Journal of Nutrition Explorations
Vol. 4, No. 3, August 2026, pp. 300~320
e-ISSN: 2987-761X
DOI: 10.36568/jone.v4i3.758

Curcumin as a Cancer Nutraceutical Candidate: Systematic Review of Preclinical Antiproliferative, Anti-Metastatic, and Formulation Evidence

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ARTICLE INFO

Article History:
Received June 6, 2026
Accepted July 10, 2026
Published online July 11, 2026

Keywords:
Cancer;
Curcumin;
Metastasis;
Nanoformulation;
Nutraceutical

ABSTRACT

Curcumin, a polyphenolic constituent of turmeric (*Curcuma longa*), has been investigated as a food-derived nutraceutical with potential anticancer properties, although clinical translation remains limited by poor aqueous solubility, chemical instability, rapid metabolism, and low systemic exposure. This systematic review, conducted in accordance with the PRISMA 2020 statement, evaluated whether native or formulated curcumin, compared with untreated or vehicle controls, exerts antiproliferative and anti-metastatic effects in cancer cell lines, 3D models, or tumor-bearing animal models. Studies on synthetic curcumin analogs, undefined turmeric extracts, and multi-phytochemical combinations were excluded. The protocol was submitted for PROSPERO registration. A systematic search of PubMed/MEDLINE, Scopus, ScienceDirect, and SpringerLink from January 2016 to 20 June 2026 identified 15 eligible studies: nine investigating native curcumin and six investigating formulated curcumin. Across breast, ovarian, colorectal, thyroid, pancreatic, hepatocellular, and meningioma models, curcumin generally reduced cancer-cell viability, proliferation, migration, invasion, epithelial–mesenchymal transition, and tumor growth, mainly through pathways governing cell survival, signal transduction, and metastatic behavior. Ten studies (67%) were exclusively in vitro, while five (33%) included in vivo or xenograft components. Formulated curcumin studies showed that anticancer performance depended on carrier type: an ionic-liquid system increased aqueous solubility by approximately 8,750-fold and reduced MDA-MB-231 viability by about 60% at 10 µg/mL without comparable toxicity in normal fibroblasts, curcumin nanocapsules showed a lower IC_{50} than microcapsules in breast cancer cells, and curcumin spanlastics produced stronger anticancer activity than nanocrystals, which instead showed the most rapid dissolution. Overall, curcumin demonstrated promising preclinical bioactivity, but the evidence remained limited by substantial heterogeneity in models, formulations, doses, exposure durations, and outcome measures, which precluded meta-analysis. These findings support curcumin as a biologically active nutraceutical candidate requiring further pharmacokinetic, safety, and in vivo validation before translational application in cancer care.

INTRODUCTION

Cancer progression is characterized by uncontrolled cellular proliferation and the acquisition of invasive and metastatic phenotypes. Metastatic progression involves several interrelated biological

processes, including epithelial–mesenchymal transition (EMT), extracellular-matrix remodeling, migration, invasion, angiogenesis, and survival of tumor cells in secondary tissue environments. These processes are influenced by multiple interacting molecular pathways, indicating that cancer progression cannot be explained by a single signaling mechanism. This has encouraged growing interest in multi-target bioactive compounds, particularly those capable of affecting both tumor-cell proliferation and metastasis-related processes.[1–3]

Curcumin is the main bioactive polyphenol found in turmeric (*Curcuma longa*), which is commonly used as a culinary spice and traditional medicinal ingredient. However, in preclinical cancer research, curcumin is usually studied as a purified nutraceutical compound or as a formulated pharmacological agent. Therefore, the anticancer effects observed in experimental studies should not be directly equated with the effects of regular dietary intake of turmeric.[4,5]

From a nutritional standpoint, curcumin intake through ordinary diet differs substantially from the concentrations tested in preclinical cancer models and even in clinical trials. In phase I chemoprevention trials in colorectal cancer patients, curcumin doses as high as 8,000 mg per day have been administered without identifying a maximum tolerated dose[6], a level far above what any dietary source of turmeric could provide. This gap is compounded by curcumin's inherently poor absorption: native curcumin's oral bioavailability in serum is typically below 1%, and even advanced co-grinding formulations have achieved only up to a 178-fold increase in plasma exposure relative to standard crystalline curcumin in healthy volunteers.[7] These values illustrate why the antiproliferative and anti-metastatic concentrations reported in preclinical studies cannot be assumed to be achievable through ordinary turmeric consumption or unformulated oral curcumin supplementation.

Curcumin remains highly relevant in cancer nutraceutical research because it continues to be widely investigated in preclinical oncology, particularly through formulation-based approaches designed to improve its delivery and biological activity. Preclinical studies suggest that curcumin may influence several key processes in cancer development, including tumor-cell growth, apoptosis, inflammation, angiogenesis, migration, invasion, and metastasis. These effects are generally associated with signaling pathways involved in cell survival, inflammatory regulation, EMT, and extracellular-matrix degradation, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), transforming growth factor beta/Smad (TGF-β/Smad), and matrix metalloproteinase (MMP)-related pathways. However, because these signaling mechanisms are complex and interconnected, curcumin's effects may vary across cancer types, formulations, doses, exposure times, and experimental models.[8–11]

Despite its promising biological activity, the clinical translation of curcumin remains limited by poor aqueous solubility, instability under physiological conditions, limited gastrointestinal absorption,

rapid metabolism, and low systemic exposure.[5,12] These limitations create uncertainty regarding whether the concentrations associated with anticancer activity in vitro can be achieved through dietary turmeric consumption or conventional curcumin supplementation.

To address these limitations, various curcumin formulation strategies have been developed, including nanoparticles, liposomes, micelles, vesicular systems, polymeric carriers, nanocrystals, and other solubilization platforms. These systems are designed to improve curcumin solubility, stability, controlled release, cellular delivery, and biological activity.[13] However, improved physicochemical properties or cellular uptake should not automatically be interpreted as evidence of improved systemic bioavailability or clinical effectiveness unless supported by pharmacokinetic, tissue-distribution, or in vivo efficacy data.

Previous narrative reviews have summarized curcumin's broader pharmacological profile and delivery technologies. Naksuriya *et al.*[13] reviewed nano-sized curcumin delivery systems including liposomes, polymeric nanoparticles, micelles, conjugates, and lipid nanoparticles alongside efficacy data from cell-line, in vivo, and clinical studies across multiple disease contexts. Tomeh *et al*.[8] summarized the medicinal chemistry, pharmacology, and mechanisms of curcumin and its derivatives as anticancer agents, drawing on experimental, animal, and human data, and briefly noted advances in drug-delivery systems. However, both reviews were narrative rather than systematic in design, without a predefined protocol, systematic search strategy, or risk of bias appraisal, and neither presented an integrated framework linking formulation-related physicochemical improvements to specific antiproliferative and anti-metastatic signaling outcomes in cancer models. Furthermore, neither review consistently distinguished turmeric as a dietary source, curcumin as an isolated nutraceutical compound, and formulated curcumin as a pharmacologically engineered agent a – distinction that is central to interpreting translational relevance.

The primary objective of this review was to synthesize preclinical evidence on the antiproliferative and anti-metastatic effects of native and formulated curcumin in cancer models. Secondary objectives were to characterize the molecular pathways underlying these effects and to evaluate the physicochemical and formulation-related properties reported to influence curcumin's biological activity.

MATERIALS AND METHODS

Study Design

A systematic review was conducted and reported in accordance with the PRISMA 2020 statement[14] to evaluate the antiproliferative, anti-metastatic, and formulation-related effects of native and formulated curcumin in preclinical cancer models. The protocol has been submitted for registration in PROSPERO.

Eligibility Criteria

Studies were included if they were original full-text articles evaluating native or formulated curcumin in cancer cell lines, 3D models, tumor-bearing animal models, or clinically derived cancer materials, and reported at least one relevant biological or physicochemical outcome. Studies were excluded if they involved synthetic curcumin analogs, undefined turmeric extracts, non-cancer outcomes, or multi-phytochemical combinations in which curcumin's contribution could not be distinguished. For the purposes of this review, anti-metastatic evidence was defined broadly as outcomes related to cancer-cell migration, invasion, epithelial–mesenchymal transition, matrix metalloproteinase expression, and distant-organ metastasis. Because distant-organ metastasis was evaluated in only a limited number of studies, most evidence represented metastasis-related phenotypes rather than direct demonstration of metastatic suppression. The search was restricted to English-language original research articles; conference proceedings, dissertations, preprints, clinical trial registries, and review articles were not eligible for inclusion.

Search Strategy

A systematic literature search was conducted in PubMed/MEDLINE, Scopus, ScienceDirect, and SpringerLink for articles published from January 2016 to 20 June 2026. The literature search and its reporting were guided by the PRISMA-S extension.[15] The search strategy combined terms related to curcumin, cancer, antiproliferative activity, metastatic phenotypes, and formulation characteristics using the Boolean operators “AND” and “OR.”

The core search strategy was: (“curcumin” OR “nanocurcumin” OR “nano-curcumin” OR “curcumin nanoparticle*” OR “curcumin formulation*” OR “curcumin micelle*” OR “curcumin niosome*” OR “curcumin nanocrystal*” OR “curcumin capsule*” OR “curcumin-loaded”) AND (cancer OR carcinoma OR tumor OR neoplasm* OR malignan*) AND (proliferat* OR viability OR cytotoxicity OR apoptosis OR “cell cycle” OR “colony formation” OR migration OR invasion OR metastas* OR EMT OR “epithelial-mesenchymal transition” OR “matrix metalloproteinase*” OR MMP-2 OR MMP-9 OR solubility OR dissolution OR stability OR encapsulation OR “drug loading” OR “drug release” OR “cellular uptake” OR “drug delivery”).

The search syntax was adapted to the requirements of each database; complete database-specific search strategies are provided in Supplementary Table S1. Reference lists of eligible studies and relevant reviews were also screened to identify additional publications.

Study Selection and Data Extraction

All identified records were imported into Parsifal, and duplicate records were removed. Study selection was conducted in two stages: title and abstract screening followed by full-text eligibility

assessment. Screening was performed by one investigator and independently verified by a second investigator. A formal pilot test of the data-extraction form and a quantitative inter-reviewer agreement statistic (e.g., Cohen's kappa) were not conducted; disagreements were instead resolved through discussion, with consultation of a third reviewer when consensus could not be reached. This is acknowledged as a methodological limitation.

A standardized data-extraction form was used to collect information on author and year, cancer type, experimental model, curcumin form, formulation or carrier material, dose, exposure duration, comparator, assay method, antiproliferative outcomes, anti-metastatic outcomes, molecular pathways, physicochemical characteristics, safety findings, and major study limitations. The study-selection process was documented using a PRISMA 2020 flow diagram.[14]

Data Synthesis and Quality Assessment

Meta-analysis was not performed due to substantial heterogeneity across studies. Findings were narratively synthesized and categorized into: antiproliferative effects, anti-metastatic effects, molecular pathways, physicochemical outcomes, comparative formulation performance, and safety or in vivo evidence.

Risk of bias and reporting reliability were evaluated using a modified preclinical assessment framework informed by SYRCLE's risk-of-bias guidelines[16] for animal studies and ToxRTool-style reliability principles[17] for in vitro mechanistic studies. These frameworks were used to guide the selection of appraisal domains, but were not applied as standalone numerical scoring instruments. Seven domains were assessed: clarity of controls, dose-response reporting, replication, blinding or bias control, outcome measurement, reporting completeness, and mechanistic support. The overall judgment for each study was determined narratively based on the number and severity of concerns across domains.

Formal certainty-of-evidence grading (e.g., GRADE) was not performed, as this framework is primarily designed for clinical intervention studies with comparable outcome measures and is not well suited to heterogeneous preclinical models with divergent cell lines, assays, and endpoints. Instead, methodological confidence was appraised narratively through the seven-domain risk-of-bias framework described above.

RESULTS

Study selection

A total of 1,337 records were identified through searches of four databases, comprising 4 records from PubMed, 923 from ScienceDirect, 284 from Scopus, and 126 from SpringerLink. After the removal of 40 duplicate records, 1,297 records were screened based on their titles and abstracts.

Of these, 1,205 records were excluded, and 92 reports were sought for full-text retrieval. Thirteen reports could not be retrieved; therefore, 79 full-text articles were assessed for eligibility. Following the exclusion of 64 articles that did not meet the predefined eligibility criteria, 15 studies were included in the final narrative synthesis. The study-selection process is presented in the PRISMA 2020 flow diagram in **Figure 1.**

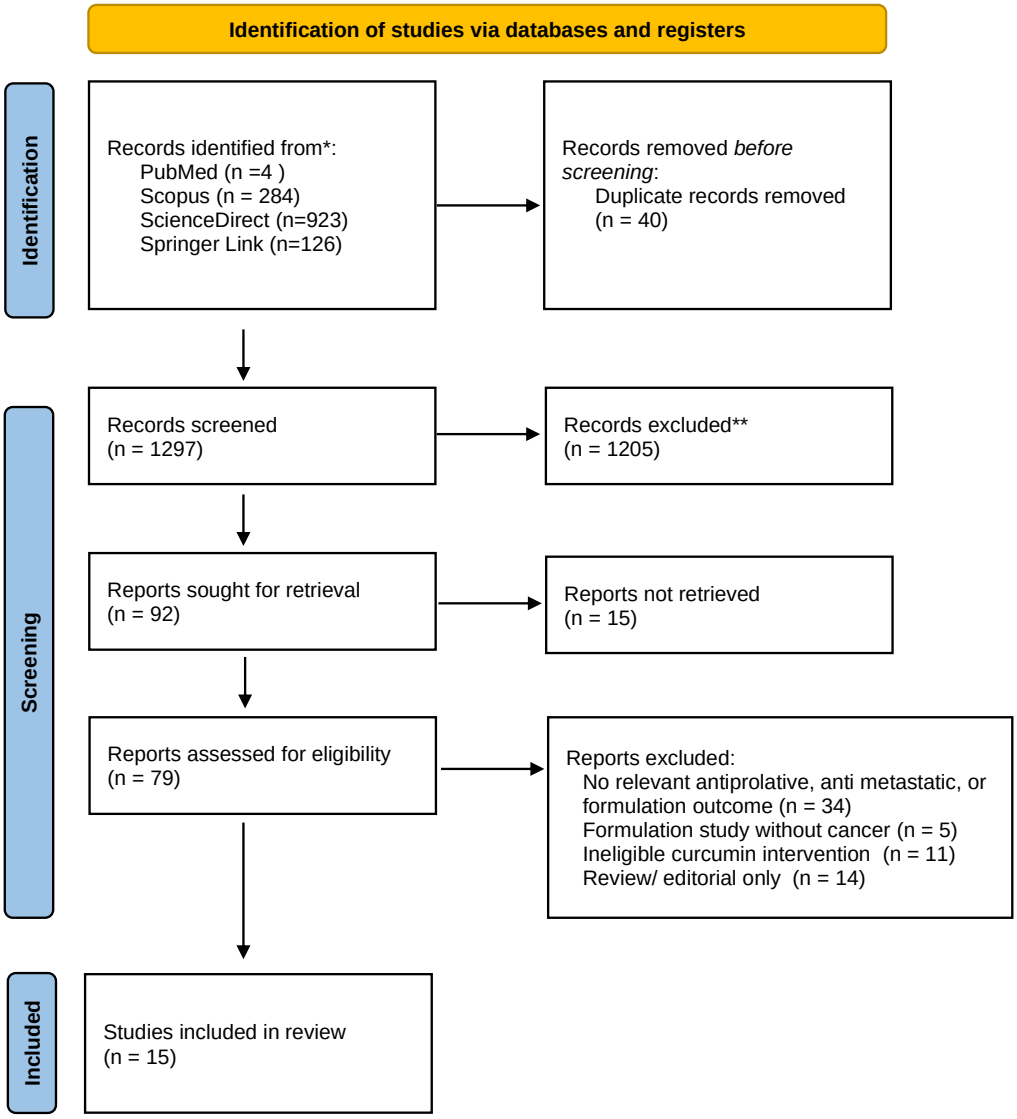

Figure 1. PRISMA 2020 flow diagram of the study-selection process[14]

Study characteristics

The 15 included studies were published between 2016 and 2026. Nine studies evaluated native curcumin, either alone or in mechanistically interpretable combination with standard treatment or

signaling stimulation, whereas six studies evaluated curcumin formulations. Of the 15 studies, 10 (67%) were exclusively in vitro and 5 (33%;[9,10,18–20]) incorporated an in vivo or xenograft component. Cancer models were heterogeneous across seven categories: breast/triple-negative breast (n=5), colorectal (n=4), papillary thyroid (n=2), ovarian (n=1), hepatocellular (n=1), pancreatic (n=1), and malignant meningioma (n=1), with correspondingly diverse doses, exposure durations, and assay endpoints that precluded pooled quantitative synthesis.

Table 1. Summary of Research Articles on the Anticancer Effects and Molecular Mechanisms of Curcumin in Various Cancer Models

Study	Cancer model and study design	Intervention	Main outcomes	Molecular pathway	Principal finding	Dose and Duration
Yin et al., 2019	Colorectal cancer (HCT116, SW480); Nude mice xenograft model	Curcumin combined with Oxaliplatin (OXA)	Reversed OXA resistance, inhibited proliferation, and induced apoptosis	TGF-β/Smad2/3 and NF-κB pathways	Curcumin reverses OXA resistance by inhibiting TGF-β/Smad-mediated EMT	In vitro: 1-64 μM (optimum 8 μM), 48h. In vivo: 60 mg/kg daily, 3 weeks
Yu et al., 2025	Colorectal cancer (RKO, HCT116, SW480, HT29); Subcutaneous xenograft model	Curcumin treatment and TRIM2 knockdown	Decreased cell proliferation and migration; inhibition of tumor growth in vivo	TRIM2 and mTOR pathways (p-AKT, p-p70S6K)	Curcumin suppresses CRC by downregulating TRIM2, which subsequently inhibits the mTOR pathway	In vitro: 60 μM, up to 5 days. In vivo: Monitoring for 22 days
Liu et al., 2024	Ovarian cancer (SKOV3)	Curcumin nanoparticles (CUR-NPs) compared to pure curcumin	Inhibition of cell proliferation and migration; suppression of inflammatory response	NF-κB/PRL-3 pathway (TNF-α, IL-6, Vimentin)	CUR-NPs are significantly more effective than regular curcumin in regulating the NF-κB/PRL-3 pathway to inhibit cancer	In vitro: 20 and 40 μM, 12-48h
Almutairi et al., 2026	Breast cancer (MCF-7)	Curcumin spanlastics nanoparticles and nanocrystals	Reduction in cell viability, increased apoptosis (Caspase 3), and antioxidant properties	PI3K/AKT/mTOR and NF-κB pathways; VEGF/Cyclin D1 markers	Spanlastics formulations provide the most potent anticancer activity compared to nanocrystals and pure curcumin	In vitro: IC50 dose (37.18 μg/mL for spanlastics), 48h
Bisht et al., 2026	Triple-negative breast cancer (MDA-MB-231) and healthy fibroblasts (L929)	Curcumin formulated with Superbase Ionic Liquid (SBIL)	8,000-fold increase in solubility; ~60% reduction in cancer cell viability	Enhanced cellular uptake and curcumin stability	SBIL-based formulations drastically improve curcumin's bioavailability and anticancer efficacy without toxicity to healthy cells	In vitro: 10 μg/mL active curcumin, 24h
Özerkan et al., 2026	Colon cancer (HCT116, HT29); 3D co-culture model with endothelial cells	Curcumin-gelatin nanoparticles (Cur-GelNPs) activated with near-infrared (NIR) light	Decreased viability, invasion, and migration; mitochondrial damage and apoptosis	NF-κB pathway (decreased IL-6 and TNF-α)	NIR activation triggers controlled curcumin release, enhancing targeted efficacy against colon cancer cells	In vitro: 25 μg/mL; NIR exposure at 38 °C for 30s
Zhang et al., 2016	Papillary thyroid carcinoma (BCPAP)	Curcumin combined with TGF-β1 stimulation	Inhibition of cell attachment, spreading, migration, and MMP-2/9 secretion	TGF-β/Smad2/3 pathway	Curcumin inhibits PTC metastasis by disrupting the Smad pathway that controls the EMT transition	In vitro: 12.5–50 μM, 6-24h

Hu et al., 2019	Breast cancer (MCF-7, MDA-MB-231); Mammospheres (cancer stem cells/BCSCs) model	Pure curcumin	Decreased stem cell viability, inhibition of mammosphere formation and differentiation	Stemness markers (Oct4, Nanog, Sox2) and EMT pathway (E-cadherin, β-catenin)	Curcumin inhibits metastasis by suppressing stem cell-like properties and the EMT process in breast cancer cells	In vitro: 10–40 μM, 24-48h (mammospheres for 4 days)
Li et al., 2022	Triple-negative breast cancer (MDA-MB-231, MDA-MB-468); Mouse xenograft model	Curcumin and Gli inhibitor (GANT61)	Inhibition of proliferation, invasion, migration, and mammosphere formation	Hedgehog (Hh)/Gli1 pathway	Curcumin inhibits TNBC metastasis by targeting the Hedgehog pathway and preventing Gli1 entry into the nucleus	In vitro: 10–35 μM (optimum 20 μM), 24-72h. In vivo: Monitoring for 20 days
Zhao et al., 2022	Human hepatoma (HepG2, SK-Hep-1); Mouse lung metastatic model	Curcumin and Bclaf1 knockout	Inhibition of in vitro invasion and migration; reduction of in vivo lung metastasis	Bclaf1-mediated Wnt/β-catenin pathway	Curcumin inhibits hepatoma cell metastasis by regulating Bclaf1 expression and the Wnt/β-catenin pathway	In vitro: 10-60 μM, 24-72h. In vivo: 20-60 μM (injection dose), 10 days
Cao et al., 2016	Pancreatic cancer (Panc-1) under hypoxic conditions	Pure curcumin	Inhibition of hypoxia-induced proliferation, migration, and invasion	Hedgehog pathway (SHH, SMO, GLI1)	Curcumin plays a key role in suppressing hypoxia-induced pancreatic cancer metastasis by inhibiting the Hh pathway	In vitro: 24, 48, and 72h (limited concentration details in abstract)
Liang et al., 2021	Papillary thyroid cancer (TPC-1, BCPAP-R)	Curcumin combined with miR-301a-3p	Reduction in cell viability, migration, and invasion	miR-301a-3p/STAT3 and JAK/STAT pathways	Curcumin inhibits PTC progressiveness by regulating the miR-301a-3p/STAT3 axis	In vitro: 0-40 μM (IC50 ~23.31-26.43 μM), 24h
Chen et al., 2021	Human meningioma (IOMM-Lee); Nude mouse xenotransplantation model	Curcumin combined with HGF stimulation	Blocking HGF-induced proliferation, migration, invasion, and EMT	c-MET/PI3K/Akt/mTOR pathway	Curcumin inhibits HGF-induced EMT by targeting c-MET and blocking the PI3K/Akt/mTOR pathway	In vitro: 10-30 μmol/l, 24-72h. In vivo: 100-300 mg/kg daily, 30 days
Moawad et al., 2026	Breast cancer (MCF-7)	Curcumin microcapsules (CMC) vs. nanocapsules (CNC)	45-60% reduction in viability, induction of apoptosis, and G2/M cell cycle arrest	MAPK, PI3K/Akt, WNT, and HER2 (via EGFR/VEGFR2) pathways	Nano-formulated curcumin demonstrates stronger multi-target anticancer activity than micro-formulations	In vitro: 100 μM; IC50 CMC (8.88 μM) vs CNC (4.76 μM), 48h
Bahreyni Toossi et al., 2026	Colorectal cancer (HT-29) and normal cells (HFF)	Bulk curcumin, nanomicelles, and nanoniosomes combined with Radiotherapy	Radiosensitization of cancer cells (HT-29) and radioprotection of normal cells (HFF)	Caspase-3 activation, Nrf2 (radioprotection), and NF-κB suppression	Curcumin nanomicelles effectively enhance radiation sensitivity in tumors while protecting healthy tissues	In vitro: 10 μM, pre-treatment 24h before radiation (1-6 Gy)

Risk Of Bias

The methodological quality of the included studies was generally acceptable, although several reporting limitations were identified across domains. Most studies provided adequate experimental controls, dose-response characterization, and outcome measurement, and all studies reported relevant biological or mechanistic endpoints. The main recurring concern was the limited reporting of blinding or other bias-control procedures, which was unclear in most assays across nearly all included studies, particularly those involving image-based assays, migration or invasion assessment, and animal or xenograft models. Based on the overall assessment across the seven domains, nine studies (60%) were categorized as low-to-moderate concern, while six studies (40%) were categorized as moderate concern; no study was rated as low concern alone or high concern overall. Studies rated moderate concern most often combined unclear blinding with less comprehensive mechanistic support, either due to a narrower range of pathway markers assessed [21,22] or limited pathway-level data despite otherwise adequate outcome reporting [23].

Table 2. Risk of Bias and Methodological Quality Assessment of Included Studies

Study	Controls	Dose-response	Replication	Blinding	Outcome measurement	Reporting completeness	Mechanistic support	Overall concern
Yin et al., 2019	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — in vitro and in vivo outcomes reported	Strong — TGF-β/Smad2/3, EMT, apoptosis, and xenograft response	Low-moderate
Yu et al., 2025	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	High (Detailed clinical data included)	Strong — TRIM2 knockdown, mTOR pathway, and rescue experiment	Low-moderate
Liu et al., 2024	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — uptake, proliferation, migration, EMT, and inflammatory markers reported	Moderate-high — NF-κB/PRL-3 pathway with LPS and p65 overexpression	Moderate
Almutairi et al., 2026	Adequate	Adequate	Reported	Unclear in most assays	Adequate	Adequate — formulation, viability, apoptosis, and ELISA markers reported	Strong — PI3K/AKT/mTOR, NF-κB, Cyclin D1, VEGF, BAX, P53, and Bcl-2	Low-moderate
Bisht et al., 2026	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — solubility, stability, cancer-cell viability, and normal-cell compatibility reported	Limited-moderate — mainly solubility and functional anticancer evidence	Moderate
Özerkan et al., 2026	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — 2D/3D model, viability,	Moderate — apoptosis, mitochondrial damage,	Moderate

Study	Controls	Dose-response	Replication	Blinding	Outcome measurement	Reporting completeness	Mechanistic support	Overall concern
						migration, invasion, apoptosis, and selectivity reported	and IR-triggered delivery reported	
Zhang et al., 2016	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — migration, invasion, EMT, MMP-2/MMP-9, and Smad phosphorylation reported	Strong — TGF-β/Smad2/3 pathway and EMT/MMP markers confirmed	Low-moderate
Hu et al., 2019	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — proliferation, stemness, EMT, migration, and invasion reported	Moderate — stemness and EMT markers reported, but no rescue experiment	Moderate
Li et al., 2022	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — proliferation, invasion, migration, stemness, EMT, and xenograft-related data reported	Strong — Hedgehog/Gli1 pathway, Gli1 overexpression, EMT, and stemness markers	Low-moderate
Zhao et al., 2022	Adequate	Reported/likely	Reported/likely	Unclear in most assays	Adequate	Adequate — migration, invasion, tumor growth, and lung metastasis reported	Strong — Bclaf1-mediated Wnt/β-catenin pathway and metastasis evidence	Low-moderate
Cao et al., 2016	Adequate	Reported/likely	Reported/likely	Unclear in most assays	Adequate	Adequate — proliferation, migration, invasion, EMT, and Hh pathway markers reported	Moderate-high — Hh/SHH/SMO/GLI1 and EMT markers assessed, but no rescue experiment	Moderate
Liang et al., 2021	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — viability, migration, invasion, MMPs, EMT, and JAK/STAT markers reported	Strong — miR-301a-3p/STAT3 axis tested with mimics, inhibitors, and STAT3 overexpression	Low-moderate
Chen et al., 2021	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — proliferation, migration, invasion, EMT, and tumor growth reported	Strong — c-MET/PI3K/Akt/mTOR pathway supported by inhibitor experiments	Low-moderate
Moawad et al., 2026	Adequate	Adequate	Reported	Unclear in most assays	Adequate	Adequate — viability, apoptosis, cell cycle, gene expression, and bioinformatics reported	Moderate-high — EGFR, VEGFR2, C-myc, Ki-67, Caspase-3, and pathway enrichment reported	Low-moderate

Study	Controls	Dose-response	Replication	Blinding	Outcome measurement	Reporting completeness	Mechanistic support	Overall concern
Bahreyni Toossi et al., 2026	Adequate	Adequate	Reported/likely	Unclear in most assays	Adequate	Adequate — viability, apoptosis, clonogenic survival, cancer and normal cells reported	Limited-moderate — radiosensitizing/radioprotective outcomes strong, but pathway data limited	Moderate

Direction of evidence map

A semi-quantitative direction-of-effect analysis was conducted to summarize the consistency of supportive findings across the included studies. Overall, the direction of evidence was favorable for curcumin across the main biological outcomes. Antiproliferative effects were reported in most native curcumin studies and all formulated curcumin studies. Native curcumin studies more consistently reported inhibition of migration or invasion, EMT/MMP suppression, molecular pathway modulation, and in vivo or tumor-related effects. In contrast, formulated curcumin studies primarily supported improved anticancer activity in vitro, while evidence for anti-metastatic phenotypes and in vivo tumor outcomes was less frequently reported. This pattern suggests that native curcumin studies were more focused on mechanistic and anti-metastatic endpoints, whereas formulated curcumin studies mainly emphasized enhanced delivery, solubility, stability, and cytotoxic potency.

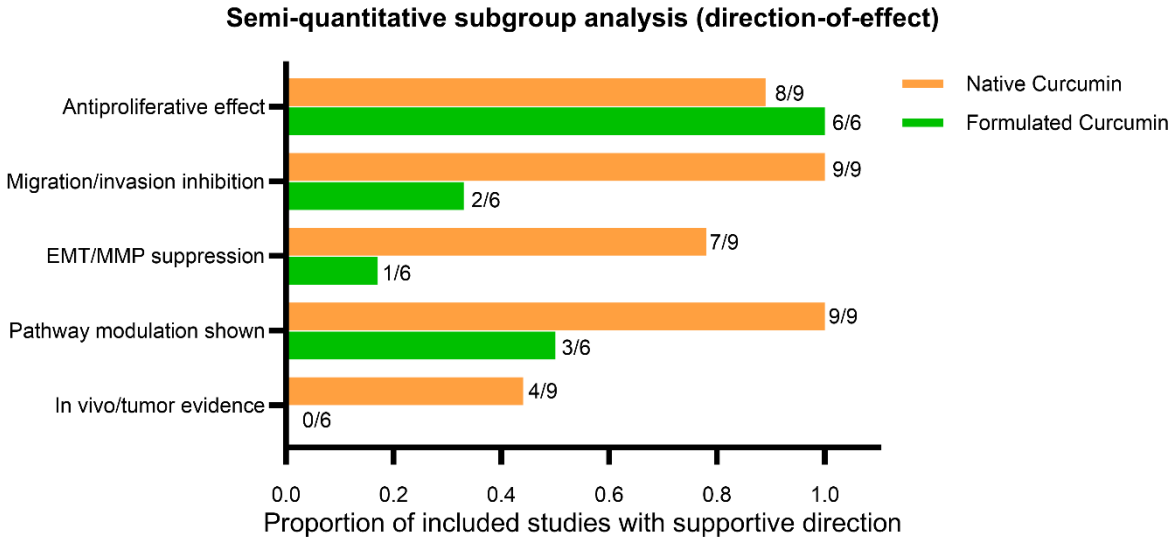

Figure 2. Semi-quantitative direction-of-effect analysis of native curcumin and formulated curcumin studies. The graph shows the proportion of included studies reporting a supportive direction of effect for each outcome category. Values are presented as n/N. This analysis summarizes the direction of evidence only and does not represent a pooled effect size or meta-analysis.

Antiproliferative effects

Across studies of native curcumin, treatment generally reduced cell viability, proliferation, colony formation, and tumor growth, with several studies reporting concentration- and/or time-dependent effects.[9,10,18–20,22,24–26] These effects were associated with the suppression of proliferative, survival, and stemness-related regulators, including Akt/mTOR, S6K, 4EBP1, Cyclin D1, Ki-67, C-Myc, EGFR, VEGFR2, and cancer stem-cell-associated factors.[10,20,22,27,28] Apoptosis was promoted through increased caspase activity and pro-apoptotic signaling, accompanied by reduced expression of anti-apoptotic proteins in several cancer models.[9,19,23,27–29]

Formulated curcumin studies generally reported improved anticancer potency or more rapid biological effects compared with free curcumin.[11,21,23,27–29] Curcumin nanocapsules produced a lower IC_{50} than microcapsules in MCF-7 cells, whereas curcumin spanlastics showed stronger suppression of proliferation and survival-related pathways than native curcumin or nanocrystals.[27,28] The curcumin/SBIL formulation reduced MDA-MB-231 cell viability by approximately 60% at 10 µg/mL after 24 hours without producing comparable toxicity in L929 fibroblasts.[21] These findings indicate that formulation strategies may alter effective intracellular exposure and biological activity. However, direct comparisons between studies remain limited because of differences in cancer models, dose units, treatment duration, and outcome measurements.

Anti-migratory, anti-invasive, and EMT-modulating effects

Curcumin reduced migration and/or invasion across breast, thyroid, pancreatic, hepatocellular, colorectal, ovarian, and meningioma models.[9–11,18–20,22,24–26] These effects were frequently accompanied by restoration of epithelial characteristics, particularly increased E-cadherin expression, and suppression of mesenchymal markers such as N-cadherin, vimentin, and fibronectin.[9,11,19,20,22,24–26] Several studies also reported reduced expression or activity of MMP-2 and MMP-9, providing a plausible mechanism for decreased extracellular-matrix degradation and cellular invasion.[24,26]

The strongest translational evidence was provided by studies incorporating animal models. In hepatocellular carcinoma, curcumin suppressed tumor growth and lung metastasis through Bclaf1-mediated regulation of Wnt/β-catenin signaling.[18] In oxaliplatin-resistant colorectal cancer, curcumin attenuated EMT and improved treatment response in vivo through modulation of TGF-β/Smad2/3 signaling.[9] In malignant meningioma, curcumin reduced xenograft growth and HGF-induced EMT through inhibition of c-MET-dependent PI3K/Akt/mTOR signaling.[19] Nevertheless, distant-organ metastasis was directly evaluated in only a limited number of studies.

Molecular pathway convergence

Despite differences in cancer type and experimental design, the included studies converged on several interconnected signaling networks. TGF-β/Smad2/3 signaling mediated EMT and treatment resistance in thyroid and colorectal cancer models.[9,24] Hedgehog/Gli1 signaling was implicated in triple-negative breast and pancreatic cancer.[20,25] Wnt/β-catenin/Bclaf1 signaling regulated hepatocellular cancer invasion and metastasis.[18] NF-κB/PRL-3 contributed to ovarian cancer proliferation and migration[11], whereas the miR-301a-3p/STAT3 axis regulated papillary thyroid cancer viability, migration, and invasion.[26] TRIM2 acted upstream of Akt/mTOR signaling in colorectal cancer[10], while c-MET-dependent PI3K/Akt/mTOR signaling mediated HGF-induced proliferation, migration, invasion, and EMT in meningioma.[19]

Solubility, stability, dissolution, and release

The formulation studies directly addressed major physicochemical limitations of native curcumin. Spanlastics and nanocrystals increased dissolution efficiency compared with curcumin powder, with nanocrystals demonstrating rapid and near-complete release during the early dissolution period.[28] The SBIL formulation increased aqueous curcumin solubility from approximately 0.0004 mg/g to 3.5 mg/g and prolonged its estimated half-life to approximately 385 hours in the optimized aqueous solution.[21] NIR-sensitive gelatin nanoparticles enabled externally activated curcumin release, with infrared stimulation accelerating early drug release and enhancing anticancer activity.[29]

These findings demonstrate improvements in solubility, dissolution, chemical stability, and controlled release.[21,28,29] However, most formulation studies did not directly measure pharmacokinetic parameters such as plasma concentration, area under the curve, Cmax, Tmax, or tissue distribution.[11,21,23,27–29] Therefore, improved physicochemical performance should be interpreted as supporting the potential for improved bioavailability rather than as direct evidence of enhanced systemic bioavailability.

Formulation strategies, selectivity, and safety

The included formulation strategies were heterogeneous and comprised curcumin nanoparticles, nanomicelles, nanoniosomes, microcapsules, nanocapsules, gelatin nanoparticles, spanlastics, nanocrystals, and ionic-liquid-mediated solubilization systems.[11,21,23,27–29] Particle size, zeta potential, encapsulation efficiency, drug loading, dissolution, stability, release kinetics, cellular uptake, and normal-cell compatibility were reported inconsistently across studies.

Several studies included non-cancer cell controls. Curcumin nanomicelles showed differential radiosensitizing effects in HT-29 cancer cells and radioprotective effects in HFF cells, although some formulation-related toxicity was also reported.[23] NIR-activated Cur-GelNPs showed lower toxicity

toward HUVECs than toward colorectal cancer cells.[29] Curcumin/SBIL remained cytocompatible with L929 fibroblasts at concentrations that substantially reduced MDA-MB-231 viability.[21] Although these findings suggest a degree of cancer-cell selectivity, they remain insufficient to establish clinical safety because long-term toxicity, biodistribution, metabolism, and interactions with conventional anticancer treatments were rarely evaluated.

DISCUSSION

Principal findings

This systematic review found that native curcumin and curcumin-containing formulations generally showed antiproliferative, anti-migratory, anti-invasive, EMT-modulating, and formulation-related benefits in preclinical cancer models. Native curcumin consistently suppressed cancer-cell proliferation and metastatic phenotypes through coordinated regulation of multiple signaling pathways [9–11,18–20,22,24–26] while curcumin-containing formulations additionally improved one or more limiting physicochemical or delivery-related properties, including dissolution, chemical stability, controlled release, cellular uptake, and anticancer potency.[11,21,23,27–29] However, the direction and strength of these findings should be interpreted cautiously, as most included studies were based on in vitro models, used heterogeneous doses and exposure durations, and reported different biological endpoints. Collectively, the evidence supports curcumin as a biologically active food-derived nutraceutical candidate, but it does not establish curcumin as a clinically proven anticancer intervention. Compared with previous systematic reviews on curcumin nanoformulations in oncology, the present review extends prior work by explicitly separating native-curcumin from formulation-based evidence and by appraising methodological quality through a structured seven-domain framework, which most existing narrative or scoping reviews in this area have not applied.

Nevertheless, the included evidence was not fully consistent. The formulation type identified as most effective differed across studies depending on the specific comparator used : curcumin nanocapsules outperformed microcapsules in one study, whereas curcumin spanlastics outperformed nanocrystals in another, such that no single formulation platform was consistently superior across the literature. Similarly, although several studies reported cancer-cell-selective toxicity, at least one formulation study also noted measurable toxicity toward normal cells, indicating that selectivity was not uniform across delivery systems. Beyond formulation-dependent inconsistencies, no study in this review reported a fully null or negative anticancer finding — a pattern that itself signals possible selective reporting rather than uniformly favorable curcumin bioactivity, and is addressed further under publication bias in the Limitations.

Relationship between proliferation and metastasis

The antiproliferative and anti-metastatic effects of curcumin were frequently interrelated. Signaling pathways such as PI3K/Akt/mTOR, STAT3, NF-κB, Wnt/β-catenin, Hedgehog/Gli1, and TGF-β/Smad regulate both tumor-cell growth and invasive plasticity.[9–11,18–20,22,24–26] Curcumin-mediated inhibition of these pathways may therefore reduce proliferation while simultaneously limiting migration, invasion, epithelial–mesenchymal transition, extracellular-matrix degradation, and stemness-related characteristics. [9–11,18–20,22,25,26].

Nevertheless, migration and invasion findings should be interpreted carefully because reduced wound closure or Transwell movement may partly result from cytotoxicity or slower proliferation rather than a specific anti-migratory effect. Future studies should therefore use non-cytotoxic concentrations, matched proliferation controls, mitosis-adjusted migration methods, and time-lapse imaging to distinguish migration-specific effects from general growth inhibition.

Curcumin as a food-derived nutraceutical

The classification of curcumin as a food-derived nutraceutical is scientifically defensible because curcumin originates from turmeric, a widely consumed culinary spice, and exhibits biological effects beyond its basic nutritional role.[4,5] However, the studies included in this review predominantly used isolated curcumin or engineered curcumin formulations rather than turmeric-containing foods, dietary patterns, or conventional dietary exposure. [9–11,18–29]

The micromolar concentrations applied in cell-culture studies cannot be directly translated into dietary intake. Consequently, the findings do not demonstrate that ordinary turmeric consumption prevents cancer progression or metastasis. Curcumin should therefore be described as a food-derived nutraceutical candidate rather than an established nutritional therapy. Its future role may be more plausible as a standardized adjunct to conventional cancer treatment than as a substitute for surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, or evidence-based medical nutrition therapy.

Formulation-related improvement and the bioavailability distinction

The formulation studies demonstrated that carrier design can improve curcumin dissolution, chemical stability, controlled release, cellular delivery, or biological potency.[11,21,23,27–29] Nano-sized formulations may enhance apparent solubility and intracellular delivery, whereas ionic-liquid-mediated systems can markedly improve aqueous dispersion and chemical stability.[21,23,29] However, bioavailability is a pharmacokinetic concept that requires direct measurement of systemic exposure or tissue availability.

Most included formulation studies did not report plasma curcumin concentrations, area under the concentration–time curve, maximum plasma concentration, time to maximum concentration, pharmacokinetic half-life, or tissue distribution.[11,21,23,27–29] Therefore, improved solubility, dissolution, cellular uptake, or in vitro potency should not be interpreted as definitive evidence of enhanced systemic bioavailability.

Future comparative studies should use matched curcumin-equivalent doses, standardized carrier characterization, free-curcumin and blank-carrier controls, pharmacokinetic and biodistribution analyses, and direct measurement of curcumin concentrations in tumor tissues. Without these comparisons, stronger in vitro activity may reflect increased local exposure rather than an inherently superior therapeutic mechanism.

Translational implications

The convergence of signaling pathways identified in this review suggests that curcumin may be investigated as a multi-target adjunct capable of modulating proliferative signaling, epithelial–mesenchymal transition, matrix remodeling, stemness, and treatment resistance.[9–11,18–20,22,24–26] This pleiotropic activity may be particularly relevant in heterogeneous tumors in which multiple pathways contribute simultaneously to progression and metastatic dissemination.

Among the formulation strategies reviewed, the ionic-liquid-mediated system showed the most substantial improvement in aqueous solubility (~8,750-fold increase) with selective cancer-cell toxicity[21] while curcumin spanlastics demonstrated the strongest anticancer activity among the particulate systems tested.[28] These two approaches may therefore warrant priority in future pharmacokinetic and in vivo validation studies, ahead of formulation types with comparatively modest or unconfirmed biological advantages.

The most informative future studies should combine optimized formulations with clinically relevant orthotopic or spontaneous metastasis models, standard-of-care treatments, pharmacodynamic biomarkers, and long-term safety assessment. Clinical trials should also distinguish among dietary turmeric, conventional curcumin supplements, and advanced curcumin formulations because these interventions are not equivalent in composition, dosage, absorption, metabolism, or systemic exposure. Until such evidence becomes available, curcumin should be regarded as a promising preclinical nutraceutical candidate rather than a clinically established anticancer intervention.

Strengths and limitations

A strength of this review is its integrated synthesis of biological effects and formulation science across 15 preclinical studies. Separating native-curcumin studies from formulation studies reduced

conceptual confusion and allowed physicochemical outcomes to be interpreted alongside cancer-related outcomes.

The review also has important limitations. Most evidence was generated in two-dimensional cell cultures, and only a minority of studies assessed tumor growth or metastasis in animals. Cancer types, formulations, dose units, exposure times, assays, and outcome definitions were highly heterogeneous, preventing meta-analysis. Several studies used complex stimulation or treatment contexts, and formulation studies did not consistently include matched free-curcumin and blank-carrier controls, while direct pharmacokinetic bioavailability was rarely measured. The review was also deliberately scoped to preclinical evidence, so recent clinical and translational studies fell outside the eligibility criteria and were not systematically searched. Finally, publication bias could not be formally assessed, as few included studies reported negative or null findings—a pattern consistent with a broader tendency in the preclinical curcumin literature to selectively report positive outcomes. These scope- and reporting-related constraints should be kept in mind when interpreting the translational relevance and overall direction of the synthesized evidence.

CONCLUSION

Preclinical evidence indicates that curcumin exerts broad antiproliferative and anti-metastatic effects across multiple cancer models. These effects involve suppression of cell-cycle and survival signaling, induction of apoptosis, reduced migration and invasion, reversal of EMT, inhibition of matrix metalloproteinases, and attenuation of stemness. Key pathways include TGF-β/Smad2/3, Hedgehog/Gli1, Wnt/β-catenin/Bclaf1, NF-κB/PRL-3, miR-301a-3p/STAT3, TRIM2/mTOR, and c-MET/PI3K/Akt/mTOR. Formulation strategies can improve curcumin solubility, dissolution, stability, release, cellular uptake, and experimental potency. However, these improvements do not yet establish systemic bioavailability or clinical effectiveness. Curcumin should therefore be regarded as a promising food-derived nutraceutical candidate requiring standardized formulations, rigorous pharmacokinetic and safety evaluation, clinically relevant metastasis models, and well-designed human trials before use as an adjunctive intervention in cancer care.

Ethical Considerations

This systematic review of publicly available published literature did not involve human participants or primary data collection and therefore did not require institutional ethics approval or informed consent.

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