferroptosis-focused trials; those with EGFR-high or lenvatinib-resistant tumors for EGFR/PI3K–AKT targeted approaches; and those with SPAG5-driven Wnt/ β -catenin activation for growth pathway studies. In immunotherapy arms, assessment of PD-L1 expression, CD8 + T cell infiltration, Treg frequency, and IFN- γ may guide stratification and monitoring.

Window-of-opportunity and translational endpoints. Short-term preoperative/ablation trials with paired biopsies (pre- and post-treatment) can confirm target engagement (ACSL4, GPX4, p-AKT, nuclear β -catenin) and correlate these with circulating biomarkers (ctDNA, cytokine signatures, ROS indices).

All clinical studies should adhere to CONSORT/SPIRIT guidelines, use mRECIST criteria for imaging endpoints, and include safety monitoring with emphasis on hepatic and gastrointestinal tolerability.

Illustrative trial concepts—summarizing potential populations, designs, biomarker strategies, and endpoints—are outlined in Supplementary Table S2 to guide the rational design of future clinical investigations.

Unique contributions compared to prior reviews

Unlike earlier reviews, which primarily summarized curcumin's antioxidant and apoptotic mechanisms, our review provides a comprehensive and updated synthesis of evidence published between 2020 and 2025. This allows us to highlight newly discovered molecular targets (e.g., ACSL4-mediated ferroptosis, SPAG5/Wnt- β -catenin, EGFR/lenvatinib resistance), as well as advanced nanoformulation strategies that markedly improve pharmacokinetics and tumor specificity. In addition, we performed a critical methodological appraisal across included studies, a feature absent from most prior reviews. Finally, we propose specific translational roadmaps—including trial designs, patient selection

strategies, and biomarker-guided enrichment—that distinguish this work from the existing literature.

Conclusion

Curcumin exhibits a broad spectrum of anticancer effects in hepatocellular carcinoma (HCC), targeting multiple molecular pathways related to proliferation, apoptosis, angiogenesis, immune evasion, and chemoresistance. Nanoformulated curcumin has demonstrated improved pharmacokinetic profiles and tumor-specific delivery in preclinical models. However, the current clinical evidence is limited to a single study, and thus curcumin should be regarded as a promising preclinical agent rather than a clinically established therapeutic.

To facilitate clinical translation, future research should prioritize the following areas:

- Rigorous phase I/II clinical trials with defined safety and efficacy endpoints;
- Identification of reliable biomarkers to enable patient stratification and response prediction;
- Standardization and regulatory alignment of nanoformulation protocols;
- Evaluation of curcumin in combination with standard HCC therapies.

These strategies are essential to assess curcumin's true therapeutic potential and to enable its integration into evidence-based cancer care.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12935-025-03988-4>.

Supplementary Material 1

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Author contributions

All authors contributed to the conceptualization of this study. ME developed the study protocol. MD and AG compiled and organized the data. The initial draft of the manuscript was authored by ME and was thoroughly reviewed and revised by all the authors.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Ethical considerations

The authors have carefully addressed ethical considerations, including monitoring for text plagiarism, duplicate publications, research misconduct, data fabrication, and falsification.

Competing interests

The authors declare no competing interests.

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