REVIEW

Nanoscale Formulations: Incorporating Curcumin into Combination Strategies for the Treatment of Lung Cancer

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Abstract: Lung cancer remains the most common cancer worldwide. Although significant advances in screening have been made and early diagnosis strategies and therapeutic regimens have been developed, the overall survival rate remains bleak. Curcumin is extracted from the rhizomes of turmeric and exhibits a wide range of biological activities. In lung cancer, evidence has shown that curcumin can markedly inhibit tumor growth, invasion and metastasis, overcome resistance to therapy, and even eliminate cancer stem cells (CSCs). Herein, the underlying molecular mechanisms of curcumin were summarized by distinct biological processes. To solve the limiting factors that curtail the clinical applications of curcumin, nanoformulations encapsulating curcumin were surveyed in detail. Nanoparticles, including liposomes, micelles, carbon nanotubes (CNTs), solid lipid nanoparticles (SLNs), nanosuspensions, and nanoemulsions, were explored as proper carriers of curcumin. Moreover, it was firmly verified that curcumin has the ability to sensitize lung cancer cells to chemotherapeutic drugs, such as cisplatin and docetaxel, and to various targeted therapies. Regarding the advantages and drawbacks of curcumin, we concluded that combination therapy based on nanoparticles would be the optimal approach to broaden the application of curcumin in the clinic in the near future.

Keywords: nanoparticles, curcumin, lung cancer, combination therapy

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Introduction

Lung cancer is the most prevalent cancer worldwide, accounting for 11.6% of newly diagnosed cancer cases in 2018, and is the leading cause of cancer-related death (18.4% in 2018).[1] Despite pronounced advances made in lung cancer screening, early diagnosis and therapy, the 5-year survival rate of lung cancer patients remains low, ranging from 4–17% depending on the different parameters and regions.[2] Surgery is recommended for non-small-cell lung cancer (NSCLC) patients with stage I–II disease, and more than 50% of patients are likely to show favorable results.[3] However, for most patients, nonsurgical regimens, including chemotherapy, molecular targeted therapy, and immunotherapy, are adopted. Owing to the progress in the molecular understanding of lung cancer, targeted therapy aimed at specific signaling pathways or abnormalities is beneficial for many patients, especially younger patients, who carry corresponding genetic aberrations.[4] After immunotherapy provided by monoclonal antibodies against PD-1 or PD-L1, one study showed that the 2-year survival rate was approximately 24% among all enrolled patients.[5] Although great advances have been made in the treatment of lung cancer,

relatively low response rates and unfavorable therapeutic endpoints have encouraged researchers to find new therapeutic agents or revised combination regimens.

Curcumin, a natural product from *Curcuma longa*, has long been used as medicine in China and India.[6] Curcumin has been exploited to treat numerous diseases, such as inflammatory bowel disease, rheumatoid arthritis, chronic obstructive pulmonary disease, asthma and many cancers, where it exhibits certain efficacy.[7–9] Curcumin displays high safety in humans and is explicitly efficient in eliminating solid tumors, exemplified by its use against lung cancer, pancreatic cancer, colorectal cancer and so on.[10] Functionally, the anticancer activity of curcumin is attributed to its antiproliferative, proapoptotic, and proautophagic activities, reducing invasion and metastasis and overcoming drug resistance. The multifaceted roles of curcumin in cancer are mediated by numerous molecular targets, which have been discussed in detail in other reviews.[11] Regarding the treatment of lung cancer, many signaling pathways and targets are involved, such as cyclin D, BCL-2, STAT3, VEGF, CXCL, and matrix metalloproteinases (MMPs).[7,12–14] In addition, accumulating evidence indicates that curcumin is sufficient to serve as an adjuvant when combined with other first- or second-line drugs.

However, several drawbacks impede the application of curcumin in the clinic, including its poor aqueous solubility, low bioavailability and rapid metabolism.[15] To achieve optimal plasma concentrations, up to 2 g/kg, 1 g/kg and 12 g/kg curcumin should be orally administered to mice, rats, and humans, respectively.[16] To overcome these obstacles, several strategies have been developed, such as the use of nanoparticles, newly synthesized derivatives, and finding more efficient analogs.[17] Owing to the many advantages provided by nanoformulations, the emergence of nanotechnology pronouncedly potentiates the feasibility of curcumin in the treatment of cancer. In comparison with free curcumin, encapsulation of this drug into nanoformulations confers high solubility, improved kinetics, reduced adverse events, sustained drug release, and improved targeting ability.[18–20] Furthermore, nanoparticles are perfect carriers for diverse drugs with distinct characteristics. The most common nanocarriers encapsulating therapeutic drugs include liposomes, polymeric nanoparticles, and inorganic nanoparticles.[21] Coadministration of curcumin and other therapeutic drugs relying on nanoparticles presents great opportunities to improve efficacy, reduce side effects, and overcome resistance to therapy in lung cancer.

In this review, we first summarized the molecular effects of curcumin against lung cancer sorted by the distinct biological processes. Then, nanoformulations of curcumin were surveyed in detail and sequentially presented according to the different nanocarriers. Furthermore, we discussed the combined strategy of curcumin with chemotherapy and targeted therapy based on nanoparticle systems for the treatment of lung cancer. Finally, we also discussed the challenges of combination therapy involving curcumin relying on nanoparticle technology.

Mechanisms of Curcumin-Mediated Lung Cancer Suppression

Curcumin possesses multifaceted functions for the treatment of lung cancer, including inhibiting proliferation, promoting apoptosis and autophagy, curbing migration and metastasis, overcoming drug resistance, and eliminating cancer stem cells (CSCs), as illustrated in Figure 1. The molecular mechanisms are summarized in Table 1.

Curcumin Inhibits Proliferation and Promotes Apoptosis and Autophagy in Lung Cancer

A prominent characteristic of cancer is the limitless proliferation ability. Initial work has shown that curcumin treatment induces a marked improvement in reactive oxygen (ROS) production and a reduction in cell growth in vitro, which was further demonstrated to be mediated by Wnt/β-catenin signaling.[22] Evidence also indicates that curcumin can activate a p53-dependent pathway, leading to the upregulation of several antiproliferative genes and the downregulation of prosurvival genes.[23,24] In addition, curcumin treatment leads to proliferation arrest and cytotoxic effects via the translocation of Bax and Bad and cytochrome c release in p53-deficient cells.[23]

Apoptosis is an important programmed cell death pathway, and a conclusive linkage between curcumin and apoptosis was strongly confirmed in lung cancer treated with curcumin. In in vivo models, the expression of COX-2, p65 and ERK1/2 decreased and was correlated with impaired tumor growth and survival via apoptosis induction by curcumin.[25] Multiple lines of evidence suggest that curcumin can modulate a wide range of molecular targets in lung cancer. XIAP, an inhibitor of caspases, is inhibited by curcumin and consequently leads to caspase-3-dependent apoptosis in NSCLC.[26] Bax and Bad, essential proteins inhibiting apoptosis, were activated by curcumin to promote cell death.[27,28] In vitro, curcumin was also demonstrated to downregulate PI3K/Akt signaling and enhance
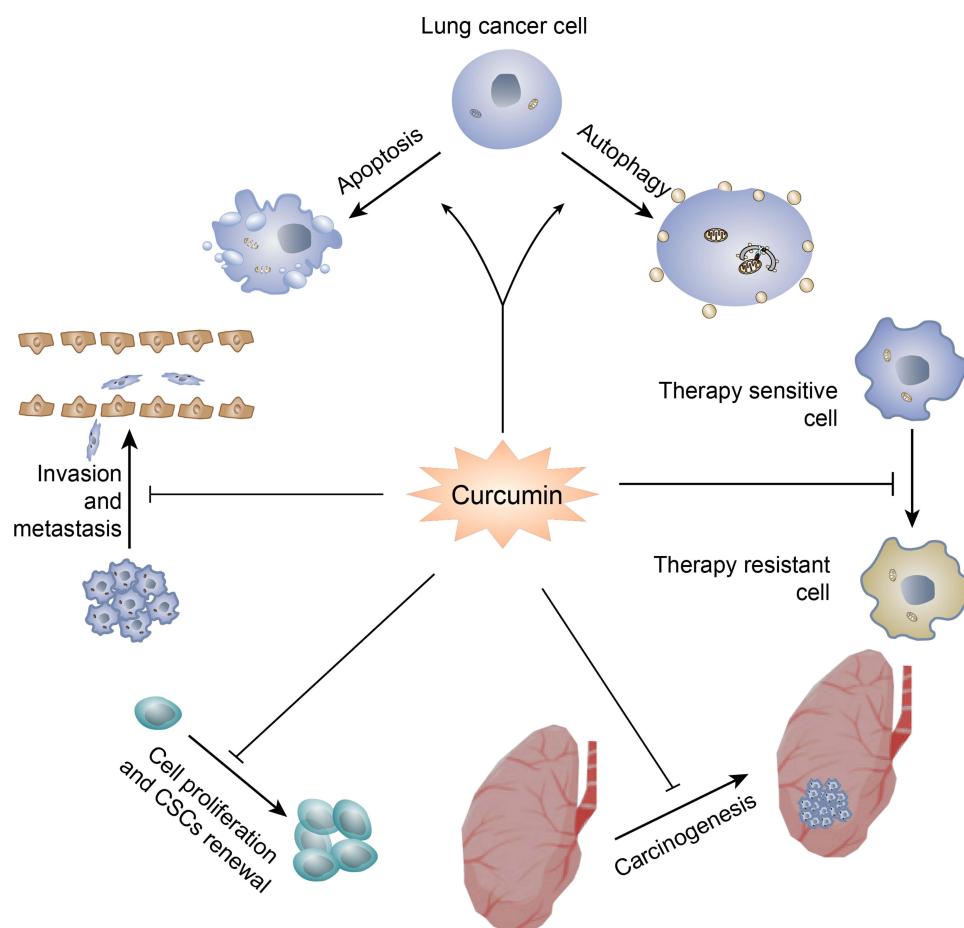
Figure 1 Schematic of curcumin exerting its effects on lung cancer. Curcumin harbors robust abilities to suppress lung cancer, and the mechanisms include promoting apoptosis and autophagy, inhibiting invasion and metastasis, ameliorating drug resistance, eliminating cancer stem cells (CSCs), and preventing lung carcinogenesis.

antiproliferative effects and apoptosis.[29] Another suggested signaling pathway, STAT3, which is accompanied by its downstream proteins, including VEGF, Bcl-xL, and cyclin D1, was reduced by curcumin in an in vivo model.[30] Moreover, anoikis is also involved in curcumin-induced apoptosis through ubiquitin-proteasomal degradation of Bcl-2, which functions as an antiapoptotic protein in various cancer cells.[31] RNA profiling by a microarray assay suggested that a series of genes associated with DNA damage, the cell cycle and cell growth and cell death were dysregulated after curcumin treatment in lung cancer cells.[32]

Autophagy, an evolutionarily conserved process, maintains intracellular homeostasis by recycling impaired cellular components or organelles. It has also been implicated in drug- or other stimulus-induced effects that lead to cell death, denominated as autophagic cell death.[33] Enhanced autophagy was observed by intense immunofluorescence staining of LC3 in lung cancer cells treated with curcumin.[34] GD3 synthase, which is responsible for ganglioside GD3 induction, was further demonstrated to be a transcriptional regulator of autophagy initiation in curcumin-induced autophagy.[35] In addition, curcumin elevates the phosphorylation of AMPK signaling and facilitates cell death, while inhibition of autophagy by a 3-MA or AMPK special inhibitor alleviates its cytotoxicity in lung cancer cells.[34] However, most studies concerning the role of autophagy in chemotherapy implicate a protective effect, where enhanced autophagy in response to drugs mitigates cell death, and the results suggesting a prodeath role of autophagy are often derived from cell models with deficient apoptosis.[36] Thus, the paradox of autophagy in the curcumin-induced response is largely unstudied.

Curcumin Inhibits Invasion and Metastasis

Invasion, angiogenesis and metastasis are intimately associated with cancer progression, and synergistic inhibition of cell growth and metastasis is beneficial for cancer patients. Mounting evidence suggests that curcumin

Table 1 Mechanisms Curcumin Exerts on Lung Cancer

Biological Process	Authors (Reference)	Targeting	Effect
Anti-proliferation	Wang et al[22] Li et al[23]	Wnt/β-catenin p53	Improvement of ROS production and reduction of cell growth Upregulation of several antiproliferation genes and downregulation of prosurvival genes
Inducing apoptosis	Lev-Ari et al[25] Ye et al[26] Hai et al[29] Xu et al[30] Pongrakhananon et al[33]	COX-2, p65, ERK1/2 XIAP PI3K/Akt STAT3 Bcl-2	Impairing tumor growth and inducing apoptosis Leading to caspase-3-dependent apoptosis Enhancing antiproliferation effects and apoptosis Downregulating VEGF, Bcl-xL, and cyclin D1 and inducing apoptosis Inducing anoikis-mediated apoptosis
Inducing autophagy	Lee et al[35] Xiao et al[32]	GD3 synthase AMPK	Serving as a transcriptional regulator of autophagy initiation Inducing autophagic cell death
Inhibiting invasion and metastasis	Chen et al[37] Lu et al[38] Chen et al[39] Chen et al[41] Fan et al[42] Tsai et al[44] Jiao et al[49]	HLJ1 Metastasis-associated protein 1 Cdc42 Rac1 PKCα, ATF-2 NFκB c-Met	Increasing E-cadherin and inhibiting metastasis Inhibiting its expression and inactivating Wnt/β-catenin pathway Dysregulating actin cytoskeleton organization Downregulation of MMP2 and MMP9 Downregulation of MMP9 Inhibiting adiponectin expression and metastasis Blocking PI3K/Akt/mTOR signaling
Ameliorating drug resistance	Zhang et al[54] Kim et al[50] Chen et al[56]	miR-186 Gas6 Sp1, HDAC1	Promoting apoptosis in resistant cells Inhibiting Axl, p21, and XIAP, leading to apoptosis Inducing autophagy-related cell death
Eliminating CSCs	Yen et al[59] Mirza et al[60]	Wnt/β-catenin, Hh JAK2, STAT3	Leading to proliferation arrest and apoptosis Inhibiting self-renewal efficacy
Preventing carcinogenesis	Puliyappadamba et al[61] Moghaddam et al[62]	NF-κB, MAPK Inflammation regulators?	Suppressing B[a]PDE-induced carcinogenesis Inhibiting intrinsic and extrinsic inflammation and Kras-induced carcinogenesis

could efficiently inhibit metastasis at various points of the metastatic cascade, including invasion from the primary site, circulation in blood or lymphatic vessels, extravasation in specific sites, and growth into new lesions. Curcumin exerts antimetastatic effects by targeting a broad range of molecular components.

An initial study revealed that curcumin could activate a tumor suppressor, HLJ1, via upregulation of the JNK/JunD signaling pathway, resulting in increased E-cadherin expression.[37] Curcumin inhibits metastasis-associated protein 1 expression, which further inactivates the Wnt/β-catenin pathway.[38] In addition, Cdc42, a Rho GTPase family member, is involved in curcumin-induced antimetastatic effects by regulating actin cytoskeleton organization.[39] Under curcumin treatment, cytoplasmic stress fibers and membrane filopodia formation were both hampered in lung cancer cells.

Various studies have indicated that curcumin decreases MMP expression and inhibits invasion and metastasis in lung cancer. MMPs, a family of proteases with the ability to breakdown the ECM via collagenase activity, are essential for cancer invasion and progression.[40] Curcumin treatment leads to the inhibition of Rac1 and downregulation of MMP2 and MMP9.[41] Another study suggested that the MMP9 content could also be decreased by reducing the activation of PKCα signaling and ATF-2 phosphorylation after curcumin treatment.[42] Furthermore, MEKK and ERK signaling are inhibited by curcumin, resulting in the downregulation of MMP2 and MMP9 in lung cancer cells.[43] In addition, inhibition of MMP expression, such as MMP-2 and MMP-9 mediated by NFκB signaling, can regulate adiponectin expression after curcumin treatment.[44] miRNA microarray analysis indicated that a series of miRNAs associated with invasion and metastasis were

dysregulated in curcumin-treated lung cancer cells compared with control cells.[45,46] Thus, a complicated regulatory network of MMP inhibition is deliberately orchestrated in response to curcumin treatment and leads to hampering invasion and metastasis in lung cancer.

In addition to MMP downregulation, curcumin also exerts an influence on epithelial-mesenchymal transition (EMT), which is a pivotal event that generates prometastatic cell types in cancers.[47,48] It was demonstrated that curcumin inhibits HGF-induced EMT in lung cancer via modulation of c-Met, which functions upstream of PI3K/Akt/mTOR signaling.[49] The potential regulatory axis was further verified in HUVECs treated with curcumin, which had impaired tubular formation ability in vitro. However, the opposite conclusion was observed in mice implanted with lung cancer cells: curcumin administration by dietary supplementation did not inhibit metastasis but rather promoted progression, probably by enhancing angiogenesis and inflammation.[50]

Curcumin Ameliorates Drug Resistance in Lung Cancer

Drug resistance inevitably limits the efficacy of chemotherapy or targeted therapy in lung cancer. Platinum-based chemotherapy, used in combination with gemcitabine, docetaxel or other chemotherapy drugs, results in an overall survival period of 8–10 months in NSCLC patients.[51] Many patients who are initially sensitive to chemotherapy tend to relapse within six months, and chemotherapy resistance is deemed to be the cause.[52] Tyrosine kinase inhibitors (TKIs) are a standard of care for patients with epidermal growth factor receptor mutations, while intrinsic resistance conferred by nonsensitizing mutations and secondary resistance conferred by the evolution of cancer cells largely diminishes the clinical effects.[53] Intriguingly, several studies have shown that curcumin can efficiently overcome drug resistance in lung cancer.

In multidrug-resistant lung adenocarcinoma cells, curcumin downregulates miR-186 and promotes apoptosis.[54] Similarly, the cytotoxic effects of curcumin on cisplatin-resistant and paclitaxel-resistant cells are carried by the Axl protein, which is activated by Gas6 in these resistant cells.[55] Furthermore, the combination of curcumin and gefitinib, a TKI, significantly inhibits proliferation and colony formation by reducing EGFR phosphorylation through the suppression of Sp1 activity and its interaction

with HADC1 in gefitinib-resistant NSCLC cells.[56] This report also suggested that combination therapy induces autophagic cell death and apoptosis, contributing to the augmentation of cytotoxic effects and the ability to overcome TKI resistance. These studies unveiled that curcumin is beneficial in mitigating drug resistance in lung cancer and might be an alternative for combination therapy.

Curcumin Eliminates Cancer Stem Cells

In recent years, increasing evidence has indicated that cancer is highly heterogeneous, consisting of bulk tumor cells, stromal cells, endothelial cells, and a special subtype of cells, cancer stem cells (CSCs).[57] Accumulating data suggest that CSCs are critically responsible for cancer progression, drug resistance, metastasis and relapse.[58] Thus, therapeutic regimens targeting CSCs have attracted great attention in pharmacological research.

Initial research has shown that curcumin markedly suppresses lung cancer CSCs, as reflected by impaired tumorsphere formation and the decreased expression of stemness markers such as CD133, CD44 and Nanog.[59] Regarding the mechanisms, curcumin suppressed the Wnt/β-catenin and Hh pathways, which play pivotal roles in stemness maintenance, as they promote tumorsphere formation in vitro and have a striking ability to promote tumorigenicity in vivo.[58] Similarly, circulating lung cancer CSCs were isolated and treated with curcumin, resulting in significant DNA damage, decreased sphere formation, and cell death via dysregulation of JAK2/STAT3 signaling.[60] Thus, curcumin has been suggested as an efficient agent for the treatment of CSCs.

Curcumin Prevents Lung Carcinogenesis

Apart from inhibiting lung cancer in vitro and in vivo, evidence also suggests that curcumin can prevent lung carcinogenesis arising from intrinsic and extrinsic carcinogenic factors. Benzo[a]pyrene, a component of the environment and cigarette smoke, is a carcinogen that leads to DNA adducts and induces mutations via transformation to B[a]PDE in vivo.[61] Dietary curcumin suppressed B[a] PDE-induced carcinogenesis by inhibiting the NF-κB and MAPK signaling pathways, as indicated by reverted histopathological deviations in mice.[61] Furthermore, curcumin suppressed the progression of Kras-induced lung cancer in mice by mitigating inflammation.[62] However, a study found that dietary curcumin did not prevent lung cancer metastasis but rather promoted it; this evidence suggests that curcumin might not be a proper agent for

carcinogenesis prevention.[50] Thus, the exact mechanisms by which curcumin prevents lung carcinogenesis should be more thoroughly elucidated in further studies.

Please insert Table 1 here.

Curcumin Formulations Based on Nanoparticles

Although the versatile role of curcumin in the treatment of lung cancer has been solidly established, the drawbacks of free curcumin delay and weaken its application in clinical situations. Curcumin nanoformulations show great potential in solving these issues and provide proper platforms for combination therapy, which are discussed below.

Liposomal Curcumin

Liposomes, nanoscale phospholipid bilayer vesicles, have attracted great attention for the delivery of curcumin in various cancer types (Figure 2A), including lung cancer, cervical cancer, prostate cancer, breast cancer and liver cancer.[63,64] Several key characteristics of liposomes facilitate their use as drug carriers, including low systemic side effects, high biosafety and easy preparation.

Several reports have shown that liposomal curcumin significantly improves the efficiency and safety both in vitro and in vivo compared with free curcumin for the treatment of lung cancer. Zhang et al observed that curcumin liposomes markedly increased cell death compared with free curcumin at 25 μM, as the cell viabilities were approximately 13.5% and 38.5%, respectively.[65] Lin et al reported a cationic liposome-PEG-PEI complex encapsulating curcumin and tested its delivery efficiency and cytotoxic activity in lung cancer cells.[66] They observed a rapid accumulation of liposomal curcumin in A549 cells over a 2.5 hour incubation period, but no signal from free curcumin appeared even after 4 hours of incubation. Liposomal curcumin markedly arrested the cell cycle and led to apoptosis and also curbed invasion and metastasis.[67]

Since liposomes are convenient and easily captured and metabolized by the reticuloendothelial system, the half-life of these drugs is relatively short. Studies using liposome-based technology have taken these factors into account, and various long-circulating liposomes have been designed and developed, such as PEGylation-modified phospholipids and hyaluronic acid-liposomes.[68,69] As the cancer cell membrane, which is formed by phosphatidyl-serines, proteoglycans and other components, is negatively charged, cationic liposomes with positive changes have been conceived to have a greater affinity for the cancer
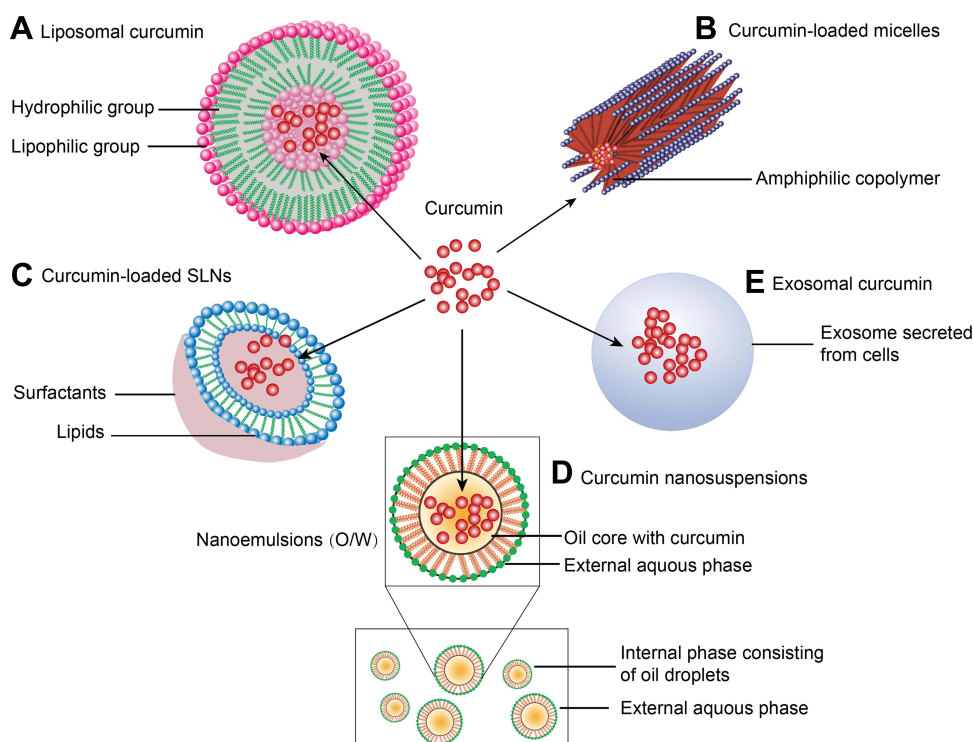

Figure 2 Schematic of nanoscale formulations of curcumin applied for the treatment of lung cancer. (**A**) Liposomal curcumin; (**B**) Curcumin-loaded micelles; (**C**) Curcumin-loaded Solid lipid nanoparticles (SLNs); (**D**) Curcumin nanosuspensions; (**E**) Exosomal curcumin.

cell membrane.[70,71] These advances should pave the way for liposomal curcumin to be applied in the clinic.

Curcumin-Loaded Micelles for Lung Cancer Treatment

Polymeric micelles have attracted great attention as drug carriers in recent years, showing several advantages, such as easy preparation, drug solubilization, high biocompatibility, good pharmacokinetics, and potential modifications.[72] Typically, polymeric micelles are spherical particles with sizes less than 100 nm consisting of hydrophobic blocks, such as polyesters, polyethers and hydrophilic blocks, such as PEG. This biblock (hydrophilic-hydrophobic) structure provides high stability in aqueous solutions and good compatibility for drug loading (Figure 2B).

Self-assembled methoxy polyethylene glycol–polylactide (mPEG–PLA) polymeric micelles, which encapsulate curcumin in the hydrophilic core, have been designed and developed.[66] Another polymeric micelle derived from Pluronic F, an amphiphilic nonionic polymer mixed with Gelucire@ 44/14, a surface-active lipid excipient used for improving water solubility, was developed and loaded with curcumin.[73] Transmission electron microscopy images revealed spherical-shaped curcumin-loaded mixed micelles with a rather uniform size distribution. The authors further showed that curcumin-loaded micelles markedly improved cytotoxic effects by approximately 5-fold compared with free curcumin in A549 cells.[73] In addition, the plasma curcumin concentration after oral administration was measured, and the analysis unveiled a relatively slow and controlled increase of the drug into plasma.

Curcumin-Loaded Carbon Nanotubes (CNTs) in Lung Cancer

CNTs with several features, including high aspect ratios, large surface areas, rich surface chemical functionalities, and size stability on the nanoscale, have greatly extended exploration and biological applications.[74] As ALG-coated nanoparticles largely increase loading efficiency and SWNTs with CHI coating release agents faster, dual-coated SWNTs were suspected to be ideal nanoplatforms for drug delivery.[75] Fiegel et al developed a CNT coating with a small pore (mesoporous) silica and an HSA layer to carry curcumin and camptothecin.[76] The drug loading capacity of the conjugates was in the range of 0.4–0.7%,

which was among the standard values for hydrophobic drug loading using a mesoporous silica system.

In addition, curcumin-loaded SWNTs have shown high solubility and stability.[77] Modifying the physicochemical parameters of SWNTs by incubation with strong acids, sonication, oxidative modification and noncovalent functionalization conferred a marked enhancement in the biocompatibility of the system. An in vitro study showed enhanced antitumor cell activity of SWNT-curcumin compared with that of free curcumin, as a higher dose-dependent and time-dependent increase in efficiency was observed with SWNT-curcumin. This evidence indicates that CNT-curcumin is an efficient delivery system for safely administrating curcumin in vitro, but in vivo results are not available.

Curcumin-Loaded Solid Lipid Nanoparticles (SLNs) in Lung Cancer

SLNs have several striking advantages compared with other nanosystems, including reduced systemic adverse events due to bypassing the reticuloendothelial system, enhanced biocompatibility, high capability to engulf both hydrophobic and hydrophilic drugs, and high biosafety via lipid biodegradation (Figure 2C).[78] Baek et al generated and developed multifunctional SLNs for the codelivery of curcumin and paclitaxel.[79] SLNs loaded with drugs were prepared by emulsification and solvent evaporation, and the encapsulation efficiency was greater than 75%, whereas the folate-modified SLNs showed lower efficiency. The nanoparticle system significantly improved the uptake of paclitaxel and curcumin compared with that of free paclitaxel and curcumin in breast cancer cells, and as predicted, the targeted system further improved the internalization of both drugs.

In a Hodgkin's lymphoma model, SLNs loaded with curcumin significantly increased the level of plasma curcumin and decreased tumor growth by 50.5% compared with free curcumin, while no adverse events were observed.[80] In lung cancer, a study systematically investigated the in vitro and in vivo effects of SLN-curcumin. SLN-curcumin led to markedly enhanced cytotoxicity, as the IC_{50} decreased from 185 μM to 32 μM, although the SLNs also slightly inhibited cell proliferation.[81] In vivo, SLN-curcumin increased the level of curcumin in plasma, which was attributed to its prolonged release, preventing rapid metabolism and increasing the bioavailability in SLN formulations. Moreover, tissue distribution analyses

showed that SLN-curcumin improved the concentration of curcumin in the lung and tumor by 32.6- and 4.3-fold compared with that of curcumin. As expected, the SLN formulation significantly inhibited the tumor growth of lung cancer xenografts, whereas no effect was observed in response to curcumin administration alone.

Curcumin Nanosuspensions in Lung Cancer

Recent advances have demonstrated that nanosuspensions are suitable and efficient for in vitro and in vivo drug delivery owing to their extended surface area and physicochemical properties.[82] Generally, nanosuspensions are equipped with surfactants or polymeric steric stabilizers, and the specific nanoparticle features allow 100% drug loading capacity, which assists in researching valid concentrations and minimizing adverse effects. A study reported the feasibility and efficiency of nanosuspensions prepared by precipitation ultrasonication technology for curcumin delivery in vitro and in vivo.[83] Most of the curcumin was retained in the nanosuspensions after 24 hours of incubation with plasma, and no hemolysis was observed, indicating high safety after intravenous administration.

As the solubility and stability of curcumin are very low in aqueous solution, various stabilizers have been attached to nanosuspensions. A study using β-lactoglobulin as a stabilizer for curcumin nanosuspensions prepared by the antisolvent precipitation method showed that β-lactoglobulin markedly modified the morphology of the curcumin nanocrystals, which were more stable in vitro and displayed much higher solubility in vivo than free curcumin.[84] A similar study applied the commercially available stabilizers TPGS and Brij78 to nanosuspensions and suggested that these formulations elevated the bioavailability of curcumin after oral administration.[85] Collectively, curcumin nanosuspensions significantly improved the aqueous solubility, bioavailability, circulation time and efficiency of curcumin against cancers.

Curcumin Nanoemulsions in Lung Cancer

Nanoemulsions are oil-in-water (O/W) or water-in-oil (W/O) dispersions of two immiscible liquids stabilized using an appropriate surfactant.[86] Nanoemulsions have several features, including high solubilization capacity, great aqueous stability, long-term physical stability, protection of drugs against harsh conditions, avoidance of metabolism by the reticuloendothelial system, and a great capacity to load very hydrophobic drugs.[86] Accumulating evidence suggests that nanoemulsions could be suitable carriers for loading curcumin (Figure 2D).

Wan et al generated curcumin nanoemulsions by loading water-in-oil nanoemulsions into lipid nanoparticles using a nanoemulsion-film dispersion sonication method and evaluated the release profiles and killing effects in -vitro.[87] This nanoformulation significantly improved the bioavailability, decreased adverse events and led to enhanced efficiency compared with free curcumin in lung cancer. Curcuminoid nanoemulsions prepared by sonication efficiently arrested the cell cycle and promoted apoptosis in lung cancer cells.[88] Recent evidence suggests that ultrasound-responsive perfluorocarbon nanoemulsions can be properly used as multifunctional smart drug carriers, and this method integrates diagnostic and therapeutic applications. Baghbani et al developed doxorubicin/curcumin codelivery nanoemulsions that displayed increased cytotoxicity to ovarian cancer in vitro and in vivo.[89] In addition, biosafe curcumin-loaded nanoemulsions exhibited considerably prolonged release after topical application compared with that of free curcumin and sufficiently suppressed cancer recurrence and metastasis after surgical removal of primary cancers.[90]

Curcumin-Loaded Exosomes in Lung Cancer

Although nanoparticles based on natural and synthetic lipids possess incredible advantages, some defects, such as their relatively limited retention in circulation and potential toxicity, limit their pharmacological applications. Exosomes are the smallest extracellular vesicles secreted from cells, with sizes ranging from 30–150 nm.[91] Recent advances have indicated that exosomes have several advantages over conventional nanoparticles, including high biocompatibility, considerably decreased systemic toxicity, high tissue and biological barrier penetration, and immune supervision evasion.[92]

With regard to loading curcumin, evidence has demonstrated the feasibility and efficiency of exosomes as nanoscale carriers for the treatment of cancers (Figure 2E). Curcumin was loaded into exosomes with an entrapment efficiency of approximately 54%, and the exosomal formulation was stable for more than 6 months at −80°C.[93] Considerably enhanced curcumin levels were observed in liver and brain tissues compared with tissues after free curcumin treatment, indicating that exosomes improved the bioavailability of curcumin. Exosomal curcumin displayed much higher lung cancer cell killing efficiency and cancer growth inhibition in vivo. Collectively, exosomes might be superior to synthetic carriers for carrying curcumin.

Combined Strategies Utilizing Nanoparticles to Improve Curcumin Application

Cumulative preclinical evidence has shown that curcumin could inhibit tumor growth by inducing cell cycle arrest, inhibiting migration and invasion, and inducing pronounced apoptosis in lung cancer. However, currently, no reports have indicated similar effects under clinical conditions. Apart from its limitations of low aqueous solubility and bioavailability, curcumin unfavorably promoted Kras-driven lung tumorigenesis in one study, hampering its application.[94] Furthermore, poor efficacy was also observed in one preclinical study using solely curcumin for lung cancer treatment (overall efficacy was less than 30%).[95] This evidence indicates that curcumin as a single agent is not suitable for the treatment of cancer. Alternatively, researchers are exploring the potential of curcumin as an adjuvant or combined agent with first-line drugs for the treatment of lung cancer, which are summarized in Table 2 and discussed below.

Synergistic Effects of Curcumin and Chemotherapy in Lung Cancer

For NSCLC, cisplatin is the first-line therapeutic agent and is recommended for application with other second- or third-line agents.[96] Compared with cisplatin, the combination of cisplatin and curcumin exhibited an obvious synergistic effect on cytotoxicity and the inhibition of cell viability and colony formation in lung cancer cells.[96] Mechanistically, p-p38 activation and the expression of X-ray repair cross complementing group 1 (XRCC1), an essential regulator of DNA single-strand break repair, were markedly enhanced by curcumin and cisplatin. The mechanism was further confirmed by the observations that the downregulation of XRCC1 or p-p38 resulted in decreased cell viability in two lung cancer cell lines.

On the other hand, curcumin decreased the level of copper ions and thus promoted the expression of the CTR1 gene, a key copper transporter, through transcriptional activation of Sp1 and CTR1.[97] Decreased cellular copper ion levels in response to curcumin promoted cisplatin uptake and chemotherapy sensitivity in lung cancer.

Table 2 Synergistic Effects of Curcumin and Chemotherapy or Targeted Therapy in Lung Cancer

Drug	Authors (Reference)	Combination Mechanism or Nano-Carrier	Effect
Cisplatin	Tung et al[96]	Activating p-38, downregulating XRCC1	Exhibiting synergistic effect on cytotoxicity, cell viability, and colony formation
Cisplatin	Zhang et al[97]	Inhibiting Cu-Sp1-CTR1 regulatory loop	Enhancing apoptosis and inhibited tumor growth in in vitro and in vivo; killing CSCs
Cisplatin	Baharuddin et al[98]	Inhibiting p21 and cyclin D1	Killing CSCs
Carboplatin	Kang et al[99]	Dysregulating caspase-3, caspase-9 and p21	Synergistically inhibiting cell proliferation and induced apoptosis
Docetaxel	Yin et al[100]	Inhibiting cell viability and tumor growth	Satisfying synergistic antitumor efficacy
Mitomycin C	Ko et al[102]	Downregulating MKK1/2–ERK1/2-mediated Rad51 expression	High efficacy of antitumor effect in vitro model
Fenretinide	Chen et al[103]	Downregulating GRP78	Enhancing cytotoxic effects and apoptosis
Paris saponin II	Man et al[104]	Activating the PI3K/AKT, MAPK and NF-κB	Inducing cell cycle arrest and apoptosis
Erlotinib	Yamauchi et al[108]	Inhibiting the activation of NFκB	Enhancing cytotoxicity of erlotinib
RTK inhibitors	Lin et al[109]	Not presented	Suppressing proliferation in vitro and tumor growth in vivo
Doxorubicin	Wang et al[111]	MPEG-PCL micelles	Better inhibition of lung cancer growth in vivo and in vitro
Paclitaxel	Jiang et al[113]	RGD-modified liposomes	Better efficacy of antitumor in vivo and in vitro
Doxorubicin	Jyoti et al[116]	Inhalable bioresponsive nanoparticle	Much pronounced cytotoxicity and apoptosis in vitro

As expected, the combination of curcumin and cisplatin significantly enhanced apoptosis and inhibited tumor growth in vitro and in vivo. Furthermore, the combined strategy was also beneficial in killing potentially problematic CSCs. Curcumin sensitized lung cancer CSCs to cisplatin by enhancing apoptosis and cell cycle arrest by increasing the expression of several key proteins.[98] Curcumin combined with carboplatin, another platinum drug widely used in the treatment of lung cancer, also demonstrated a great synergistic effect in lung cancer cells. The results showed that this combination therapy synergistically inhibited cell proliferation and induced apoptosis via dysregulation of caspase-3, caspase-9 and p21.[99] Furthermore, combined treatment significantly inhibited cell migration by downregulating MMP-2 and MMP-9. This evidence firmly verified that combination therapy with curcumin and platinum drugs was an effective strategy to eliminate lung cancer cells.

According to National Comprehensive Cancer Network guidelines, docetaxel is preferred in advanced or metastatic lung cancer. To achieve greater antitumor efficacy and reduce adverse events, docetaxel combined with curcumin was exploited. A substantially decreased IC_{50} was observed, and considerable inhibition of tumor growth was also achieved in the combination group compared with the single treatment groups.[100,101] Furthermore, combination therapy showed no significant adverse events.

Mitomycin C, a first- or second-line chemotherapy drug for lung cancer, combined with curcumin demonstrated high antitumor efficacy in an in vitro model.[102] Curcumin potentiated the cytotoxicity of mitomycin C in two lung cancer cell lines via activation of MKK1/2-ERK1/2 signaling, which further suppressed the expression of Rad51, a strand transferase.

Fenretinide, a synthetic retinoid acid (RA), has been suggested as a suitable chemotherapy drug in various studies.[103] The combination of fenretinide with curcumin led to enhanced cytotoxic effects and apoptosis in lung cancer cells via downregulation of GRP78, a well-recognized endoplasmic reticulum-chaperone protein.[103]

Another study showed that curcumin could promote the antitumor effects of Paris saponin II (PSII), isolated from Rhizoma Paridis saponins, in lung cancer cells.[104] They analyzed the proliferation rate, and a combination index of less than 1 was found, showing an obvious synergistic effect between curcumin and PSII in four lung cancer cell lines. The combination treatment promoted the cellular uptake of drugs and induced cell cycle arrest and apoptosis by activating the PI3K/AKT, MAPK and NF-κB signaling pathways. Similarly, epigallocatechin gallate (EGCG), a natural compound from green tea, showed a higher antiproliferation effect and depressed DNA replication in lung cancer cells and animal models after coadministration with curcumin.[105]

Synergistic Effects of Curcumin and Targeted Drugs in Lung Cancer

Apart from chemotherapy drugs, studies have also suggested that curcumin can sensitize lung cancer cells to various targeted drugs. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFRs), such as erlotinib, afatinib, and dacomitinib, are the preferred regimens for patients with EGFR mutations.[106] Although great success has been achieved, primary or acquired resistance still limits the application and efficacy of these drugs in the clinic.[107] Curcumin inhibited the activation of NFκB by modulating the level of IκB, which was the underlying mechanism of the enhanced cytotoxicity exerted by erlotinib combined with curcumin in lung cancer cells.[108] Moreover, combination therapy significantly attenuated tumor growth in vivo, as reflected by tumor volume and histological results. Similar to EGFR inhibitors, other receptor tyrosine kinase (RTK) inhibitors, such as insulin-like growth factor 1 (IGF-1R) and fibroblast growth factor receptor (FGFR) inhibitors, have also been suggested as suitable drugs for combination with curcumin in lung cancer treatment.[109] Collectively, curcumin robustly sensitizes lung cancer cells to multiple targeted agents.

Combination Therapy Based on Nanoparticles

It has been firmly verified that curcumin efficiently eliminates lung cancer via multiple pathways that have been suggested to make up a complicated regulatory network and can serve as a largely versatile agent to potentiate responses to conventional chemotherapy or targeted drugs. Strikingly, various studies have indicated that a low dose of curcumin (less than 10 μM) combined with a low dose of chemotherapeutic or targeted drugs led to considerably enhanced cytotoxicity compared to either agent alone. This means that a combination strategy might significantly decrease the required concentration of applied drug while maintaining a robust killing effect on lung cancer. Furthermore, combination therapy led to fewer adverse events and overcame therapy resistance.

However, a prominent problem that remains is how to achieve the most suitable ratio between different drugs. Drug delivery systems are developed and expected to facilitate drug administration, promote accumulation at the tumor site, reduce adverse events, and maximize killing effects. In recent years, nanoparticle-based delivery systems have advanced considerably, which is attributable to a deep understanding of tumor biology and the availability of biodegradable nanoscale materials. The advantages of a combined strategy based on nanoparticles include better drug solubility, a prolonged circulation period, sustained drug release kinetics, a reduction in adverse events, inhibition of multiple targets and promotion of synergetic effects, as well as the ability to overcome potential resistance.[110] Several reports have successfully developed these systems to simultaneously carry curcumin and other therapeutic drugs.

Doxorubicin combined with curcumin exhibits high efficacy in suppressing lung cancer, and various nanoparticle systems can sufficiently engulf these two drugs.[111,112] Wang et al designed and developed a drug delivery system, MPEG-PCL micelles loaded with curcumin and doxorubicin, and examined its antitumor activity in vivo.[111] The results demonstrated that this formulation inhibited angiogenesis, which was reflected by a defective vascular structure and significantly suppressed tumor growth in vivo compared to single drug treatment. Similarly, nontoxic RGD-modified liposomes were used to encapsulate curcumin and paclitaxel.[113] The in vitro drug release profile showed sustained release of both drugs in vitro, and enhanced cytotoxicity was also observed. When used at the same concentration, the nanoparticle formulation led to the most obvious inhibition in vivo compared with treatment with the single drugs. Additionally, several overwhelming advantages of inhalation delivery compared to oral and venous administration has driven researchers to investigate whether coloading nanoparticles would be suitable for the treatment of lung cancer. A nanoformulation containing curcumin and methotrexate led to significant cell growth arrest and apoptosis in lung cancer cells.[114] A coencapsulated nanosystem carrying curcumin and cisplatin exhibited greatly enhanced in vitro and in vivo antitumor effects against lung cancer.[115] Jyoti et al prepared inhalable bioresponsive nanoparticles carrying doxorubicin and curcumin that efficiently released drugs after being triggered by enzymolysis.[116] This complex synergistically induced pronounced cytotoxicity and apoptosis in lung cancer cells. This evidence indicates that combination therapy involving curcumin based on nanoparticles is promising to eliminate lung cancer.

Conclusions

We systematically summarized and discussed the evidence concerning curcumin application in lung cancer. As presented above, curcumin sufficiently inhibits lung cancer proliferation, induces apoptosis and autophagy, inhibits migration and invasion, overcomes drug resistance, eliminates CSCs, and prevents carcinogenesis. These effects are mediated by multiple signaling pathways and a complicated regulatory network. On the other hand, nanotechnology is beneficial to solve the drawbacks that limit the clinical applications of curcumin. Extensive exploitation strategies have been undertaken to incorporate curcumin within various nanoparticles, and antitumor activity has been examined via cultured cells or limited animal models. Combination therapy where curcumin serves as an adjuvant drug loaded into nanoparticles might potentiate the application of curcumin in the clinic.

However, caution should be taken when selecting drugs for combination therapy with curcumin. Many preclinical reports found very interesting mechanisms underlying combination therapy involving curcumin, while very limited clinical evidence or high-grade animal studies were available. This dilemma elicits a vital issue regarding how the reliability of those conclusions are derived from the cultured cell-based design.[117,118] Furthermore, the combination efficacy can be markedly compromised if an antagonistic regulatory pathway exists among the drugs to antagonize the effects and facilitate cancer development.[119] Thus, the prominent mechanism of action of curcumin and its partner agent should be explored and summarized in detail.

Challenges in designing effective combination therapy systems for lung cancer also exist. First, it is essential to provide an optimal concentration ratio of each drug encapsulated in the nanoscale system according to pharmacokinetics data and maximum efficacy.[120] Second, targeting systems armed by specific response factors, such pH responsive, ROS responsive, or enzyme-mediated elements, are helpful for differentiating between tumor cells and nontumor cells or for differentiating between extracellular and intracellular targets.[121] Third, the adverse effects of nanoparticles should be carefully surveyed.[122] In addition, optimized delivery systems highly rely on the entrapped drugs where proper modifications of the nanoparticles are certainly beneficial. Finally, it is crucial to

develop ligand-conjugated nanosized delivery systems that actively target receptors specifically expressed in cancer cells; in response, due to the overwhelming accumulation in tumor sites, this strategy is speculated to outperform the passive targeting strategy.[21,123,124]

Thus, significant efforts are needed to fully elucidate the underlying mechanisms of combination therapy, achieve optimal delivery systems and extensively evaluate efficacy and safety.

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Disclosure

The authors declare that there are competing interests.

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