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New advances and applications of phyto-constituent based NLCs in drug delivery for lung cancer

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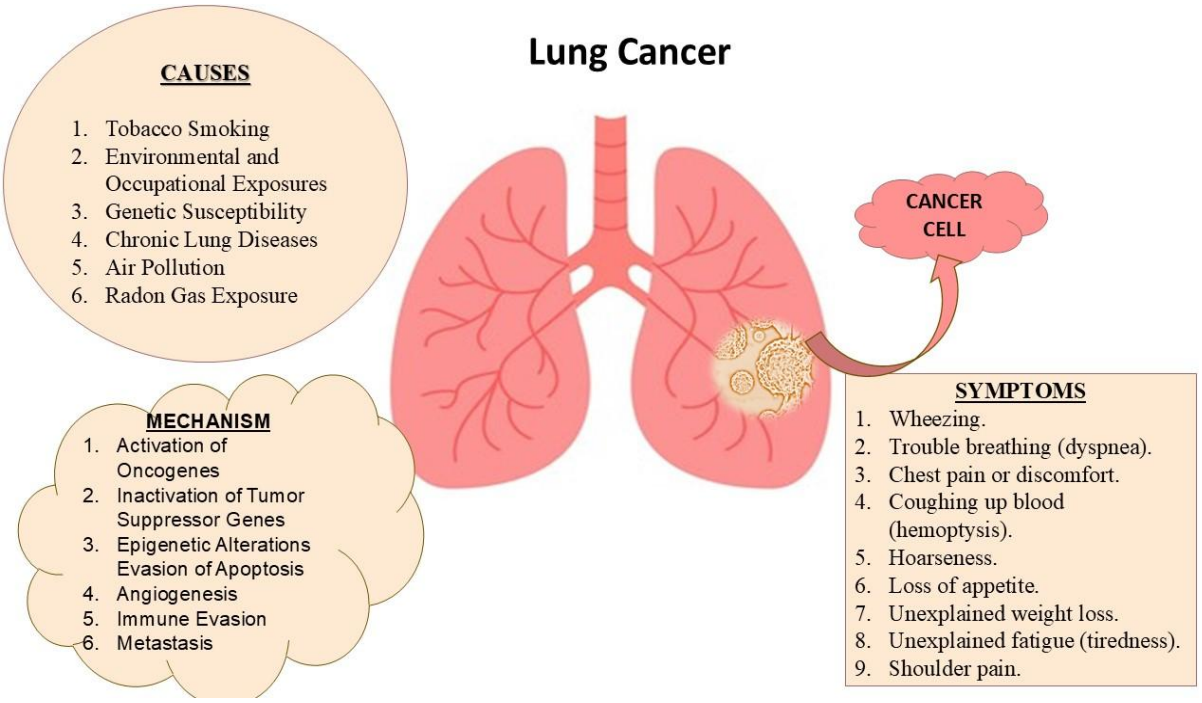
1. INTRODUCTION

Lung cancer is a primary malignant neoplasm that arises in the respiratory tract epithelial cells, either in the bronchioles, bronchi, or alveoli. It is defined by uncontrollable cell growth, invasion of the surrounding tissue, and the ability to spread to distant sites. Lung cancer remains the top cause of death due to cancer in the world, causing nearly 1.8 million deaths every year. It eclipses the mortality of breast, prostate, and colorectal cancer combined, which also indicates how fast-growing and fatal lung cancer. Lung cancer is classified on a histologic basis into two main types: Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). NSCLC makes up nearly 85% of lung cancer cases and consists of three main subtypes: adenocarcinoma, the most prevalent type, predominantly in non-smokers, that arises in mucus-producing glandular cells located in the periphery of the lungs; squamous cell carcinoma, which has strong ties to smoking, that arises in airway lining epithelial cells and tends to occur in the central lungs in the vicinity of the bronchial openings; and large cell carcinoma, an undifferentiated and fast-growing type of cancer of poor survival prognosis that does not exhibit specific characteristics of the other subtypes of NSCLC. On the other hand, SCLC accounts for roughly 15% of cases and is defined by the high aggression of the tumor, fast cell division, and early spread of cancer. SCLC arises in neuroendocrine cells and is nearly exclusively associated with the use of tobacco. Responding well to chemotherapy and radiotherapy initially, it quickly relapses and is related to brief survival periods



Based on World Health Organization (WHO) and GLOBOCAN 2020 estimates, lung cancer is still one of the leading diagnosed cancers in the world, with over 2.2 million new cases each year. It is more prevalent in males, yet female incidence increases as a result of escalating trends of smoking and environmental exposure. Lung cancer is predominant in developed countries, especially in Eastern Europe, North America, and East Asia, yet death rates are also very high in low- and middle-income countries where screening and healthcare availability is low.

There are several modifiable and non-modifiable risk factors that lead to lung cancer. Tobacco smoking is the strongest risk factor, causing more than 85% of cases, as it exposes the individual to PAHs and other carcinogens like benzene and nitrosamines that trigger mutations in the DNA. Both active smoking and passive exposure to tobacco smoke raise lung cancer risk significantly. Environmental and occupational exposure are also important; naturally occurring radioactive gas radon can concentrate in homes and underground mines, while asbestos in construction material is synergistic in risk when added to cigarette smoking. Exposure to air pollutants like fine PM2.5 and NO_2 over a long term, and inhalational exposure in the workplace to silica dust, heavy metal, and diesel exhaust, also increase lung cancer cases. Genetic susceptibility exists, with a family history of lung cancer and certain genetic polymorphisms—like TP53, KRAS, and EGFR mutations—modifying individual susceptibility. Other chronic diseases of the lung, consisting of COPD, pulmonary fibrosis, and a history of tuberculosis infection, can make one susceptible to lung cancer by establishing a pro-inflammatory and damaged pulmonary environment. (8-15)

Lung cancer carcinogenesis involves a complex interplay between genetic and epigenetic changes that initiate and advance the disease. Some of the critical molecular events are the activation of oncogenes like EGFR, ALK, and KRAS that stimulate aberrant cell growth and survival. Concurrently, the inactivation of important tumor suppressor genes like TP53 and RB1 eliminates crucial regulatory brakes that prevent uncontrolled cell growth. In addition, these genetic dysfunctions are augmented by the capability of the cancer cells to escape premature death by evading apoptosis, induce angiogenesis to support tumor maintenance, and escape immune surveillance. All these changes collectively enable malignant transformation, stabilize uncontrolled cell growth, allow new vessel formation to supply the tumor, and facilitate metastatic dissemination to distant organs.

Lung cancer tends to be clinically silent in the initial stages, which makes early detection and early intervention challenging. Symptoms usually occur in the later stages of the disease, if and when the tumor infiltrates the surrounding tissue or metastasizes to distant organs. Respiratory symptoms are predominant and may involve a chronic or persistent cough, hemoptysis (cough), pleuritic chest pain aggravated by deep breathing or by cough, dyspnea, wheezing, hoarseness of the voice caused by involvement of the recurrent laryngeal nerves, and recurring respiratory infections like bronchitis or pneumonia. Apart from these local symptoms, systemic symptoms like unexplained loss of body weight, generalized weakness, loss of appetite or associated loss of taste, and fever or night sweats may signify disease progression. Some cases in selected groups of patients, especially of small cell lung cancer (SCLC), may also present in the form of paraneoplastic syndromes—conditions resulting from the production of ectopic hormones by tumor cells. These syndromes constitute the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Cushing's syndrome, hypercalcemia, and various neurologic complications, which may conceal the underlying disease and complicate the management of disease.15-25

Diagnosis of lung cancer is made using a holistic approach in which imaging, histopathology, and molecular analysis are integrated to establish the presence of malignancy and inform the choice of therapy. Evaluation starts often in the initial phases of assessment by means of imaging studies like chest X-rays and CT imaging to identify abnormalities, followed by positron emission tomography-computed tomography (PET-CT) for the purpose of staging and confirming distant spread. Histopathologic examination of tissue samples acquired by means of procedures like bronchoscopy, CT-guided biopsy, or surgical biopsy confirms definitive diagnosis. Molecular analysis is important in the identification of specific mutations or biomarkers like EGFR, ALK, ROS1, and PD-L1, which guide the use of the corresponding targeted therapies and immunotherapies. Staging of lung cancer according to the TNM system of classifying tumor size (T), lymph nodes (N), and presence of distant metastasis (M) is utilized. Proper staging is important as it establishes the disease extension and prognosis as well as guides therapy.

The prognosis of lung cancer overall is still poor, mainly due to the fact that a majority of cases are diagnosed in an advanced stage when curative therapies are few and far between. The 5-year overall survival rate in all types of lung cancer and in all stages is roughly 20% due to the disease's aggressive behavior and the difficulty in early detection. Survival is greatly dependent on the stage of presentation: it is 56% in localized disease, which decreases to 30% in cases of regional spread and to approximately 6% in distant metastases. Small cell lung cancer (SCLC) tends to have a worse prognosis compared to non-small cell lung cancer (NSCLC) due to the former's fast doubling time, increased propensity for metastases, and early systemic dissemination. Although the survival of selected patients harboring specific genetic mutations or biomarker expression, e.g., EGFR, ALK, or PD-L1, is markedly improved by the use of newer targeted therapies and immunotherapies, these therapies are not universally successful and are reserved for specific subgroups of patients.

Aspect	Details
Most common type	Non-Small Cell Lung Cancer (85%)
Primary risk factor	Smoking (responsible for >85% of cases)
Early symptoms	Often asymptomatic; later stages show cough, dyspnea, chest pain
Main diagnostic tools	CT scan, biopsy, molecular profiling
Prognosis	Poor; 5-year survival rate ~20% across all stages

Challenges in Conventional Lung Cancer Treatment: Even in light of decades of advances in the therapy of cancer, traditional treatments of lung cancer remain plagued by several shortcomings, particularly in relation to long-term efficacy, specificity, safety, and accessibility to the patient. Heterogeneity, aggressively growing behavior, and high propensity for metastasis of lung cancer complicate therapy in particular.

Surgical excision is still the gold standard for the management of early-stage Non-Small Cell Lung Cancer (NSCLC), especially in stages I and II, providing the greatest potential for long-term survival. Popular procedures include lobectomy (excision of a whole lung lobe), pneumonectomy (excision of a whole lung), and segmentectomy (excision of a lung segment), all designed to excise the primary tumor and surrounding lung tissue for clear margins. Although it has the potential for cure, operation is subject to several formidable obstacles. As few as 20–25% of lung cancer patients are considered reasonable candidates for operation, mainly based on the advanced stage of presentation or pre-existing lung dysfunction that makes it unsafe to resect. In addition to other perioperative risks, postoperative complications of infection, bleeding, respiratory insufficiency, and extended postoperative stay may negatively affect recovery and outcomes. Even in the successful complete extirpation of the tumor, recurrence remains a significant risk, mainly as a result of the presence of occult micro metastases or subclinical malignant cell contamination.

Chemotherapy continues to be a mainstay in the management of stage-advanced Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC), particularly when the disease is deemed inoperable. Cisplatin, carboplatin, paclitaxel, gemcitabine, and etoposide are frequently utilized chemotherapeutic agents that operate by disrupting the cancer cell cycle and triggering cell death by apoptosis. Although extensively used, chemotherapy is subject to several limitations, mainly relating to its non-selective mechanism of action. These drugs affect all rapidly dividing cells, and as a consequence, non-malignant cells in the bone marrow, lining of the gastrointestinal system, and hair follicles also get damaged. As a result, the patient suffers a plethora of toxicities in the form of nausea, vomiting, fatigue, alopecia, and myelosuppression expressed as anemia, neutropenia, and thrombocytopenia. Immunosuppression further exacerbates the risk of infection, and certain drugs—platinum-based drugs, in particular—also trigger peripheral neuropathy and renal intolerance. These side effects often oblige the clinician to reduce the dose or discontinue the drug, thus compromising the quality of the given therapy and the patient's quality of life.

Radiotherapy, including modalities like external beam radiation therapy (EBRT) and stereotactic body radiation therapy (SBRT), is essential in lung cancer management in patients who are unfit for or are not appropriate candidates for surgery or in cases where adjuvant therapy is administered to enhance local tumor control. Although radiotherapy can effectively address localized tumors, it comes with some significant shortcomings. One of them is the unintended injury to neighboring normal tissue, which is particularly problematic in the presence of tumors in central or near-central locations near critical organs. Some of the usual side effects of radiotherapy are radiation pneumonitis, a life-threatening inflammatory lung disease, as well as esophagitis, fatigue, and fibrosis leading to pulmonary hardening over the long term. Further, radiotherapy is of limited value in treating distant metastases, which makes it less useful in the presence of advanced disease. Tumors in proximity to critical structures like the heart, spinal cord, or large arteries usually cannot be subjected to full utilizable radiation dose for fear of causing extensive complications, thus curtailing the therapeutic value of this modality in specific anatomical settings.

Development of drug resistance is one of the biggest hurdles in lung cancer therapy that severely compromises the long-term efficacy of both chemotherapy and targeted treatments. Resistance can be intrinsic, pre-existing, or acquired, arising during the course of therapy. A number of molecular mechanisms underlie this resistance. These involve the overexpression of drug efflux pumps like P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1), which actively efflux drugs from cancer cells, hence impairing intracellular drug accumulation. Point mutations in drug targets—like the secondary T790M mutation in EGFR—render the tyrosine kinase inhibitors ineffective. Alternatively, cancer cells can escape cell death by overexpression of anti-apoptotic markers like Bcl-2 by becoming proficient in repairing their DNA in the presence of chemotherapy or radiation-induced genotoxic stress. These cells also activate bypass pathways in the form of MET, PI3K/AKT, and KRAS, which allow them to circumvent blocked targets to keep growing. Development of resistance also often requires combination therapies to bypass these adaptation mechanisms, which are in turn often related to increased

toxicity, increased cost of therapy, and complicated management in the clinic.

Targeted therapies have made significant inroads in lung cancer therapy by providing greater selectivity and less systemic side effects compared to conventional chemotherapy. These therapies are developed to disrupt specific molecular pathways that are crucial for tumor growth and survival. Among them, the tyrosine kinase inhibitors (TKIs) are key and comprise EGFR inhibitors erlotinib, gefitinib, and osimertinib, ALK inhibitors crizotinib and alectinib, among others, that target ROS1, RET, and BRAF mutations in corresponding genetic aberrations. Another prominent category consists of immune checkpoint inhibitors (ICIs), including PD-1 inhibitors (e.g., nivolumab, pembrolizumab) and PD-L1 inhibitors (e.g., atezolizumab), that function by inducing the immune system to attack tumor cells. Although initially successful in biomarker-positive populations, the targeted therapies are confronted by various issues. Only 15–20% of NSCLC patients harbor actionable mutations, restricted in application of the treatments in the majority of cases. Further, in mutation-carrier patients, response may be heterogeneous, and many develop acquired resistance by mechanisms involving target gene amplification, alternative pathway activation, or mechanisms of immune escape. Finally, immune checkpoint inhibitors may cause immune-related adverse events (irAEs), which include pneumonitis, colitis, hepatitis, endocrinopathies, and dermatologic manifestations, among which several are life-threatening or severe, and therefore require strict vigilance in monitoring as well as managing the patients.

Lung tumors are genetically and phenotypically heterogeneous, even within the same patient, leading to variable therapeutic responses. This intra-tumoral heterogeneity complicates treatment planning and contributes to relapse. (26-36)

Conventional therapies lack tumor-specific delivery mechanisms, leading to:

Systemic toxicity

Suboptimal drug accumulation at the tumor site

Destruction of normal proliferating cells, resulting in organ dysfunction

Challenge	Description
Late-stage diagnosis	Limits eligibility for surgical intervention
Non-selective therapies	Lead to severe systemic toxicity
Drug resistance	Reduces efficacy of chemotherapy and targeted therapy
Limited biomarker expression	Restricts applicability of targeted therapies
Tumor heterogeneity	Causes variable treatment responses and recurrence

Role of Phytoconstituents in Cancer Therapy: Phytoconstituents are natural bioactive molecules obtained from medicinal plants, spices, vegetables, fruit, and spices. They were utilized centuries ago in ancient systems of traditional medicine like Ayurveda, Unani, and Traditional Chinese Medicine (TCM). In the last few decades, there has been increasing scientific evidence of the anticancer effects of various phytochemicals, which made them potential candidates in the design of new and less harmful cancer therapies.

Classification and Examples of Anticancer Phytoconstituents

Phytoconstituents encompass a broad spectrum of chemical classes, each with unique structural and functional properties. Common classes with anticancer potential include:

Alkaloids: e.g., Vincristine, Vinblastine, Camptothecin

These interfere with microtubule formation and inhibit cell division.

Flavonoids: e.g., Quercetin, Apigenin, Luteolin

Known for antioxidant, anti-inflammatory, and pro-apoptotic activities.

Polyphenols: e.g., Curcumin, Resveratrol, Epigallocatechin gallate (EGCG)

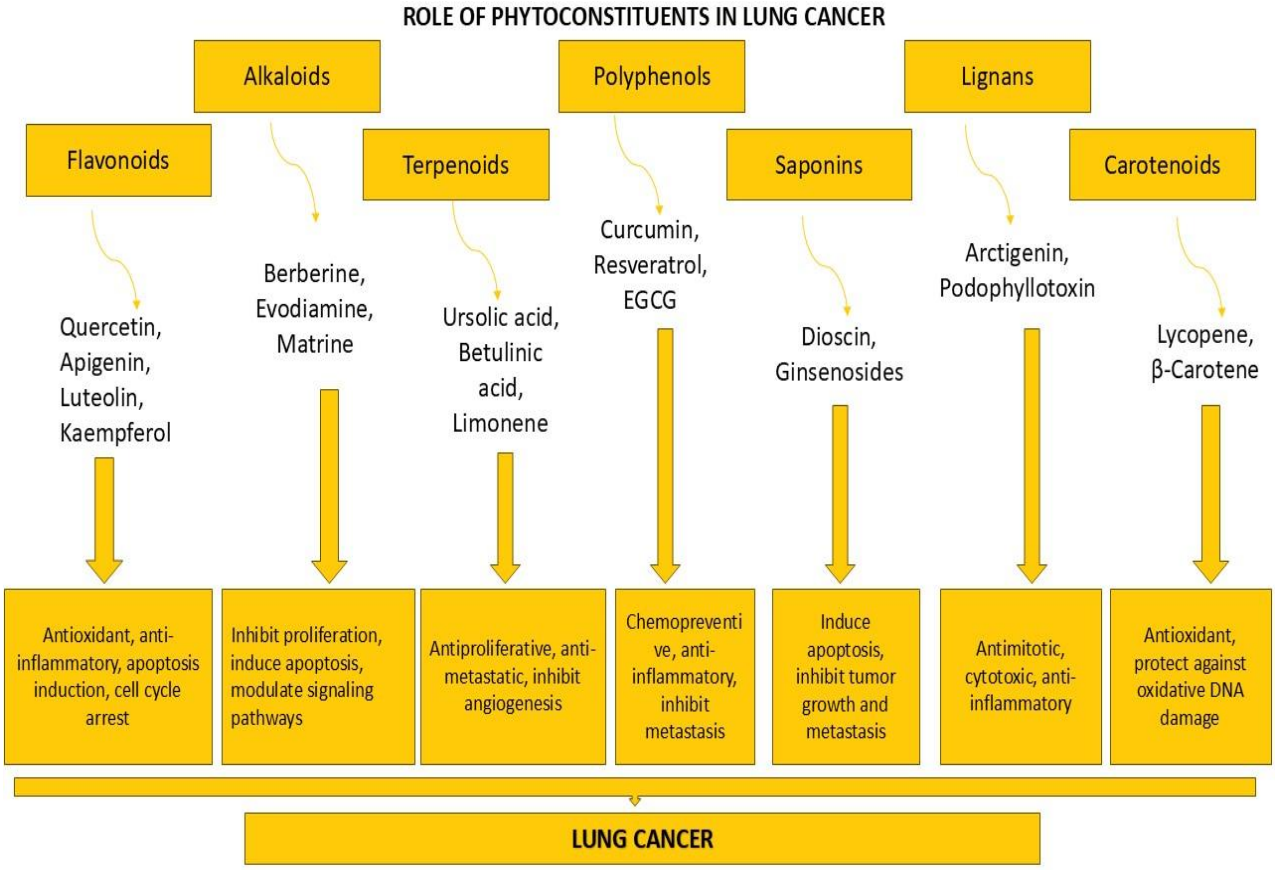
These modulate cell signaling pathways, including those involved in inflammation, proliferation, and angiogenesis.

Terpenoids: e.g., Paclitaxel (Taxol), Artemisinin, Betulinic acid

These have demonstrated potent cytotoxic activity against a variety of tumor types.

Saponins: e.g., Diosgenin, Ginsenosides

Known to modulate immune responses and disrupt cancer cell membranes.



Mechanisms of Anticancer Activity

Phytoconstituents mediate anticancer effects by engaging in a wide range of molecular mechanisms that modulate various signaling pathways concurrently. This pleiotropic property endears them to the management of polygenic diseases such as cancer in which very many cell processes are dysregulated. One of them is induction of apoptosis in which quercetin and curcumin induce the activation of caspases, rupture of mitochondrial membrane potential, and disbalance of pro-apoptotic (e.g., Bax) and anti-apoptotic (e.g., Bcl-2) proteins. Other effects include induction of cell cycle arrest in the G0/G1 or G2/M checkpoint by inhibiting CDKs which results in halting of aberrant cell division in apigenin and genistein. An additional mechanism where phytochemicals discourage cell inflammation is that agents such as curcumin inhibit pro-inflammatory agents like NF-κB, COX-2, and interleukins which are usually implicated in cancer causation and progression. Next, other phytoconstituents like resveratrol and EGCG interfere in angiogenesis by inhibition of the VEGF pathway, depriving tumors of essential nutrients and oxygen. Their antioxidant behavior also quenches free radicals (ros), reduces oxidative damage to DNA, and induces protective enzymes like superoxide dismutase and catalase. To inhibit the establishment of metastases, agents like luteolin prevent matrix metalloproteinases (MMPs), inhibiting tumor invasion. Finally, other phytochemicals also modulate epigentic effects by inducing modifications of DNA methylation, acetylation of histones, and microRNA expression which result in tumor suppressive gene reactivation and inhibition of oncogene pathways. Cumulatively, these diverse mechanisms reflect the promise of phytoconstituents as significant agents in lung cancer therapy.

Lung cancer, especially in the later stages, is generally refractory to conventional chemotherapy and radiation. Phytoconstituents have a number of advantages in lung cancer therapy:

Curcumin: Exhibited to inhibit growth of lung cancer cells by suppressing NF-κB, STAT3, and PI3K/AKT pathways.

Resveratrol: Suppresses HIF-1α and decreases VEGF production, inhibiting angiogenesis and lung tumor

Quercetin: Causes apoptosis in A549 lung cancer cells and increases the drug cytotoxicity of agents such as cisplatin and doxorubicin.

Berberine: Induces mitochondrial-mediated apoptosis and suppresses the proliferation of NSCLC cells by modulating EGFR and MAPK signaling.

Genistein: It decreases oxidative damage and inflammation, slows cell growth, and sensitizes lung cancer cells to radiation

and chemotherapy.

They are not only cytotoxic to tumor cells, yet tend to leave normal cells unharmed, lessening the risk of the side effects typically found in synthetic chemotherapies.

One of the most significant features of the potential of the phytoconstituents is that they can increase the efficacy of the traditional therapies. They synergize with the chemotherapeutic agents by:

Overcoming multidrug resistance (MDR): Phytochemicals inhibit drug efflux pumps like P-gp and MRP1.

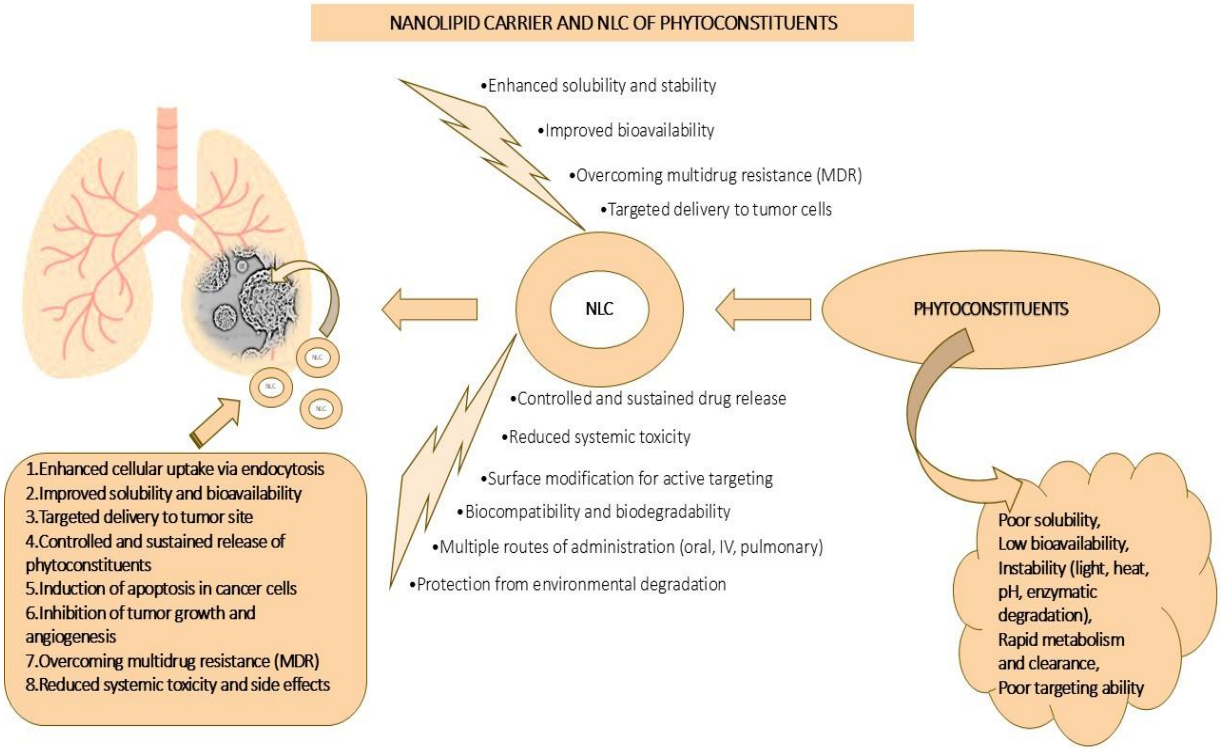
Sensitizing tumor cells: Several of the phytoconstituents increase the drug and radiation sensitivity of cancer cells, thus reducing the dose needed.

Protecting normal tissues: They reduce chemotherapy-induced normal tissue toxicity by acting as antioxidants and anti-inflammatory agents.

In spite of their potential therapeutic effects, phytoconstituents are plagued by several formulation and pharmacokinetic issues that greatly restrict their application in the clinic. One of the main setbacks is their low water solubility, as the majority of phytoconstituents are naturally hydrophobic in nature and poorly soluble in aqueous biological medium, which restricts their absorption. It is also accompanied by their limited oral bioavailability, as they get extensively metabolized during the first pass through the liver and gastrointestinal tract, ultimately leading to limited systemic exposure. Additionally, numerous phytoconstituents experience fast metabolic elimination, where the fast degradation and excretion shorten their plasma half-life and prevent them from accumulating in the tumor environment in medication concentrations. They are also sensitive to environmental conditions like light, pH, and temperature, leading to degradation prior to reaching the target site of action. Further, in the form of free suspensions, phytoconstituents also show non-specific distribution in the body and hence, besides decreasing the drug concentration in the tumor environment, also increase the risk of off-target effects. These restrictions necessitate the utilization of innovative drug delivery systems like nanostructured lipid carriers (NLCs) that increase the stabilization, delivery to the tumor environment, and bioavailability of phytoconstituents for potent application in the clinic. (37-48)

Need for Advanced Delivery Systems

In order to combat the strong formulation and pharmacokinetic hurdles of phytoconstituents, new-generation nanocarriers have arrived on the scene, of which Nanostructured Lipid Carriers (NLCs) are one of the more promising platforms. NLCs are engineered to facilitate better delivery of poorly bioavailable phytoconstituents by enhancing solubility and stability parameters critical to absorption and pharmacological action. They also provide high entrapment efficiency, which ensures that a higher percentage of the active ingredient reaches the site of interest. Through both passive and active targeting mechanisms, NLCs enable tumor-selective delivery, making it possible to amplify the therapeutic effect while lowering off-target toxicity. In addition, NLCs allow for extended and drug-releasing behavior, which sustains therapeutic drug levels for protracted periods and minimizes dose frequency. Their capability to increase the plasma half-lives of components further enhances bio-accessibility and tumor accumulation. Overall, these advantages lead to a better therapeutic index by maximizing both efficacy and minimizing side effects. In summary, although phytoconstituents provide a natural, multi-function, and generally better-tolerated alternative or adjunct to traditional cancer therapies—particularly in diseases such as lung cancer—their full therapeutic potential can be realized only by innovative delivery systems in the form of NLCs, which provide optimum bio-accessibility, retention, and selective therapeutic effects. (49-56)



Nanostructured Lipid Carriers (NLCs): An Overview

Nanostructured Lipid Carriers (NLCs) are a new and innovative category of lipid-based nanocarriers, which were engineered to overcome the shortcomings of previous lipid nanoparticle systems, especially those of Solid Lipid Nanoparticles (SLNs). Even though SLNs were a milestone in nanomedicine for regulated drug delivery, they had limited drug loading capability, drug ejection upon storage, and crystalline transformations in the solid lipid matrix, usually impairing the stability and availability of the entrapped bioactive agents.

In order to surpass these shortcomings, NLCs were developed as the second-generation lipid nanoparticles that bring together the advantages of both solid and liquid lipids. Intermixing of liquid lipids (fats or oils) in a matrix of crystalline solids leads to the breakage of ideal crystalline arrangements of the host lipid structure. It leads to a less ordered, nanostructured, or amorphous lipid matrix that produces greater imperfections and voids, improving the loading capacity of the drug and minimizing the possibility of drug expulsion in the later stages.

Main features of NLCs:

Particles of sizes between 50–500 nm that are appropriate for intravenous, oral, pulmonary, and cutaneous delivery.

Enhanced drug encapsulation efficiency as a result of the disordered matrix

Controllable and prolonged drug delivery patterns.

Potential of surface modification for purposeful delivery.

Composition of Nanostructured Lipid Carriers:

The formulation of NLCs involves four main components: solid lipids, liquid lipids (oils), surfactants, and sometimes co-surfactants or stabilizers. Each component plays a crucial role in defining the physicochemical properties and performance of the final formulation.

A. Solid Lipids

They constitute the basic structure of the NLC and ensure that it is in a solid form at body and room temperature. Solid lipid confers mechanical strength, retains drug in the matrix, and controls drug release behavior.

Typical examples:

Glyceryl monostearate (GMS) – a commonly used biocompatible lipid that is GRAS (Generally Recognized as Safe)

Stearic acid – a fatty acid of long chain that increases the matrix stability.

Compritol 888 ATO (glyceryl behenate) – utilized due to its high melting point and superior biocompatibility.

Tripalmitin - a triglyceride that is utilized

B. Liquid Lipids (Oils)

Liquid lipids are oils that exist in the liquid state at room temperature. They cause disturbance to crystallinity upon inclusion in the solid lipid matrix by forming an imperfect lattice structure, which accommodates the drug.

General examples:

Oleic acid – a monounsaturated fatty acid that is known to increase permeation and flexibility.

Labrafac (medium-chain triglycerides), which are derived from caprylic and capric acid and used frequently in oral and parenteral preparations.

Miglyol 812 - a low-viscous, drug-grade oil of high solubilizing capacity for lipophilic drugs.

Capryol 90 – Employed to increase oral bioavailability.

C. Surfactants

Surfactants stabilize emulsion formed in NLC preparation to ensure that the emulsion is stable. Surfactants lower the lipid and aqueous phases' interfacial tension, which in turn inhibits coalescence or aggregation of lipid particles. Surfactants also affect particle size, zeta potential (surface charge), as well as drug delivery.

Typical Examples:

Poloxamer 188 (Pluronic F68) – a nonionic surfactant used extensively in intravenous and parenteral preparations

Tween 80 (Polysorbate 80) – encourages steric stabilization and is often applied in pulmonary and oral delivery systems.

Egg or soy lecithin – natural phospholipids providing biocompatibility and improved cell uptake.

D. Co-surfactants or Stabilizers

They can also be added in small amounts to increase the physical stability of the formulation or to facilitate better emulsification upon processing. They can also impart ancillary functionality such as increased adhesivity to the mucosa, enhanced solubilization of the drug, or improved targeting.

They include:

PEG 400 – enhances steric stabilization and stops aggregation.

Ethanol or propylene glycol – frequently utilized in microemulsion-based NLC preparation procedures.

Chitosan – to provide NLCs with muco-adhesiveness and a positive surface charge.

Structural Types of NLCs Based on Lipid Composition

Depending on the ratio and type of solid to liquid lipids used, NLCs can be classified into different structural models:

Imperfect Crystal Model

A low percentage of liquid lipid is incorporated.

Results in a matrix with imperfections that can accommodate more drug.

Suitable for highly lipophilic drugs.

Amorphous Model

The mixture of lipids does not recrystallize upon cooling.

Forms a completely disordered structure preventing drug expulsion.

Multiple Type (Oil-in-fat-in-water)

A high amount of liquid lipid is added, forming small oil compartments inside the solid lipid matrix.

Provides high drug loading and sustained release.

Benefits of Lipid Matrix Modulation

Modifying the ratio and type of solid and liquid lipids allows researchers to:

Optimize drug loading and encapsulation efficiency.

Tailor drug release profiles (e.g., burst release vs. sustained release).

Improve physical stability by avoiding lipid crystallization during storage.

Enhance compatibility with specific drugs or delivery routes.

Nanostructured Lipid Carriers (NLCs) provide a versatile, stable, and biocompatible system for the delivery of hydrophilic as well as hydrophobic therapeutic agents, including those plant-derived phytoconstituents that are poorly soluble in water. Its design based on a disordered lipid matrix allows for better drug encapsulation in addition to inhibiting drug leakage, ensuring delivery in a regulated fashion, and enabling targeted delivery by means of functionalized surface. Proper choice of lipids, surfactants, and additives is crucial in tailoring the NLCs according to the desired medical application, particularly for lung cancer therapy.

Advantages Over Other Nanocarriers

Nanostructured Lipid Carriers (NLCs) boast a number of unique advantages relative to other nanocarriers like liposomes, polymeric nanoparticles, and solid lipid nanoparticles (SLNs), making them a very potent drug delivery system, particularly for plant-based constituents. One of the important benefits of NLCs is the increased drug loading capacity achieved by the presence of both solid and liquid lipids, which introduces imperfections in the lipid matrix. These imperfections enable the accommodation of larger amounts of lipophilic or poorly water-soluble ingredients in an efficient manner. Regarding stability, NLCs are superior to liposomes and polymeric nanoparticles, as they are less prone to drug leakage, aggregation of particles, and degradation over a period of time. NLCs also exhibit drug delivery in a controlled and sustained manner, which results in constant therapeutic levels during administration and minimizes the requirement for dosing frequencies. NLCs' composition of physiological lipids is known for outstanding biocompatibility and biodegradability, which enhances their safety profile. NLCs ensure effective protection for drugs encapsulated in them, which protects sensitive phytoconstituents from enzymatic degradation, pH changes, exposure to light or oxygen. These carriers greatly increase bioavailability by enhancing solubility, membrane permeability, and lymphatic delivery, resulting in higher systemic exposure of the drug. NLCs are also very versatile and support various forms of administration like oral, intravenous, pulmonary, topical, and transdermal delivery based on formulation requirements. These combined benefits make NLCs a superior nanocarrier system of choice for delivery of difficult therapeutic agents like phytoconstituents.

Mechanism of Drug Delivery via NLCs:

The therapeutic potential of Nanostructured Lipid Carriers (NLCs) in drug delivery, particularly in cancer therapy, is mainly due to their capacity to facilitate drug transport, accumulation, and cell uptake by one or a combination of complementary mechanisms. To begin with, NLCs greatly enhance the solubilization and transport of poorly water-soluble plant secondary metabolites, enabling them to permeate across biological membranes by endocytosis or passive diffusion. After oral administration, their lipid matrix composition ensures lymphatic uptake, evading the hepatic first-pass metabolism, which greatly increases systemic availability. NLCs also make use of the increased permeability and retention (EPR) effect in the tumor microenvironment of tumors, such as lung cancer, passively accumulating in tumor sites where leaky tumor vasculature allows preferential nanoparticle retention. Finally, incorporation of stealth components such as PEGylated lipids enables NLCs to avoid recognition and clearance by the reticuloendothelial system (RES), ensuring extended bloodstream circulation. Their capacity to provide controlled drug delivery, responsive to environmental signals such as pH change or enzymatic activity, ensures extended therapeutic concentrations in the tumor environment. More importantly, upon cancer cell internalization, NLCs escape endosomal entrapment and discharge their drug payload directly to the cytoplasm, maximizing intracellular delivery and intensifying anticancer efficacy. Cumulatively, these capabilities make NLCs an exceptionally potent nanocarrier system for systemic and localized cancer therapy. (54-59)

Phytoconstituents in Lung Cancer Therapy

Potential Anti-Cancer Phytoconstituents

Phytoconstituents, or plant secondary metabolites, are bioactive molecules that are produced by plants to protect them from environmental stressors, pathogens, and herbivores. These molecules are known to contain a diverse range of pharmacologic characteristics that include anti-inflammatory, antioxidant, antimicrobial, and anticancer effects. In lung cancer, various phytoconstituents also showed considerable cytotoxicity, antiproliferative, and chemopreventive effects both in monotherapy as well as in combination with conventional chemotherapeutic drugs.

Following is a comprehensive overview of certain important phytoconstituents which have confirmed anticancer effects in lung cancer models:

Curcumin, a polyphenolic compound obtained from the rhizome of Curcuma longa (turmeric), holds immense interest for therapeutic applications in lung cancer. As a multi-targeting drug, curcumin induces anticancer effects by modulating various prominent signaling pathways implicated in tumor growth and resistance. It significantly inhibits the NF-κB pathway that is critical in cell proliferation, inflammation, and cell survival. It also blocks the STAT3, Akt, and mTOR pathways that are essential for tumorigenesis and metastasis. On a molecular level, curcumin induces cell death by activating pro-apoptotic

protein Bax and inactivating anti-apoptotic protein Bcl-2, shifting the balance in favor of cell death. It also affects G2/M phase cell cycle arrest, inhibiting cell division in cancer cells, and impairs angiogenesis by inhibiting vascular endothelial growth factor (VEGF) expression, restricting tumor growth by halting nutrition supply. Clinicically, curcumin also exhibits potential in chemotherapy and radiation sensitization of lung cancer cells, improving their efficacy and possibly minimizing systemic toxicity. It thus emerges as a strong natural adjuvant in lung cancer therapeutic strategies

Resveratrol, a plant metabolite present in grapes, berries, and peanuts, has drawn immense interest due to its powerful antioxidant and anti-inflammatory functions, especially in lung cancer therapy. Mechanistically, resveratrol causes anticancer effects by triggering apoptosis by activating the tumor suppressor protein p53, causing generation of reactive oxygen species (ROS), and activating caspase-3, the executioner of cell death. It also inhibits angiogenesis and invasion by suppressing vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), which are critical for tumor vascular supply and tissue invasion. In addition, resveratrol alters the metabolism of cancer cells by activating AMP-activated protein kinase (AMPK), disturbing the tumor growth-requiring break in the energy balance. Clinically, resveratrol is synergistic in combination with conventional chemotherapeutic drugs like cisplatin or paclitaxel in models of non-small cell lung cancer (NSCLC), improving efficacy without exacerbating drug resistance and side effects.

Quercetin, a flavonoid naturally present in onions, apples, and green tea, possesses strong anticancer efficacy, especially in lung cancer. It acts mainly by triggering intrinsic apoptosis, which is characterized by mitochondrial membrane depolarization, increased levels of reactive oxygen species (ROS), and activation of caspases, resulting in programmed death of cancer cells. Quercetin also inactivates the PI3K/Akt/mTOR pathway, a key controller of cell growth, survival, and metabolism in tumor cells. It also functions by inhibiting cancer dissemination by suppressing the expression of epithelial–mesenchymal transition (EMT) markers, thus inhibiting the metastasizing capacity of lung cancer cells. Quercetin clinically was also known to bypass multidrug resistance, a key problem in lung cancer treatment, and sensitize tumor cells to conventional chemotherapies, which increases the efficacy of drugs while potentially lessening side effects. Quercetin thus emerges as a strong natural adjunct in lung cancer therapy.

Epigallocatechin gallate (EGCG), the predominant catechin in green tea, is a potent anticancer compound that has been well studied in relation to lung cancer. Mechanistically, EGCG targets various pathways that contribute to tumor growth. EGCG inhibits epidermal growth factor receptor (EGFR) signaling, a pathway that is commonly overactivated in lung cancer, inhibiting cell growth and survival. EGCG also induces cell cycle arrest in the G1 phase, arresting cancer cell progression, and inhibits vascular endothelial growth factor (VEGF), decreasing angiogenesis and tumor vascularity. Importantly, EGCG increases gap junction intercellular communication (GJIC), a function that is compromised in cancer cells, to normalize cell signaling and inhibit malignancy. Clinically, EGCG exhibits chemopreventive potential and a capacity to act as a radiosensitizer in models of lung cancer, constituting a valuable natural compound for augmenting the efficiency of radiotherapy and potentially lowering resistance to treatments. Berberine, an isoquinoline alkaloid plant extract of the Berberis species, is known to exhibit strong anticancer activity against lung cancer. It induces G0/G1 cell cycle arrest, autophagy, and apoptosis, thus limiting tumor growth and cell proliferation. One of the principal mechanisms by which anticancer effects of berberine are mediated is by inhibiting the Wnt/β-catenin signaling pathway, which is critical for the migration and invasion of cancer cells. In addition, berberine-loaded nanoparticles also exhibit higher cell uptake and cytotoxicity, especially in the A549 lung carcinoma cell line, improving the overall therapeutic efficacy. Aside from berberine, various other interesting phytoconstituents also exhibit potential in lung cancer therapy. Luteolin exerts its anticancer effects by inhibiting the Akt/NF-κB pathway and inducing apoptosis. Apigenin inhibits COX-2 and activates the DNA damage response mechanism, resulting in anticancer effects. Kaempferol induces ROS-mediated cell death and inhibits anti-apoptotic protein expression, and genistein targets estrogen receptor pathways and inhibits cancer cell growth. Collectively, the natural compounds present in a diverse group of phytochemicals, each of which acts by means of a multi-pronged mechanism, provide complementary strategies for lung cancer therapy. (60-75)

Mechanisms of Action of Phytoconstituents in Lung Cancer

Phytoconstituents trigger anticancer effects by interacting on various cancer hallmarks, hence exhibiting strong potential as multitarget anticancer agents. Such wide-range efficacy contributes to their potential in combinational therapies and adjuvants in traditional cancer therapies. Induction of apoptosis is one of the major mechanisms where phytochemicals trigger critical enzymes such as caspases-3, -8, and -9, increase pro-apoptotic proteins that include Bax and p53, and inhibit anti-apoptotic molecules that include Bcl-2. They also destabilize mitochondrial membrane potential, a mandatory step in cell death induction. Further, phytoconstituents drive cell cycle arrest by controlling cyclins and CDKs, and in the process, arrest cell growth at G1, S, or G2/M phases. Anti-angiogenic activities restrict tumor expansion by inhibiting angiogenesis inducers such as VEGF and angiopoietins that are indispensable in tumor angiogenesis. Additionally, phytochemicals may prevent tumor spread by inhibiting EMT apparent by E-cadherin elevation and N-cadherin repression, as well as by inhibiting MMP-2, MMP-9, as well as integrin and chemokine receptor-dependent signaling pathways. Inflammatory signaling and oxidative stress, both of which are significant contributors to tumor development, are also regulated by phytoconstituents by inhibiting pro-inflammatory cytokines (e.g., TNF-α, IL-6) as well as signals mediated by activation of NF-κB, COX-2, and iNOS. Depending upon the cell context, these molecules may act as antioxidants or pro-oxidants and regulate the balance of free

radicals. Some phytochemicals also regulate epigenetic processes by inhibiting DNMTs, suppressing HDACs, and controlling microRNAs that include miR-21 and miR-34a. These combined actions make phytoconstituents valuable molecules in lung cancer therapy.

2. LIMITATIONS OF PHYTOCONSTITUENTS IN FREE FORM

Despite the therapeutic potential of phytochemicals, their clinical translation is limited due to several biopharmaceutical and pharmacokinetic drawbacks:

1. Poor Solubility

Many phytoconstituents are hydrophobic, leading to poor dissolution in gastrointestinal fluids and, hence, low absorption following oral administration.

2. Low Oral Bioavailability

Extensive first-pass metabolism in the liver and intestinal walls results in rapid breakdown and elimination, reducing systemic exposure.

3. Short Circulation Half-life

Phytochemicals are often rapidly cleared from systemic circulation, necessitating frequent dosing and potentially causing sub-therapeutic plasma levels.

4. Instability

Exposure to heat, light, or oxidative environments can degrade sensitive phytoconstituents during storage or in vivo administration.

5. Lack of Tumor Specificity

In their free form, phytoconstituents distribute non-specifically, which limits their accumulation in tumor tissues and increases the potential for off-target effects.

6. Resistance Development

Like synthetic drugs, prolonged exposure to phytochemicals may lead to cellular adaptation and resistance mechanisms in cancer cells.(76-90)

Addressing These Limitations with Nanocarriers

The use of Nanostructured Lipid Carriers (NLCs) has emerged as a powerful strategy to circumvent these challenges. NLCs:

Enhance solubility and permeability

Protect phytoconstituents from enzymatic degradation

Allow controlled and sustained release

Facilitate passive and active tumor targeting

Improve oral and intravenous bioavailability

Reduce systemic toxicity and enhance therapeutic index

The integration of phytoconstituents into NLCs offers a promising route to realizing their full potential in lung cancer therapy.

Development of Phytoconstituent-Loaded NLCs

Selection of Lipids and Surfactants

The foundation of an effective NLC formulation lies in the rational selection of lipids and surfactants, which play a critical role in determining not only the structural integrity but also the drug-loading potential, release profile, and stability of the carrier system.

Solid Lipids

Solid lipids are the base matrix of nanostructured lipid carriers (NLCs), functioning as areliable and structured matrix that encases and shields phytoconstituents. Choosing the right solid lipid is important as it directly affects multiple important parameters of the formulation. These include melting behavior—crucial in the case of hot homogenization procedures—as well as active compound solubility in the lipid matrix, controlling drug load capacity. Solid lipids impact particle size due to their capacity for modulating interfacial tension as well as play an important role in specifying the extent of crystallinity, in turn controlling drug retention as well as release rates. Glyceryl monostearate is one of the most commonly utilized lipids in NLC formulations due to its emulsification capacity in addition to its balanced drug loading potential; Compritol® 888 ATO, a polyingredient system of mono-, di-, and triglycerides that forms a less acceptable crystalline structure, perfect for drug

entrapment enhancement; Precirol® ATO 5, whose controlled release is due to its high melting point as well as thecompactness of its structure; and stearic acid, an ambiocompatible fatty lipidally often combined with other lipids in order optimize matrix features as well as overall performance.

Liquid Lipids (Oils)

The addition of liquid lipids in nanostructured lipid carriers (NLCs) is important in increasing their capacity for drug loading as well as stability. Liquid lipids disrupt the close packing crystalline structure of lipids as solids, generating an imperfect or less organized matrix that can entrap more drug molecules as well as prevent drug expulsion in storage. Liquid lipids enhance the solubility of hydrophobic phytoconstituents as well, such as making their uniform distribution in the system easier in the form of carriers. Typical examples include oleic acid, whose skin as well as mucosal permeating activity is especially prized, making it a candidate suitable for transdermal as well as pulmonary delivery routes. Caprylic/capric triglycerides like Miglyol® 812 are excellent solvent capacity providers for drugs that are poorly soluble in water as well as having minimal viscosity, making their formulating as well as processing easier. Squalene, being a natural lipid, enhances the fluidity in the lipid matrix while providing antioxidant protection, thus making the NLCs' functionality as well as biocompatibility better.

Surfactants

Surfactants are key constituents in nanostructured lipid carriers (NLCs), whose main function is reduction in interfacial tension and stabilization of the lipid dispersion through prevention of agglomeration of nanoparticles. In addition to stabilization, surfactants play an important role in affecting major formulation features such as drug release profile, size distribution of particles, biocompatibility, as well as zeta potential—depending on the involvement of ionic surfactants. Tweens like Tween 80 (also known as Polysorbate 80), non-ionic in nature, are preferred due to their mildness as well as compatibility with biological systems. Pluronic F68, a triblock copolymer, improves colloidal stability and prolongs circulatory half-life through resistance towards opsonization. Lecithin, being naturally occurring phospholipid (phosphatidylcholine), not only supports emulsification but is also conducive for ensuring enhanced bioavailability through membrane fusion. In most cases, the combination of hydrophilic and lipophilic surfactants is utilized for better stabilization, enhanced drug encapsulation, as well as controlled release patterns in the NLC system. (90-97)

Development of Phytoconstituent-Loaded NLCs (including lipids and surfactants)

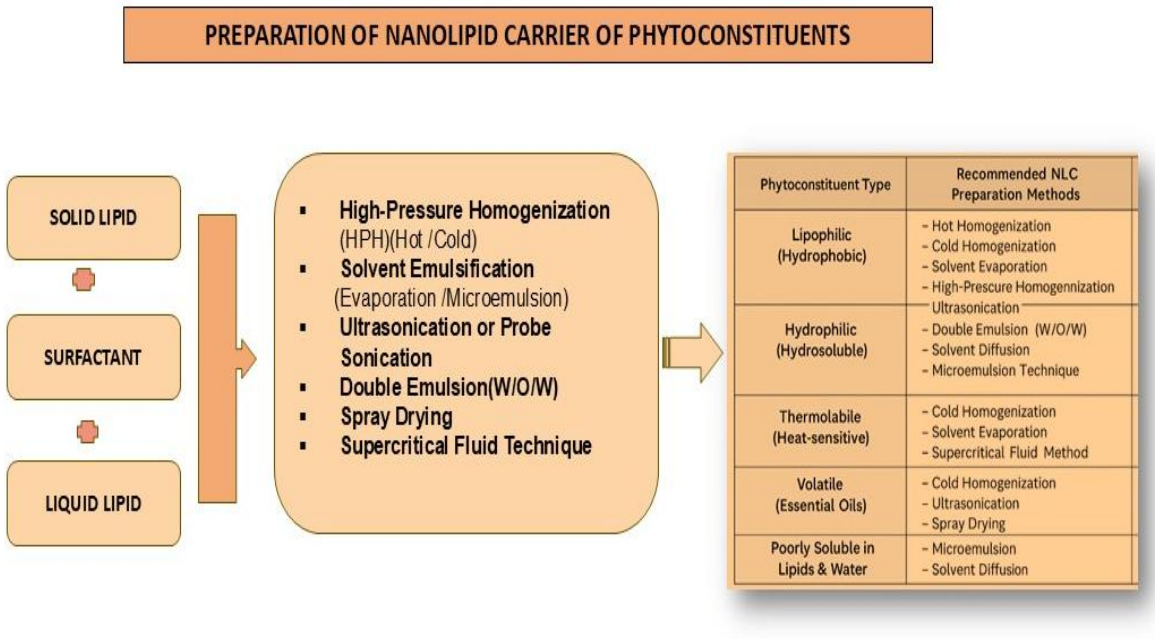
Preparation Methods

The method used to prepare NLCs significantly influences their size, morphology, drug loading, and reproducibility. Each method has its own advantages and limitations based on the physicochemical nature of the phytoconstituent and scalability requirements.

High-Pressure Homogenization (HPH) is the most extensively used method for bulk production of Nanostructured Lipid Carriers (NLCs) for reasons of scalability, reproducibility, and absence of organic solvents. Two major variations exist: Hot HPH and Cold HPH. In Hot HPH, lipids are melted above their melting point, and the drug is infused in this molten lipid. The lipid phase is emulsified in a hot aqueous solution of a surfactant under high pressure (usually 500–1500 bar) to create a nanoemulsion, then cooled instantly as an ice bath to crystallize the lipid into nanoparticles. It is applicable for thermally stable compounds. On the other hand, Cold HPH is suitable for thermolabile phytoconstituents. In this, the drug-lipid melt is chilled and hardened, milled into fine particles, and then dispersed in cold surfactant solution. It is homogenized without heating, resulting in nanosuspension. HPH has numerous benefits such as the absence of organic solvents, excellent scalability, and nanoparticles of uniform size generated. However, hot HPH may be unsuitable for heat-sensitive molecules. Another method is Ultrasonication or High-Shear Homogenization, in which the lipid melt is combined with an aqueous solution of the surfactant to create a coarse emulsion, which is then ultrasonicated in a probe sonicator to decrease the size of the particles. Though this is easy, inexpensive, and amenable for laboratory-scale or pilot-scale production, it is prone to metallic contamination using the probe as well as usually leading to higher particle sizes with higher polydispersity index (PDI) as opposed to HPH.

Solvent Emulsification-Evaporation is a multi-purpose method applied for the production of Nanostructured Lipid Carriers (NLCs), especially for thermolabile and poorly water-soluble phytoconstituents. By this method, both the drug and the lipid are initially dissolved in an organic solvent such as ethanol or dichloromethane. An aqueous solution of the surfactant is then emulsified with this organic phase under agitation, resulting in an oil-in-water emulsion. During emulsification, the organic solvent is progressively removed under vacuum, leading to the precipitation of the lipid and the creation of nanoparticles. This method is useful in having tight controls on the formulations in terms of size of the particles as well as encapsulation efficiency, but it is especially suitable for compounds having heat sensitivity or aqueous media poor solubility. However, the employment of possibly cytotoxic organic solvents demands great care in their removal for ensuring safety as well as biocompatibility of the final product. Moreover, this method is problematic in terms of environmental safety due to the use of solvents as well as their disposal, so it is not preferred for commercial applications on a bulk scale unless green solvent substitutes or recycling processes are utilized.

Microemulsion Technique involves the creation of an oil, surfactant, and co-surfactant hot microemulsion, subsequent rapid dilution in cold water, resulting in the precipitation of nanoparticles of lipid. This is an advantageous method in that it is a low-energy input, thermodynamically stabilized system that can be applied on the laboratory scale but is limited in that it tends to require high concentrations of surfactant that are potentially cytotoxic in in vivo applications. It is not a favored method for considerable scale-up due to challenges in stabilizing the microemulsion as well as controlling dilution on an industrial scale.



Drug Loading and Encapsulation Efficiency

Therapeutic efficacy of Nanostructured Lipid Carriers (NLCs) is directly related to the level of phytoconstituent encapsulation because DL (drug loading) and EE (encapsulation efficiency) have direct effects on dosage, cost, and therapeutic efficacy. Various parameters affect those parameters, such as drug solubility in the lipid matrix, compatibility between phytoconstituent and lipid phase, homogenization rate and duration, concentration and nature of the surface-active agent, as well as the drug-lipid ratio. Higher drug loading decreases the volume of the required formulation, thus minimizing therapeutic costs as well as improving compliance of patients. In addition, higher encapsulation efficiency reduces the concentration of free drug in the systemic circulatory system, hence minimizing off-target toxicity. Such factors are especially important for phytoconstituents with low efficacy or high expense, such as curcumin or paclitaxel, for maximization of delivery efficiency in such molecules significantly increases their therapeutic value.

Characterization of NLCs

Adequate characterization is important for successful development of Nanostructured Lipid Carriers (NLCs) as well as for their in vivo performance, particularly in lung cancer treatment. Particle size and polydispersity index (PDI) are generally measured with Dynamic Light Scattering (DLS). An optimal size between 100–200 nm is most suitable for efficient tumour targeting through the enhanced permeability and retention (EPR) effect. PDI below 0.3 is an indicator of the homogenous nanoparticles' population, necessary for expected biological behaviour. Smaller particles can increase cellular uptake as well as penetration in tumours, making them especially beneficial for lung cancer delivery.

Zeta potential is a measure of the charge at the surface of nanoparticles and is an indicator of their physical stability. An absolute zeta potential value high (generally above ±30 mV) gives rise to electrostatic repulsion among particles, discouraging aggregation as well as shelf-life enhancement. In addition, zeta potential affects the interaction between NLCs and biological membranes, influencing cellular localization as well as biodistribution.

Morphological studies using methods such as Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) reveal details about the shape as well as surface features of the NLCs. These studies ensure successful formation of nanoparticles as well as assess the spherical and smooth nature of the particles, as is typically required for improved drug bioavailability as well as for controlled drug delivery.

Thermal analysis methods like Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) are utilized in order to assess crystallinity as well as drug-lipid interactions in the NLCs. DSC detects thermal transitions as well as drug-lipid

compatibility, whereas XRD picks up polymorphic transitions or drug amorphization, both of which have significant effects on drug solubility as well as release rates.

In vitro drug release experiments are crucial in determining how the phytoconstituent is released over time. In vitro experiments are commonly carried out using dialysis or Franz diffusion cells, utilizing release media like phosphate-buffered saline (PBS), simulated lung fluid, or simulated intestinal/gastric fluids (SIF/SGF). The resultant data are evaluated based on kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas, each providing information on drug release mechanism.

Finally, stability studies following ICH regulations at varying storage environments (such as 4°C, 25°C, and 40°C) are important in establishing the shelf life of the product. Stability studies measure the changes in particle size, zeta potential, encapsulation efficiency, as well as how visual aspects like aggregation or phase separation are affected over time. Stability data confirm that the NLCs are safe, effective, and in line with their intended storage duration. (109-111)

5 Recent Formulations and Studies

Recent developments in NLCs loaded with phytoconstituents mirror the increasing synergy between natural product-oriented cancer therapies and nanotechnology. These novel formulations are not just transcending solubility as well as stability issues but are also enhancing therapeutic efficiency in lung cancer models.

Curcumin, a bioactive molecule of Curcuma longa origin, is extensively known for its anti-inflammatory, antioxidant, and anticancer activities. Though those benefits are valuable, its therapeutic applicability has been hampered due to its poor aqueous solubility, stability, and poor bioavailability. Encapsulation of curcumin in Nanostructured Lipid Carriers (NLCs) has been found to increase its therapeutic activity significantly. Curcumin-loaded NLCs provide enhanced solubility as well as stability, ensuring higher protection against degradation as well as efficient intracellular delivery, especially in lung epithelial cancer cell lines like A549 and H1299. These formulations have been found to result in significant reduction of tumor volume in lung cancer xenograft models. Curcumin-loaded NLCs are found to suppress epithelial-to-mesenchymal transition (EMT), the central process in cancer metastasis. Mechanistically, the NLC format increases the capability of curcumin in downregulating pro-survival markers such as NF-κB as well as STAT3, inducing apoptosis via caspase-3 activation, as well as suppressing the expression of proliferation-associated proteins like cyclin D1 as well as the anti-apoptotic protein Bcl-2.

Resveratrol, a natural polyphenolic stilbenoid, shows broad-spectrum anticancer efficacy through targeting multiple oncogenic signaling routes. However, it does not hold therapeutic value due to rapid metabolism and poor availability. Encapsulation of resveratrol in Nanostructured Lipid Carriers (NLCs) has shown promising results in resolving these issues. Resveratrol loaded in NLCs significantly increases plasma half-life as well as systemic circulation, improving availability and therapeutic reach. In lung cancer models, such formulations show remarkable efficacy in suppressing vascular endothelial growth factor (VEGF) expression, suppressing angiogenesis in the tumor microenvironment. Moreover, resveratrol-loaded NLCs exhibit synergy in combination with radiation or chemotherapics such as doxorubicin, increasing anticancer efficacy in preclinical models. Mechanistically, resveratrol administered via NLCs causes DNA fragmentation, induces mitochondrial dysfunction leading to apoptosis, as well as modulates key signaling routes such as PI3K/Akt as well as Wnt/β-catenin, both of them critical for cancer cell proliferation as well as survival.

Quercetin, whose established apoptosis-inducing and anti-proliferative activities have made it promising for cancer therapy, especially for lung cancer, is compromised in its clinical use due to poor solubility in water and fast metabolism. Quercetin encapsulated in Nanostructured Lipid Carriers (NLCs) has been found to significantly improve its therapeutic value. Quercetin-NLCs result in significantly higher drug deposition in lung tissue, ensuring higher local drug concentrations at the tumor site. These formulations ensure controlled drug release for up to 48 hours and thereby prolong the therapeutic window while minimizing frequent dosing requirements. These formulations minimize systematic toxicity as well as inflammation associated with free drug administration. Mechanistically, quercetin delivered through NLCs is found to confer anticancer action through inducing the generation of ROS, cell cycle arrest at the G2/M phase, as well as suppression of proliferation pathway mediated through MAPK as well as EGFR, thereby leading to an improved and targeted lung cancer therapeutic approach.

Other phytoconstituents have also been investigated for their therapeutic value in lung cancer through encapsulation in Nanostructured Lipid Carriers (NLCs), again demonstrating the versatility of this drug delivery platform. Berberine, an isoquinoline alkaloid, shows pronounced anti-proliferative activity, and when encapsulated in NLCs, its solubility is enhanced along with its ability to exert hepatoprotective action. Thymoquinone from Nigella sativa induces apoptosis through downregulation of anti-apoptotic proteins, and NLC encapsulated thymoquinone has been found to decrease hepatotoxicity, increasing the safety profile of the compound. Betulinic acid, a pentacyclic triterpenoid, activates apoptosis via the intrinsic mitochondrial pathway, whereas EGCG, a green tea catechin, prevents metastasis as well as reverts epithelial-to-mesenchymal transition (EMT), an important step in cancer progression. Together, these studies support the position of NLCs as an incredibly versatile and useful platform for increasing the therapeutic efficacy as well as

bioavailability of a range of phytochemicals for lung cancer therapy.

Targeted Drug Delivery Approaches

To enhance the precision of drug delivery, NLCs have been modified to specifically target tumor cells using passive and active targeting mechanisms, reducing off-target effects and increasing therapeutic efficiency.

Passive Targeting via Enhanced Permeability and Retention (EPR)

Solid tumors, including lung tumors, exhibit:

Abnormal vasculature with leaky capillaries (100–800 nm pores)

Poor lymphatic drainage

NLCs in the 100–200 nm size range can:

Accumulate at tumor sites due to the EPR effect

Remain at the tumor longer, enhancing local drug concentration

NLCs exploit the tumor microenvironment's architecture to increase site-specific drug localization without needing specific ligands.

Active Targeting via Surface Ligands

Functionalization of NLCs with ligands enables receptor-mediated endocytosis in cancer cells.

Examples:

Folic acid (FA): Targets folate receptors overexpressed in NSCLC. FA-NLCs increase internalization and cytotoxicity in A549 cells.

Transferrin: High affinity for transferrin receptors; enhances uptake in rapidly dividing lung tumor cells.

EGFR-targeted peptides: Useful in EGFR-mutant NSCLC, especially T790M-resistant variants.

Hyaluronic acid (HA): Targets CD44 receptors, abundant in metastatic lung tumors.

These ligands increase selectivity and reduce systemic toxicity, offering a major advancement over untargeted systems.

Stimuli-Responsive NLCs

Smart drug delivery systems are sophisticated frameworks for releasing their therapeutic content in response to certain internal or external cues, allowing for controlled drug release in targeted fashion. These include pH-sensitive NLCs, taking advantage of the acidic tumor microenvironment (pH ~6.5–6.8), distinct from the normal physiological pH of 7.4. These systems frequently involve acid-cleavable linkages, such as hydrazone bonds that are destroyed in acidic environments, leading to localized release of the drug. Redox-sensitive NLCs are another system, based on the high intracellular glutathione (GSH) content found in cancerous cells. These exploit disulfide bonds that are cleaved in high-GSH environments, leading to drug release within cancerous cells. Enzyme-sensitive NLCs are designed to be degraded in the presence of enzymes like matrix metalloproteinases (MMP-2/9) or cathepsins, commonly overexpressed in lung cancer, allowing for target delivery. Externally triggered systems—such as magnetic or thermo-sensitive NLCs—allow for site-specific deposition and release through external stimulation in the form of magnetic fields or heat. These intelligent NLCs reduce drug leakage before reaching the target, improve tumor selectivity, and have significant applications in precision oncology.

Combination Therapy: Phytoconstituents with Chemotherapeutic Agents

One of the most encouraging nanomedicine breakthroughs in lung cancer therapy is co-encapsulation of phytoconstituents together with conventional anticancer drugs within the single nanostructured lipid carrier (NLC) system. Such drug combination in one system allows for synergistic therapeutic action, enhanced efficacy, as well as minimizing drug resistance. Rationale in this two-component combination is based on the capacity of phytoconstituents for modulating drug-resistant cellular pathways, as well as for stimulating apoptosis in combination with concurrently protecting normal cells, thereby minimizing the unfavorable effects typical for chemotherapy. For example, co-delivery of curcumin together with cisplatin in NLCs demonstrates enhanced cytotoxic action toward A549 and H460 lung cancer cell lines. Not only does curcumin enhance the pro-apoptotic effect of cisplatin but it also suppresses its nephrotoxic side effects. In the same manner, quercetin in combination with doxorubicin in double-loaded NLCs exerts cardioprotection due to the antioxidant nature of quercetin while amplifying regression of the tumor as well as minimizing systemic toxicity. Another effective combination is that of resveratrol in combination with erlotinib, where NLCs overcome resistance toward EGFR tyrosine kinase inhibitors due to resveratrol's action on the PI3K/AKT pathway that restores cancer cell sensitivity toward erlotinib significantly improving the therapeutic efficacy. These examples highlight the promising capacity of combination-loaded NLCs as a revolutionary platform in lung cancer therapy.

Mechanistic Insights

Inhibition of MDR proteins like P-glycoprotein (P-gp), which expel chemotherapy drugs

Suppression of survival pathways (e.g., NF-κB, MAPK) that are upregulated during chemotherapy

ROS generation, leading to increased DNA damage in cancer cells

Such combination-loaded NLCs serve as multi-targeted platforms, disrupting cancer progression on several fronts simultaneously.

Here are references in Vancouver style supporting the information provided on nanostructured lipid carriers (NLCs) loaded with phytoconstituents for lung cancer therapy:

Please ensure to verify these references and adjust the author names and details according to the specific articles you are citing. (111-137)

6. Applications of Phytoconstituent-Based NLCs in Lung Cancer

Nanostructured lipid carriers (NLCs) provide a versatile platform that can be adapted for various routes of drug administration. Depending on the clinical objective, site of action, and properties of the phytoconstituent, NLCs can be designed for oral, pulmonary, intravenous, and even transdermal delivery.

Oral Drug Delivery

Oral administration remains the most preferred route for drug delivery due to its non-invasive nature, ease of self-administration, and high patient compliance. However, its application in delivering phytoconstituents is often limited by challenges such as poor water solubility, instability in the gastrointestinal (GI) environment, and significant first-pass hepatic metabolism. Nanostructured lipid carriers (NLCs) offer a promising solution to these issues by encapsulating phytochemicals in a protective lipid matrix, which shields them from enzymatic degradation and pH-related instability. Furthermore, NLCs enhance the solubility and absorption of lipophilic compounds, extend gastric residence time through mucoadhesive interactions, and can inhibit efflux mechanisms like P-glycoprotein (P-gp), which otherwise reduce drug uptake. For instance, curcumin-loaded NLCs have demonstrated up to an eight-fold increase in oral bioavailability in animal studies, leading to improved systemic circulation and tumor targeting. Similarly, quercetin-NLCs have shown significantly higher plasma levels and sustained drug release over 24 hours. Mechanistically, NLCs are absorbed via specialized M cells in Peyer's patches, undergo lipid digestion to form mixed micelles that facilitate lymphatic transport, and can promote chylomicron formation—thus partially bypassing the liver's first-pass metabolism. This makes oral NLC formulations particularly suitable for chronic lung cancer management, where long-term, nutraceutical-like, or adjunctive therapy may be beneficial. (135-147)

Pulmonary Drug Delivery (Inhalable NLCs)

Inhalation therapy is an efficacious mode of lung cancer therapy through direct drug administration into the lungs, allowing localized action, systemically decreased toxicity, as well as the ability for lower effective doses. In terms of size, nanostructured lipid carriers (NLCs) are ideal for inhalation due to their favorably compact size, allowing for deep lung deposition, in particular in the alveolar space where the tumor usually is located. NLCs can be designed for aerosol delivery via nebulization or in dry powder inhalers (DPIs), allowing versatility in administration routes. NLCs' action at the target area increases their local availability as well as their onset of action, due to the high surface area of the lungs as well as the thin epithelial membrane covering it. For optimal deposition, particles ranging between 1–5 μm are optimal; as such, NLCs are generally encapsulated within larger carriers such as lactose for DPIs. For stability in aerosolization, aids such as surfactants as well as cryoprotectants such as mannitol are utilized, especially in spray-drying processes. Research conducted has proved effective in this regard—EGCG-loaded NLCs administered via inhalation showed better regression of the tumor in comparison to oral or intravenous routes, whereas curcumin-DPI-NLCs showed sustained lung retention as well as reduced systemically-exposed amounts. In summary, inhalation of NLCs is dependent on their direct, localized, as well as efficient targeting at the lung tumor site. (145-150)

Intravenous Drug Delivery

Intravenous (IV) administration is an important route for the management of advanced or metastatic lung cancer, providing for the rapid entry of therapeutic compounds into the systemically flowing blood for immediate action on cancer sites. Nanostructured lipid carriers (NLCs) improve the efficacy of IV delivery through protecting sensitive phytochemicals against enzymatic degradation in plasma as well as enabling controlled, sustained drug release. In contrast to conventional formulations often requiring the use of cytotoxic solvents such as Cremophor EL (used with paclitaxel), NLCs minimize the occurrence of infusion-associated hypersensitivity reactions, ensuring enhanced patient safety. In addition, NLCs allow for passive targeting by the enhanced permeability and retention (EPR) effect as well as active targeting upon functionalization with ligands, ensuring preferential localization in cancer tissue. In order for NLCs to be acceptable for IV administration, they should be sterile, isotonic, free of pyrogens, as well as physiologically stabilized. PEGylation is often used for surface modification in order to prevent their rapid removal by the mononuclear phagocytic system (MPS), thereby prolonging the

circulation half-life. For example, resveratrol-loaded NLCs injected intravenously showed extended plasma half-life, decreased clearance, as well as enhanced targeting of the tumor, whereas paclitaxel-phytochemical co-loaded NLCs exerted synergistic anticancer effects with decreased systematic toxicity. In summary, IV-administered NLCs are an effective approach towards the treatment of late-stage lung cancer as well as for systemically metastatic disease.These studies highlight the efficacy of IV-administered NLCs in enhancing the delivery and therapeutic effects of phytoconstituents for lung cancer treatment. (151-159)

Topical and Transdermal Applications

Intravenous (IV) administration is an important route for the management of advanced or metastatic lung cancer, providing for the rapid entry of therapeutic compounds into the systemically flowing blood for immediate action on cancer sites. Nanostructured lipid carriers (NLCs) improve the efficacy of IV delivery through protecting sensitive phytochemicals against enzymatic degradation in plasma as well as enabling controlled, sustained drug release. In contrast to conventional formulations often requiring the use of cytotoxic solvents such as Cremophor EL (used with paclitaxel), NLCs minimize the occurrence of infusion-associated hypersensitivity reactions, ensuring enhanced patient safety. In addition, NLCs allow for passive targeting by the enhanced permeability and retention (EPR) effect as well as active targeting upon functionalization with ligands, ensuring preferential localization in cancer tissue. In order for NLCs to be acceptable for IV administration, they should be sterile, isotonic, free of pyrogens, as well as physiologically stabilized. PEGylation is often used for surface modification in order to prevent their rapid removal by the mononuclear phagocytic system (MPS), thereby prolonging the circulation half-life. For example, resveratrol-loaded NLCs injected intravenously showed extended plasma half-life, decreased clearance, as well as enhanced targeting of the tumor, whereas paclitaxel-phytochemical co-loaded NLCs exerted synergistic anticancer effects with decreased systematic toxicity. In summary, IV-administered NLCs are an effective approach towards the treatment of late-stage lung cancer as well as for systemically metastatic disease. (160-168)

Summary Table: Route-Specific Applications of Phytoconstituent-Loaded NLCs

Route of Administration	Advantages	Phytoconstituents	Examples/Outcomes
Oral	Non-invasive, enhanced bioavailability, lymphatic uptake	Curcumin, Quercetin, Resveratrol	Improved systemic levels, prolonged release
Pulmonary (Inhalation)	Local targeting, rapid action, reduced systemic toxicity	EGCG, Curcumin	High lung accumulation, direct tumor targeting
Intravenous	Rapid onset, systemic distribution, active targeting	Paclitaxel, Resveratrol, Betulinic acid	Enhanced circulation time, reduced side effects
Transdermal/Topical	Bypasses liver, prolonged delivery, skin access	Quercetin, Curcumin	Potential for palliative therapy or systemic delivery

7. Pharmacokinetics and Bioavailability of NLCs

A therapeutic agent's clinical effectiveness, especially phytoconstituents, is mostly dependent on its pharmacokinetic profile—how the drug is metabolized, absorbed, distributed, and excreted in the body. Because of their poor solubility, instabilities, and high rate of metabolism, most phytoconstituents are poorly absorbed in the gut orally, thereby restricting their therapeutic applications.

NLCs are engineered to overcome such limitations by enhancing such compounds' absorption, stability, as well as controlled release. This section emphasizes how NLCs impact the pharmacokinetics as well as the bioavailability of phytoconstituents, as substantiated through in vitro as well as in vivo data.

Enhancement of Bioavailability of Phytoconstituents

Bioavailability challenges in free phytoconstituents and the role of NLCs

Free phytoconstituents are greatly hindered in their bioavailability by multiple physiological as well as biochemical barriers.

Their poor aqueous solubility is one of the main issues, as it impedes their absorption through biological membranes. Moreover, extensive first-pass metabolism in the liver can metabolize these active compounds prematurely as they enter systemic circulation, significantly lowering their efficacy. Efflux action of P-glycoprotein (P-gp) in intestinal cells is another factor that reduces absorption as it actively pumps out the drugs into intestinal lumens. Moreover, numerous phytoconstituents have a brief plasma half-life, for which therapeutic drug concentrations are required through frequent dosing.

These constraints are overcome by nanostructured lipid carriers (NLCs), which are an effective delivery system that greatly enhances the hydrophobic phytoconstituents' bioavailability, such as curcumin, quercetin, and resveratrol. NLCs enhance dissolution rate as well as solubility with the help of lipid matrices that enhance the solubilization of poorly water-soluble drugs. NLCs enhance lymphatic uptake due to chylomicron-mediated transport through the intestinal lymphatic system, circumventing hepatic first-pass effect and raising the level of active compounds in the systemic circulation.

An important action is the inhibition of efflux pumps; surfactants like Tween 80 and Poloxamers, and lipids such as glyceryl behenate suppress P-gp, thus ensuring that more drug is absorbed. NLCs ensure sustained as well as controlled drug release, frequently yielding a biphasic drug release profile—the initial burst after a slow drug release, ensuring therapeutic levels are maintained continuously. Lipid encapsulation prevents phytoconstituents from enzymatic as well as oxidative degradation in the gut.

Studies have established the ability of NLCs to increase phytoconstituents' bioavailability. An increase in oral bioavailability by 6–8-fold compared to free curcumin is evident in curcumin-loaded NLCs, for instance. Quercetin-NLC significantly improved the half-life, increasing it from about 1.5 hours to the range of 8–10 hours in rats, whereas Resveratrol-NLC improved plasma retention as well as postponed the time required reaching peak plasma concentration (Tmax).

Overall, NLCs provide a revolutionary method of drug delivery in that they enhance the pharmacokinetic profile of phytoconstituents, providing the active ingredients in higher concentrations at the targeted site of action at therapeutic concentrations.(168-70)

In Vivo and In Vitro Studies on Phytoconstituent-Loaded NLCs

In vitro analysis is vital in assessing the performance of nanostructured lipid carriers (NLCs) based on drug release kinetics, cytotoxicity, cellular uptake, as well as permeability on suitable cell lines and synthetic membrane systems. Studies on cytotoxicity have indicated phytoconstituent-loaded NLCs having significantly higher cytotoxic activities on lung cancer cell lines like A549 and H1299 in comparison with their free drug forms. This is reflected in significantly lower IC_{50} values, showing that lower concentrations of NLC formulation are necessary for inhibiting cell viability in 50%. Fluorescence-labeled uptake studies on NLCs reveal higher cellular uptake via clathrin- as well as caveolae-mediated endocytosis. Targeted NLCs like folic acid modified NLCs reveal even higher uptake in receptor-overexpressing lung cancer cells, reflecting effective active targeting. Drug release studies on phytoconstituent-loaded NLCs confirm the delivery system having sustained release within 24-72 hours, with release exhibiting Higuchi or Korsmeyer-Peppas type kinetics in many cases, reflecting diffusion-controlled release.

Supporting in vitro findings, in vivo studies reveal important pharmacokinetic as well as biodistribution information on NLCs, establishing their in vivo efficacy in real-time. Pharmacokinetic parameters like Cmax (peak plasma concentration) are remarkably higher in NLC formulations, whereas Tmax is retarded, indicating sustained drug release. In addition, elevation in AUC (area under plasma concentration-time curve) as well as t½ (half-life) suggests enhanced systemic exposure as well as extended duration of circulation, enabling less frequent administration dosing. Biodistribution measurements further reveal the efficacy of NLCs in accumulating in lung tissue, particularly in the case of pulmonary or intravenous administration routes.

Notably, decreased drug deposition in such off-target organs as the kidney and the liver suggests lower systemic toxicity.

Notably, therapeutic efficacy measurements in lung tumor-bearing mice with phytoconstuent-loaded NLCs have revealed considerable reduction in tumor volume, improved survival, as well as beneficial histopathological effects. Cumulatively, these studies highlight that NLCs are not only improving pharmacokinetic profiles but are also leading to significant enhancements in therapeutic efficacy in vivo, supporting their roles as effective drug delivery vehicles for phytoconstituents. (172-78)

Toxicity and Safety Considerations

Safety and Toxicity Profile of Phytoconstituent-Loaded NLCs

In vitro testing is important in assessing the performance of nanostructured lipid carriers (NLCs) based on drug release kinetics, cytotoxicity, cellular uptake, and permeability using suitable cell lineages and synthetic membranes. Studies on cytotoxicity revealed that phytoconstituents are found in NLCs with significantly higher cytotoxic activity against lung cancer cell lineages like A549 and H1299 as compared to free drug controls. This is reflected in considerably lower IC_{50} values, demonstrating that fewer concentrations of the NLC construct are necessary in order to inhibit 50% of cell survival

rates. Fluorescence-labeled cellular uptake studies reveal While nanostructured lipid carriers (NLCs) are mostly made of lipids and GRAS (generally regarded as safe) surfactants, it is important that their safety profile is extensively evaluated, especially for therapeutic use for an extended duration of time. In vitro toxicity investigations have ascertained that NLC formulations are tolerated in the cellular level quite adequately. Hemolysis analyses depict negligible damage on erythrocytes, demonstrating considerable hemocompatibility. Interestingly, cell viability assays affirm that blank NLCs (drug-free formulations) are non-toxic at therapeutic doses, supporting their biocompatibility.

In vivo toxicity testing confirms NLC safety as well. Acute as well as sub-chronic toxicity studies indicate no remarkable changes in body weight, haematological values, or biochemical markers in drug-treated animals. Histological evaluation of important organs, such as the liver, kidneys, as well as spleen, confirms normal tissue structure, demonstrating the lack of organ toxicity. From an immunogenicity point of view, PEGylation of NLCs has been found to suppress opsonization and evade immune detection, minimizing the likelihood of accelerated blood clearance. In addition, long-term administration of NLCs does not trigger substantial immune responses, highlighting the use of NLCs in chronic applications.

Compliance at the regulatory level, the development of NLCs is guided with stringent regulations requiring the use of compatible lipids like glyceryl monostearate and Compritol, without the use of irritants or allergens. Notably, therapeutic concentrations of phytoconstituent-loaded NLCs are kept within approved indices of safety for their safe use in clinics.

In summary, phytoconstituent-incorporated NLCs have a great safety and tolerability profile such that they are suitable for long-term administration in lung cancer therapy, even for diseases with a long duration and in palliative treatments.

increased internalization through clathrin- and caveolae-mediated endocytosis. Targeted NLCs, for example, those surface modified with folic acid, exhibit even greater uptake in receptor-overexpression lung cancer cells, reflecting successful active targeting. Further, drug release studies validate that phytoconstituents-loaded NLCs exhibit sustained release in the range of 24-72 hours, with release profiles following Higuchi or Korsmeyer-Peppas kinetics, reflecting diffusion-controlled release.

While complementing the in vitro findings, in vivo studies reveal important information on the pharmacokinetics and biodistribution of NLCs, ascertaining in vivo efficacy in real-time. Pharmacokinetic values of chief importance such as peak plasma concentration are higher for NLC formulations, whereas Tmax is slowed, substantiating prolonged release of the drug. Besides, enhanced values of AUC (area under the plasma concentration-time curve) as well as t½ (half-life) indicate enhanced systemic exposure and extended duration of blood flow, making possible less frequent dosing. Biodistribution studies emphasize the effectiveness of NLC in lung tissue targeting, in particular, upon delivery through pulmonary or intravenous routes. Notably, drug deposition in off-target organs such as the kidney as well as the liver is decreased, ensuring lower overall toxicity.

Notably, therapeutic efficacy in lung tumor-bearing mice that were treated with phytoconstituent-loaded NLCs has been shown to result in the reduction of tumor volume, enhanced survival, as well as beneficial histopathological effects. Together, these data highlight that NLCs do not just promote pharmacokinetic enhancement but are also capable of providing genuine enhancements in therapeutic activity in vivo, supporting their value as effective drug delivery vehicles for phytoconstituents.

Parameter	Free Phytoconstituents	NLC-Encapsulated Phytoconstituents
Solubility	Low	Significantly improved
Bioavailability	<5%	Up to 10–15 fold increase
Plasma half-life	Short (~1–2 hrs)	Extended (~8–12 hrs)
Targeting	Non-specific	Tumor-specific (EPR, ligands)
Toxicity	Dose-dependent	Lower due to controlled release
Efficacy	Limited	Enhanced due to higher accumulation

8. Challenges and Future Perspectives

Despite the promising preclinical outcomes of phytoconstituent-loaded NLCs in lung cancer, several scientific, technological, and regulatory challenges still need to be addressed for successful clinical translation. These challenges span across formulation development, scale-up, biological safety, regulatory hurdles, and patient-specific considerations.

Limitations of NLC Technology in Lung Cancer Therapy

Difficulties and Shortcomings of Phytoconstituent

Even with the huge promising of nanostructured lipid carriers (NLCs) in the improvement of phytoconstituent delivery, some challenges remain that are hampering their broad applicability and clinic translational applications. One of the main

challenges is the complexity of formulations, as choosing proper lipids involves drug solubility, stability, and release kinetics compensation. Is the compatibility between phytoconstituents and lipid matrices is another important requirement, as natural compounds are mostly unconjugated or even reactives chemicals. Finally, natural lipid sources can bring about batch-to-batch variability, influencing reproducibility as well as scalability.

One such limitation is encapsulation efficiency, particularly for phytoconstituents of high molecular weight or hydrophilic in nature that are difficult to encapsulate in lipid matrices in the first place. In addition, plant extracts are usually multi-active compounds, making it difficult for the loading strategy, resulting in variable dosing and therapeutic responses.

Instability problems otherwise affect the efficacy and shelf-life of NLCs as well. Over time, it may lead to particle aggregation as well as phase separation, whereas chemical degradation like oxidation of curcumin may affect therapeutic activity. Cold storage requirement is problematic in terms of logistics, especially in resource-limited environments.

Targeting and biodistribution pose other challenges. Although passive targeting via the EPR effect is somewhat tumor-selective, it is highly dependent on vascularization of the tumor. Active targeting through mechanisms like ligand-decorated NLCs is usually hampered by poor specificity owing to heterogeneity in receptor expression across different patients as well as the dynamic nature of tumor biology.

Biological obstacles also impact the efficiency of NLCs. For inhalation formulations, mucus within the respiratory system can block deep penetration within the lungs. Administration systemically can result in RES nonspecific uptake, leading to deposition in the spleen and liver. In addition, non-PEGylated NLCs are susceptible towards immune recognition as well as rapid deposition, decreasing their blood circulation half-lives as well as therapeutic outcomes.

Lastly, there is limited translation in clinic. While there are multiple in vitro as well as preclinical studies in favor of phytoconstituent-loaded NLCs, human clinic trials are few in numbers. It is difficult to convert encouraging findings in animal models into human therapy because of physiological variations as well as the intricacy of human disease.

In general, NLCs are beneficial for the delivery of phytoconstituents, but limitations indicate the necessity for continuous optimization of formulations, targeted delivery schemes, and extensive clinical validation for their effective use in lung cancer treatment.

Regulatory Aspects and Clinical Translation

Regulatory and translational challenges in NLC-Based phytoconstituent therapies

Although nanostructured lipid carriers (NLCs) boast therapeutic potential in phytoconstituents' delivery, there are multiple regulatory and translational challenges associated with their clinical progress. Perhaps the key challenge is standardization as it is as yet uncertain where NLCs fall under standard regulatory schemes such as those of the FDA or the EMA. Uncertainty in regulation creates complexities in approval, particularly with natural compounds due to their variability in source, purity, and stability. Increased difficulty in the use of phytoconstituents indeed compounds the problem of ensuring consistency among batches.

Toxicological evaluation remains a critical requirement for regulatory approval. Comprehensive safety assessments must include acute and chronic toxicity studies, as well as genotoxicity, reproductive toxicity, and carcinogenicity testing—particularly vital for formulations intended for cancer therapy. Long-term studies are necessary to evaluate potential immunogenicity and understand the biodistribution of NLCs within the body.

Also, there are inherent challenges in the scale-up of NLC production. Industrial scale manufacturing needs uniform particle size, encapsulation efficiency, and homogeneity of the formulation. Methods such as high-pressure homogenization as well as ultrasonication need direct calibration and validation in scale-down from lab scale to industrial scale. Moreover, sterility as well as shelf stability is necessary, particularly for injectable as well as inhalable NLC formulations used in the clinical form.

NLC-based phytoconstituent therapies need to be carefully designed for clinical trial procedures. Trials need to include pharmacokinetic and biodistribution evaluations in great detail for the NLC formulations. In combination therapies, drug-drug interactions should be carefully studied if NLCs are used in combination with other drugs. Targeted NLCs also require biomarker or receptor expression-driven patient stratification in order to maximize efficacy and minimize variability in response.

In summary, there are still major regulatory challenges in bringing NLC-based phytoconstituent therapies from the laboratory stage to the clinic. Overcoming such challenges requires stringent standardization, cutting-edge manufacturing procedures, and properly designed clinical trials for the realization of the maximum benefits of NLCs in the field of precision medicine.

Future Research Directions

The prospect of nanostructured lipid carriers (NLCs) for phytoconstituent delivery is quickly advancing, with novel avenues focusing on increasing therapeutic accuracy, safety, and environmental responsibility. One such focus area is the creation of

sophisticated targeting methods, such as the use of ligand-modified NLCs with antibodies, peptides, or aptamers for the purpose of tumor-targeting delivery. Another area is the designing of stimulus-response NLCs that can be made to release their content in response to tumor-specific markers such as acidic pH, high enzyme activity, or reactive oxygen species (ROS), thereby ensuring site-mediated drug release and avoiding off-targeting effects.

Hybrid delivery systems are increasingly being integrated, specifically through lipids-polymer hybrid nanoparticles designed that combine the biocompatibility of lipids with the structural stability of polymers. Such systems can expand further into multiple-functional NLCs, or theranostics, that encapsulate therapeutic agents as well as diagnostic markers for simultaneous therapeutic intervention along with monitoring in real-time.

With the increasing focus on personalized medicine, there are attempts to formulate NLCs that take into account an individual patient's genetic profile as well as metabolic profile. Artificial intelligence (AI) and machine learning (ML) are increasingly being applied toward streamlining lipid composition, drug loading, as well as release kinetics for optimal efficacy with minimum toxicity.

Combination therapies are another promising avenue, where NLCs are utilized for co-delivery of phytoconstituents with conventional chemotherapy agents in one compound. This can potentially increase the efficacy of the treatment, minimize side effects, as well as overcome drug resistance in multidrug-resistant cancer cells. Moreover, evaluation of synergistic activity between various phytochemicals may provide new insights in the field of integrative oncology.

To facilitate these advances, breakthroughs in clinical trials are important. Initial-phase clinical trials on the safety, pharmacokinetics, and efficacy of phytoconstituent-incorporated NLCs are being launched. Synergy between research universities, drug companies, and regulatory authorities will be pivotal for speeding up developments as well as facilitating approval processes.

Finally, the implementation of green and sustainable nanotechnology practices is gaining increasing prominence. There is research into green production methods, such as the use of biodegradable lipids as well as the removal or reduction of organic solvents in the formulation. Such advances are not only in line with environmental objectives but also ensure the scale-up and sustainable development of NLC-based therapies.

Collectively, these future developments are promising for the promotion of NLC-based drug delivery systems in terms of efficacy, personalization, and environmental sustainability.

Challenge	Implication	Future Strategy
Formulation instability	Reduced efficacy	Stabilizers, cold chain, freeze-drying
Low clinical translation	Poor human relevance	Clinical trials, better models
Regulatory barriers	Delayed approval	Defined guidelines for nanomedicines
Immune recognition	Reduced circulation time	PEGylation, stealth coatings
Manufacturing scale-up	Inconsistent batches	Process standardization

9. Conclusion

Lung cancer is among the most difficult as well as deadly malignancies globally with high incidence and mortality rates due primarily to late detection, swift progression of the disease, and poor efficacy in treatments. Traditional therapeutic options such as surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapies are accompanied by systemic toxicity, drug resistance, and poor specificity towards the tumor. These factors emphasize the urgent necessity for new as well as more efficient therapeutic options.

Phytoconstituents, plant bioactive compounds, have been promising contenders for cancer therapy based on their multi-targeting mechanisms for action, their relative nontoxicity, as well as their efficacy in modulating significant cancer progression-associated pathways like apoptosis, inflammation, oxidative stress, as well as angiogenesis. Curcumin, quercetin, resveratrol, as well as epigallocatechin gallate (EGCG) are some compounds that found considerable anti-cancer activity in in vitro as well as in vivo experiments. Numerous limitations in their therapeutic use have, however, been encountered due to their poor aqueous solubility, liability under physiological conditions, poor bioavailability, as well as fast systemic clearance.

To combat these pharmacokinetic and delivery problems, nanostructured lipid carriers (NLCs) have become increasingly popular as a next-generation drug delivery system. NLCs have numerous benefits over conventional delivery systems as well as other nanocarriers like solid lipid nanoparticles (SLNs) and liposomes. These include high drug loading, enhanced stability, controlled and sustained release, enhanced bioavailability, co-delivery of two or more therapeutic molecules, etc.

Significantly, NLCs are made of biodegradable and biocompatible lipids, which are nontoxic as well as nonallergenic in nature. As such, they are safe for administration via different routes like oral, intravenous, as well as for pulmonary administration.

NLCs loaded with phytoconstituents have established promising therapeutic effects in lung cancer preclinical models. Such nanoformulations promote greater cellular uptake, retention, and targeted accretion of phytochemicals within the vicinity of the tumor, without increasing off-target toxicity. Moreover, they exhibit the ability to overcome multidrug resistance, making the tumor sensitive towards conventional chemotherapy drugs, as well as enhance combination therapy via co-delivery systems.

Notwithstanding these encouraging advances, considerable obstacles still lie in the way for phytoconstituent-loaded NLCs to become established as standard therapeutic in cancer medicine. Among these are formulation intricacy, challenges in large-scale production, speculations on drug approval, and scarcity of clinical evidence. In addition, variability between patients, tumor heterogeneity, as well as interactions with the immune system make the systems' confinement in the clinic even more difficult. In order for NLCs to be utilized in their full capacity in lung cancer treatment, future studies must address Designing targeted and responsive NLCs for enhanced tumor selectivity Improving formulation reproducibility and shelf life for scale-up manufacture

Providing thorough pharmacokinetic, pharmacodynamic, and toxicological assessments

Conducting well-planned clinical trials in human subjects for validation of safety and efficacy

Investigating personalized medicine approaches for customizing NLC treatment based on patient profiles.

In summary, phytoconstituent-charged NLCs are an effective merging of nanotechnology with natural product pharmacology. These are versatile yet promising systems for transcending the inherent limitations associated with phytoconstituents as well as for enhanced therapeutic responses in patients with lung cancer. Interdisciplinary research, proper partnership, and support at the regulatory level are required in order for this innovative technology to become effective enough in shaping the future of lung cancer treatment as well as establish a new standard in the creation of safe, effective, and targeted anticancer drugs.

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